



REVIEW ARTICLE

Machine learning in drug safety: exploring applications and addressing challenges for improved patient safety

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ARTICLE INFO ABSTRACT



Received 03 June 2023; Revised 21 July 2023; Accepted 22 August 2023.	Artificial intelligence (AI) has emerged as a powerful tool in the pharmaceutical industry, utilizing machine learning and natural language processing to access and analyze vast amounts of research and information. AI has a wide range of applications in the field of pharmacovigilance (PV) and drug safety, including the improvement of information retrieval, the identification of medical concepts, text translation, automated illness image classification, and the gathering of adverse drug response (ADR) data. This review article explores the potential of AI in drug safety and its challenges, highlighting its applications along with examples. By embracing AI advancements, the industry can enhance drug safety monitoring, improve data analysis, and contribute to better healthcare outcomes.
Keywords: Artificial intelligence, Machine Learning, Pharmacovigilance, Drug Safety, Applications	

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Introduction

Artificial intelligence (AI) can efficiently access and analyze current research and information in the pharmaceutical sector by utilizing cutting-edge technologies like machine learning and natural language processing. By enhancing the work of experts, this improved efficiency has the potential to improve pharmaceutical innovation and lower attrition rates (Hunter, 2016; Mak & Pichika, 2019). There is always a requisite for continuous change and betterment in every industry including the pharmacovigilance (PV) and drug safety sector. Here a record breaking amount of data is flowing with the need to sort, collect, and to link the data needs advancement in the algorithmic development (Lamprecht, 2011). One of the main advantage of algorithmic development is that it helps in designing many algorithmic models which can solve complex problems easily and swiftly. These algorithmic models can be designed to perform a wide range of functions, it

can learn from the data and make decisions based on that learning and are often used in AI (Suke et al., 2015; Sarker, 2021; Xu et al., 2021). AI is utilized in providing benefits in many fields in PV such as data mining, risk prediction and assessment, Adverse event reporting (ADE), Decision support systems and signal validation (Mohammadi et al., 2023; Bate & Hobbiger, 2021).

In the following review article, we will examine the various uses of AI in PV and drug safety, emphasizing how it can improve information retrieval, recognise medical terms, translate text, classify disease images automatically, and gather data on adverse drug reactions. We will also discuss the difficulties the sector is facing.

Applications of AI in Pharmacovigilance And Drug Safety

Various applications of artificial intelligence has been presented in Table 1.



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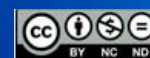
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Table 1: Applications of AI in Pharmacovigilance And Drug Safety

Applications	Examples
Enhances the efficacy of information retrieval	Term retrieval from MedDRA (Souvignet et al., 2016) Information retrieval from Pubmed citations (Wang et al., 2011)
Identifying and capturing medical concepts to assist in drug safety monitoring	Automated tool to extract AE terms(Ly et al., 2018) Drug safety through social digital media (Comfort et al., 2018) ADR mining from social media (Nikfarjam et al., 2015)
Machine readable text conversion	Optical character recognition (Park et al., 2012)
Automated Disease image classification	AutoML Diagnostic support system (Puri, 2020)
Gathering and tracking ADRs	Crowdsourcing through twitter (Lardon et al., 2017) Crowdsourcing from social media with sequence labelling and word embedding (Nikfarjam et al., 2015) Annotate and categorise tweets about ADR (Tao et al., 2017) Provides training data sets for automated systems (Gartland et al., 2021)

Enhances the efficacy of information retrieval

This article discusses about the creation of a new semantic resource called OntoADR which uses formal description logic and manual curation by pharmacovigilance experts to enhance the retrieval of terms from the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a standardized medical terminology system used for classification and coding of ADRs and other related medical events. To create OntoADR, they started by mapping MedDRA terms to SNOMED-CT (Systematized Nomenclature of Medicine - Clinical Terms) which is a standardised multilingual clinical healthcare terminology in the world. This mapping allows better sharing of the data/information between these two. Then they used semi-automatic methods to generate definitions for MedDRA terms to make it simpler to search for and retrieve concepts. Finally, they did a manual curation of the resource by pharmacovigilance experts. This ensured accurate, relevant and effective retrieval of information. Through the creation of a semantic resource they are aiming to improve the retrieval of information regarding adverse drug reactions (ADRs). By carefully and effectively choosing phrases, this resource can be utilised to enhance the retrieval of ADR-related information. The authors have set up OntoADR to dynamically integrate updates from external sources, then it's possible that changes to MedDRA could be reflected in the tool automatically when new versions are released ([Souvignet et al., 2016](#)). In this specific article they haven't discussed about non-specific terminology and the selection of the closest LLT (Lowest Level Term) in MedDRA. But if a

scenario arise where the terminology used to describe a medical event lacks specificity, many approaches such as combination of mapping strategies, semantic analysis, and expert curation to determine the most appropriate Lowest Level Term (LLT) within the MedDRA hierarchy can be employed. To tackle non-specific terminology, we can devise an algorithmic approach that involves contextual analysis and expert judgment. This approach takes into account various factors, such as the context in which the term is used, related medical information, and potential synonyms. Additionally, we can leverage semantic relationships established through mapping MedDRA terms to SNOMED-CT concepts, which aids in identifying the most closely related LLT.

On the other hand, the drug-ADE classification using PubMed citations article, focuses on automatically identifying which drugs are associated with specific adverse event based on the content of pubmed citations. This approach can be used to generate a knowledge base of drug-ADE pairs that can be used to support ADE detection and monitoring, and thus improve the retrieval of information related to ADEs from the literature. Here, they developed an AI algorithm which can detect drug-ADE relationships from PubMed citations and to provide this algorithm to support pharmacovigilance and decision support. This algorithm provides with information whether the specific drug might cause the ADE. They used a serious adverse event as neutropenia as a target ADE to develop the algorithm, they searched articles which mentioned the drug-ADE pair and classified those articles by denoting or not denoting the drug-ADE relation. In the next step they determined whether the

drug caused the ADE or not. A dataset of 400 articles (200 denoting and 200 not denoting the drug-ADE relation) was selected and used to test the classifier. It was successfully tested to 76 drugs related with neutropenia, another drug-ADE pair was also tested with myocardial infarction as the ADE. The criteria for inclusion in the dataset involved ensuring that the articles were relevant to the drug-ADE relationship under investigation and that they could be definitively classified by experts. Duplicate articles and articles that couldn't be definitively classified were removed, resulting in a final dataset of 400 articles for training and testing the classifier. In case of multiple drugs, the system considers a range of features from the text, including drug names, symptoms, and keywords, to identify and classify drug-event pairs even when multiple drugs are mentioned in the same article. To increase effectiveness generic name and brand name (using RxNorm) for each drug was provided. But the algorithm does not work for a class of drugs or pro drugs, instead only for specific drugs (Wang et al., 2011).

These examples demonstrate how AI has the ability to enhance the effectiveness of information retrieval in pharmacovigilance, which is a crucial component of maintