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ARTIFICIAL INTELLIGENCE IN PHARMACOVIGILANCE EFFICIENTLY ANALYZES DATA TO DETECT ADVERSE DRUG REACTIONS, ENHANCING DRUG SAFETY.

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Abstract: Pharmacovigilance (PV) plays a crucial role in monitoring and ensuring the safety of pharmaceutical products by detecting, assessing, understanding, and preventing adverse drug reactions (ADRs) and other drug-related problems. With the ever-increasing volume of medication-related data, there is a growing need for efficient tools to analyze and process this information. Artificial intelligence (AI) and machine learning (ML) have emerged as promising technologies to enhance PV efforts. This article explores the integration of AI and ML in pharmacovigilance, discussing their potential applications, benefits, and implications. Various AI tools and databases utilized in PV activities are outlined, along with the role of automation in streamlining PV processes. The article also delves into the types of AI and machine learning, including supervised learning, unsupervised learning, semi-supervised learning, reinforcement learning, and deep learning, highlighting their relevance in pharmacovigilance. Furthermore, the article discusses the importance of AI in individual case safety report (ICSR) processing and its role in improving data quality, accuracy, and cycle times. Lastly, it emphasizes the potential of AI and ML to revolutionize drug safety monitoring, enhance data analysis, and optimize pharmacovigilance processes for the benefit of public health.

Keywords: Pharmacovigilance, Artificial Intelligence, Adverse drug reactions, Individual case safety reports, Machine Learning, Deep Learning.

Introduction

The World Health Organization has defined "Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems, particularly long term and short term adverse effects of medicines." The history routes of the word "Pharmacovigilance" are: Pharmakon (Greek word for 'drug') and vigilare (Latin word for 'to keep watch') [1]. An ADR may be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." By a) encouraging the discovery of previously undiscovered adverse drug reactions (ADRs), interactions, and increases in the frequency of known ADRs, b) identifying risk factors for the development of ADRs, and c) estimating quantitative aspects of benefit/risk analysis and disseminating information to improve drug prescribing and regulation, pharmacovigilance (PV) supports the safe and appropriate use of drugs [2]. Pharmacovigilance efforts stand to benefit greatly from the application of artificial intelligence (AI) tools. Though not required, pharmacovigilance specialists should possess sufficient knowledge about artificial intelligence to investigate potential partnerships with experts in the field [3]. Machine learning, a form of artificial intelligence, makes predictions using prior knowledge and algorithms. More artificial intelligence has recently been a focus in pharmaceutical development and pharmacovigilance for already-marketed pharmaceuticals [4]. The field of pharmacovigilance (PV), which is in need of alternative ways to deal with the mounting amount of drug safety data accumulating as a result of developments in spontaneous reporting systems and usage of social media as a source of PV, has a great deal of potential for using artificial intelligence (AI), given its recent explosion in popularity in data science [5]. All medication-related data should be gathered and compiled by pharmacovigilance specialists, and any adverse event that a patient experience should be documented as an ICSR (Individual Case Safety Report). Between 2008 and 2017, the US FDA received reports of over 10 million adverse events, of which 5.8 million were considered serious and 1.1 million resulted in death. Thus, the pharmacovigilance industry can benefit from the advent of artificial intelligence by improving the collection of both qualitative and quantitative data. By deep learning based on prior experiences, the machine learning algorithms mimic the activity of human neurons and aggregate the data to produce a logical result [6].

What is artificial intelligence (AI) ?

AI is the ability of a machine to display human-like capabilities such as reasoning, learning, planning and creativity. AI is composed of two words Artificial and Intelligence, where Artificial defines "man-made" and intelligence defines "thinking power", hence AI means "a man-made thinking power." So we can define AI as : " It is a branch of computer science by which we can create intelligent machines which can behave like a human, think like humans, and able to make decisions."

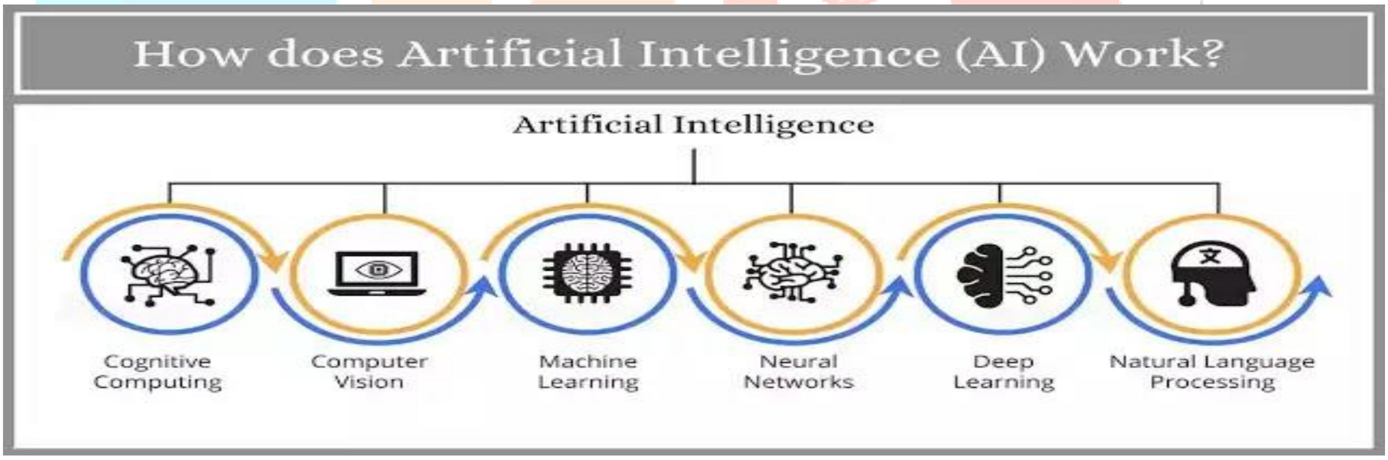

Fig 1. AI workflow.

Types of Artificial intelligence

- **Narrow AI :** These systems are trained for certain tasks and lack the ability to make decisions for themselves. They are limited in what they can do. It is also referred to as weak AI and is only employed for one task. The use of limited AI in everyday tasks is growing quickly. Examples include suggesting music and identifying spam emails, among many other things. One popular example of limited AI that employs machine learning algorithms in mobile devices is Apple's Siri. Artificial intelligence also produces face recognition, sharing predictions, weather forecasts, and Google Assistant.
- **General AI :** Artificial General Intelligence (AGI), another name for general artificial intelligence (AI), is a powerful AI that can read and analyse problems much like a person. However, there are currently no such AGI systems in existence. Because it is so difficult to articulate what human intelligence is, scientists find it extremely difficult to define these features for a machine. Humans just notice objects, differentiate them, and govern their imagination. With a wider range of applications, general artificial intelligence (AI) can mimic human intelligence.

- **Super AI :** AI, as a distinct concept, is capable of performing all tasks with greater cognitive characteristics than humans, outperforming human intellect in the process. The idea that AI is capable of thinking and making decisions like humans is still purely theoretical. [7]

Need of Artificial intelligence in PV

Pharmacovigilance (PV) is where artificial intelligence (AI) is finding more and more application. Using MEDLINE to search for "artificial intelligence" and "pharmacovigilance," we can see that the field of artificial intelligence in pharmacovigilance, or AIPV, is expanding extremely quickly. Because AI, machine learning (ML), deep learning (DL), data mining, and cognitive computing are nested and overlap areas, AIPV scoping is needed even more [8]. The first use of AI in PV is to create a new epidemiological concept based on an awareness of the distinctions between the terms "biosimilar" and "generic." By producing useful data on efficacy and safety, AI will assist to fill in the gaps in the PV ecosystem that currently exist. Artificial Intelligence is the application of machine learning to solve problems in the future by introducing learning technologies into the system and using historical data. AI boosts the success rate of clinical studies and aids with patient randomization. Diabetes, cancer, and diabetic retinopathy are the three main global health issues for which artificial intelligence has demonstrated promising outcomes in terms of identification, avoidance, mitigation, and treatment of these diseases [9].

Individual case safety reports (ICSRs) are the main kind of data utilised in PV. These are recordings of suspected adverse occurrences gathered through various routes, combined and into sizable databases, and continuously watched to identify warning signs. Electronic health records (EHRs), published literature, patient registries, patient support programmes, chatbot interactions, and even direct patient communication via social media are some of the several sources of ICSRs [10]. Annually, the volume of ICSRs may rise, but 90% of adverse events (AEs) remain undetected. Thus, technology must be required to sustain unfavourable occurrences. Making decisions in complex settings is aided by artificial intelligence. Healthcare applications of AI include anticipating asthma flare-ups, tracking insulin levels via smartphone apps, identifying osteoporosis risk groups, keeping an eye on anticoagulant medication compliance, and managing tuberculosis [11]. In the past, individual case safety report forms were gathered, packaged, and sent to regulatory bodies throughout the globe; this process took more time and labour. The 1961 Thalidomide disaster made it necessary to disclose side effects from medications. However, it took two years for an Australian obstetrician and a German doctor to determine the causal relationship between the drug's side effect and the phocomelia. As a result, the WHO established policies and initiatives to stop these kinds of catastrophes. This makes a centralised, objective software system with data regarding a drug's safety profile necessary [6].

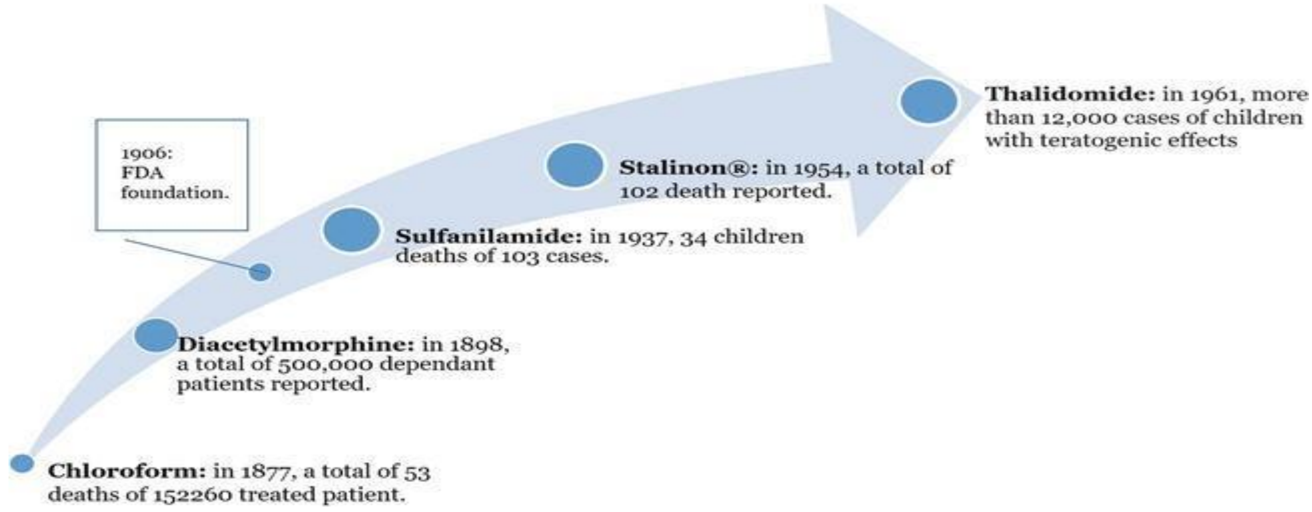

Fig 2. History of pharmacovigilance.

Databases used in PV

AI solutions can streamline and automate nearly all PV case processing tasks, including risk tracking, resulting in shorter processing times. The following are a few tools that are helpful for PV activities:

VigiBase: A PV database that organises and structures data to facilitate simple examination of the collected data. VigiBase gathered information on over 20 million reports of negative medication reactions.

VigiAccess: It is a publicly accessible web application to browse and access the data of adverse drug effects easily through VigiBase.

VigiLyze: This is an online tool that offers a concise and lucid summary of VigiBase, which can be browsed for additional research

VigiFlow: It is a web-based ICSR management system for international drug monitoring by collection, processing, and sharing of data to facilitate effective data analysis, which is supported by WHO Drug and MedDRA.

VigiGrade: To assess the degree to which clinically pertinent data is presented in an ordered manner on each individual case report. This is mostly utilised in correspondence regarding data quality with other nations.

VigiMatch: Using probabilistic pattern matching, this algorithm finds similar individual case reports. [12]

Role of artificial intelligence and automation in various pharmacovigilance processes

A lot of interest has been shown in the use of AI in medication development and life cycle management, which includes PV. PV is defined by the US Food and Drug Administration as "all scientific and data collection activities related to the detection, evaluation, and understanding of adverse events." Apart from registries, individual case safety reports, clinical pharmacology studies, and other related tools, the FDA defines pharmacovigilance as encompassing multiple scientific research methodologies. PV may benefit from the application of artificial intelligence and machine learning in the following ways: 1) automatically completing tasks related to the entry and processing of case reports; 2) identifying clusters of adverse events that indicate symptoms of syndromes; 3) conducting pharmacoepidemiological studies; 4) connecting data by conducting probabilistic matching within datasets; and 5) the prediction and prevention of adverse events through specific models using real-world data [13].

Automation is the process of using technology to perform or reduce work, therefore eliminating the need for human labour. Pharmacovigilance stands to benefit greatly from automation, which will lower case processing costs and enhance data quality. AI-powered adverse event (AE) case processing automation offers a chance to influence the biggest PV cost driver. The use of AI techniques in the field of biomedicine has grown within the last ten years. Opportunities to evaluate the usefulness of AI approaches with the automation of PV procedures have arisen as a result of some advancements in using AI techniques against publicly available consumer data. An increasing corpus of research has investigated the use of machine-learning algorithms to practice-based clinical pathways, probabilistic clinical risk stratification models, and disease models since the advent of electronic health records [14].

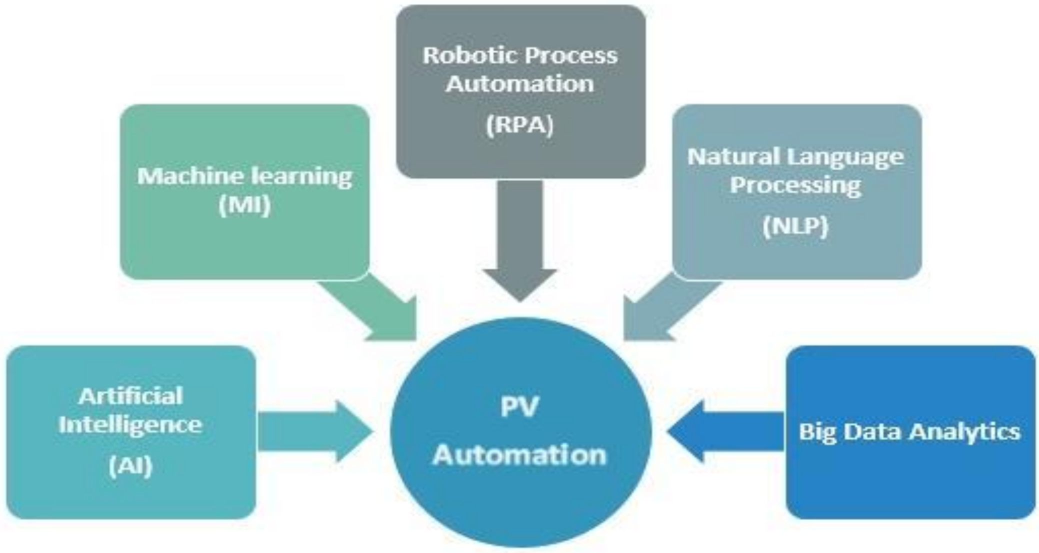

Fig 3. Various automation platforms in PV.

Effectiveness of Automation in Pharmcovigilance :

a) Faster signal adjudication and reporting.
b) Increased pharmcovigilance activity stability.
c) Automated pharmcovigilance task management.
d) Standardized pharmacovigilance process with local variations.

Benefits of Artificial intelligence in PV

1. The most important benefits of AI are reduced cycle times. Due to this method, the processing is spontaneous.
2. Improve the quality and accuracy of the information.
3. AI can handle or manage diverse types of incoming data formats.
4. It can be used for the identification of ADRs.
5. AI is useful to reduce the burden and time of case processing.
6. AI tools extract the information from the adverse drug event form and evaluate the case validity without the workforce.
7. Less human errors: AI technologies can reduce human error in detecting side effects, contributing to more accurate results.
8. AI helps in reducing mortality chances by detection of diseases at an early stage from patient's electronic footprints.

Artificial Intelligence for ICSR processing

Pharmaceutical businesses must comply with FDA-mandated ICSR. ICSRs are distributed to important parties, such as pharmaceutical firms and regulatory agencies, in order to guarantee public safety. A PV expert is needed to evaluate the case's legitimacy before the ICSR procedure may start.

Four elements must be fulfilled in order for the ICSR to be deemed genuine :

- Identifiable supplier
- Identifiable patient
- Suspected drug
- Anticipated adverse effect.

The PV specialist collects this information and develops an ICSR prepared according to FDA regulations. This entails gathering AE cases in a methodical manner, conducting the necessary research to properly comprehend the case, entering AEs into a database, categorising AEs using accepted medical terminology, and classifying AEs into groups such as expected versus unexpected, serious vs. non-serious, and related vs. unrelated [15].

The increasing rate of ICSRs has been shown in the below figure :

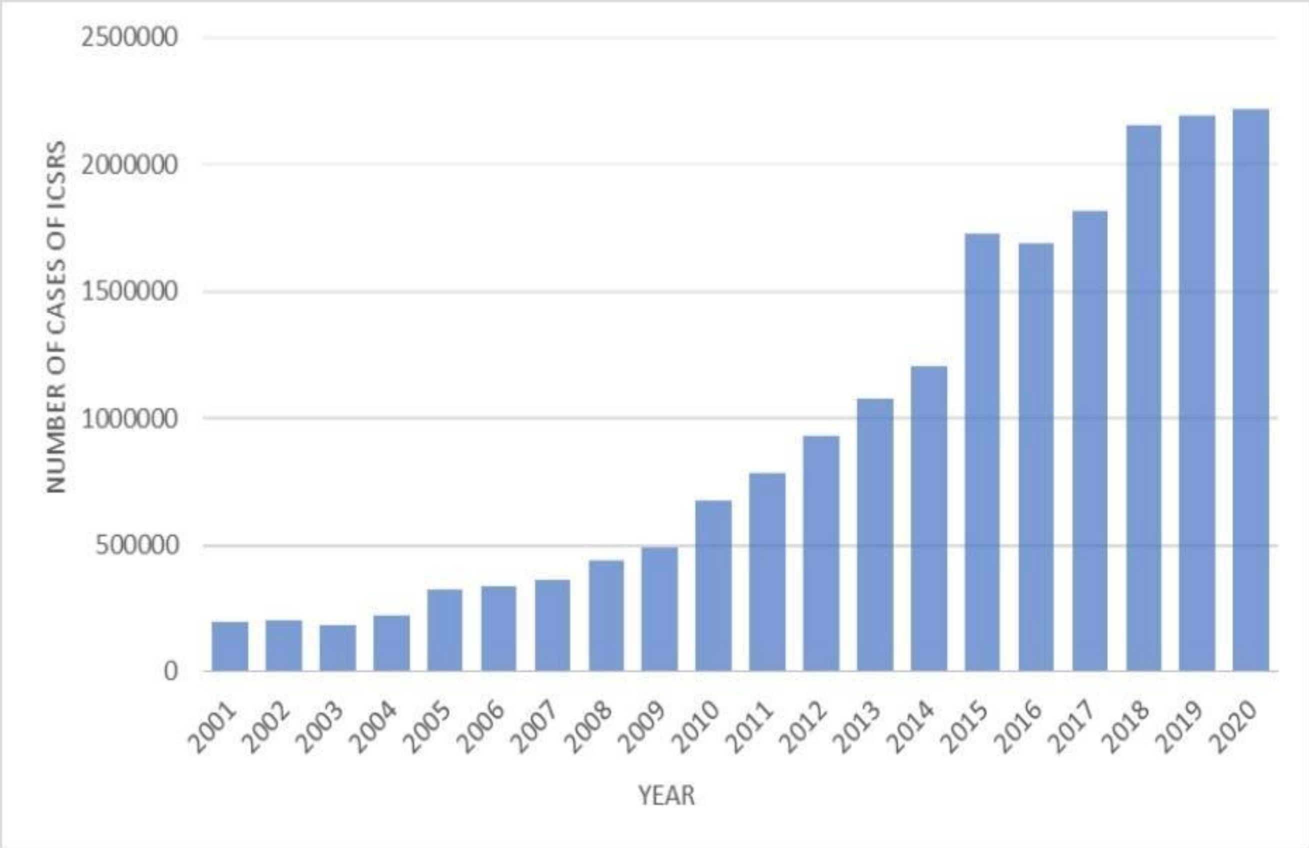

Fig 4. Individual case safety reports received by FDA'S adverse event system.

Following are the broad two categories of usage of AI technologies in ICSR Processing :

- Efficiency in decision making – Artificial intelligence is particularly important in developing hypothesis when the quality of the information in the Individual Case Safety Report is inadequate. Content correctness and speed could be facilitated by artificial intelligence.
- Ingestion of structured and unstructured content – consists of elements for reading case intake data that is sent via XML, documentation, pictures, form-tables, and PDF text. To extract ICSR information from information sources in a way that complies with regulations, OCR/ICR is utilised in conjunction with NLP/machine learning. [16]

Machine Learning (ML)

Advanced algorithms, machine learning, deep learning, and other components make up the multifaceted field of artificial intelligence technology. In 1959, Arthur Samuel first used the term machine learning (ML). He described it as an application of artificial intelligence (AI) that allows computers to automatically learn from experience and get better at it without needing to be explicitly programmed. ML, DL, conventional machine learning (CML), computer vision, robotics, reasoning, general intelligence, expert systems, automated learning, and scheduling are noteworthy components of AI.

As previously indicated, machine learning (ML) is a branch of artificial intelligence (AI) technology that uses methodologies to synthesize the underlying relationships between data and information. Machine learning (ML) is a scientific field that focuses on how computers learn from data. It is also an artificial computer intelligence system that enables computers to learn on their own without programming or help from humans. In reality, since the internet's inception, machine learning (ML) has emerged as a key player in the information technology revolution that has recently impacted our day-to-day existence [17]. Within artificial intelligence, machine learning is a subset of data analysis that automates the creation of analytical models. It is predicated on the notion that machines are capable of learning from data, spotting patterns, and making judgements with little help from humans. Target identification, drug discovery, preclinical testing, and clinical trials are just a few of the phases of drug research where these computational tools are used. AI/ML models may predict protein structures and possible drug-target interactions, which can help identify targets and reduce the amount of lab effort required for drug discovery. To further improve safety profiles and reduce failure rates in later phases, predictive models are created in preclinical testing utilising machine learning algorithms to evaluate the possible toxicity of novel substances. AI/ML algorithms in clinical trials can predict patient outcomes, monitor adverse events, and expedite patient recruitment, all of which contribute to a more patient-centered and efficient trial procedure [18]. The use of ML in medication safety serves as an example of how much the buzz surrounding ML in general society has now spread to PV. Machine learning is widely employed in several applications, such as automated clinical visit scribing using voice recognition and medical imaging applications like retinopathy that need visual pattern recognition [19].

Types of Machine learning :

Based on the methods and techniques to teach machines, Machine Learning is categorized into mainly four types, which are as follows :

A) **Supervised Learning :** Labelled samples that have been trained on supervised learning techniques include inputs for which the intended outcome is known. For example, a piece of equipment might, for instance, have data points with the labels "F" for failed or "R" for runs. The learning algorithm finds faults by comparing its real output with the correct outputs after receiving a series of inputs and the associated correct outputs. The model is then adjusted appropriately. Supervised learning makes use of patterns to forecast label values on more unlabeled data by applying techniques including gradient boosting, regression, classification, and prediction. Applications where past data forecasts anticipated future events frequently employ supervised learning. For example, it can predict when credit card transactions are most likely to be fraudulent, for instance, or which insurance customer is likely to file a claim.

B) **Unsupervised Learning :** It is used against data that has no historical labels. There is no "right answer" provided to the system. What is displayed must be determined by the algorithm. Finding some organisation within the data is the aim of the exploration process. Transactional data is a good fit for unsupervised learning. It can, for instance, be used to find client segments with like characteristics, who can therefore receive comparable treatment in marketing initiatives. Alternately, it is able to identify the primary characteristics that set apart certain client segments. Popular methods include singular value decomposition, k-means clustering, nearest-neighbour mapping, and self-organizing maps.

C) **Semi-supervised Learning :** It serves the same purposes as supervised learning. However, because unlabeled data is less expensive and requires less work to obtain, it often combines a large volume of unlabeled data in conjunction with a limited amount of labeled data for training. When completely labeled training is not feasible due to high labelling costs, semi-supervised learning can be helpful. Finding someone's face on a webcam is one of the earliest instances of this. [20]

D) **Reinforcement Learning :** It is a kind of machine learning technique that makes it possible for software agents and machines to automatically assess the best behaviour in a given context or environment in order to increase its efficiency. With reward and penalty as its guiding principles, this kind of learning seeks to maximise reward and reduce risk by using the knowledge gained from environmental activists. While it is a useful tool for developing AI models, it is not ideal to use it to solve simple or elementary problems. Instead, it can help to improve automation or the operational efficiency of complex systems like robotics, autonomous driving tasks, manufacturing, and supply chain logistics [21].

Deep Learning (DL)

Through the use of artificial neural networks and simulation learning, Deep Learning is a subfield of machine learning that seeks to create a model that can solve complicated issues in the real world on par with the human brain. Each model that is developed must successfully complete two key deep learning tasks: extracting semantic information from input and generating insightful output. Since the human brain is made up of networks of neurons, deep learning simulates the human brain using artificial neural network (ANN) techniques in an attempt to replicate the depth of these neural connections. It is composed of an input layer, an output layer, and one or more additional hidden layers, each of which has a set of weighted nodes or neurons that are attached to one another. High degrees of cognitive abilities are needed for DL, including synthesis

(integrating knowledge into a new dimension) and analysis (comparison, contrast). Furthermore, deep learning enhances lifetime learning comprehension and implementation.
The primary characteristics of DL are meaning-centered learning, integrating new knowledge with other subjects, combining expertise and real-world applications, encouraging a critical attitude and analysis, and intrinsic motivation that promotes learning as a source of fulfilment. Due to its capacity to learn from massive volumes of data that humans are unable to handle, deep learning is distinguished by its rapid learning rate. As a result, DL might make deductions and come to conclusions that people cannot. DL leverages agriculture, weather forecasting, and image recognition. Additionally, it has been used to automobile technology and medical fields. Hence, AI has been essential in supporting and enriching the lives of people and society [22]. DL may be supervised or unsupervised. Many of the recent basic improvements in machine learning have been made possible by DL approaches [23]. The perceptron serves as the foundation for neural networks in deep learning architectures, which frequently use enormous or huge datasets. Heuristics and empirical findings are also included into such architectures. Deep learning can now classify images more accurately than humans in some cases. Deep learning introduces deep neural networks with new methods and novel structures (e.g., convolutional neural networks, RNNs), whereas machine learning uses MLPs (multilayer perceptrons) [24].

Conclusion

In conclusion, the integration of AI and ML in pharmacovigilance has the potential to enhance drug safety monitoring, improve data collection and analysis, and streamline various processes. As the field of AI continues to advance, it will play an increasingly vital role in ensuring the safety and effectiveness of pharmaceutical products. Artificial intelligence is actively being used in pharmacovigilance and patient safety to gather information on ADRs and ADEs, to perform surveillance and signal detection, to process ICSRs, to process patient safety event reports and clinical narratives, to extract drug-drug interactions, to identify populations at high risk for experiencing ADRs and guide personalised care, to predict drug side effects, to simulate clinical trials, and to integrate prediction uncertainties into diagnostic classifiers to increase patient safety. AI methods will now be helpful in locating and starting a hidden relationship for ICSR processing in PV. With the use of AI, the entire process-from case receipt to reporting can be automated. These procedures will increase accuracy and quality while also lowering costs. The automation and machine learning can optimize pharmacovigilance processes and provide a more efficient way to analyse 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.

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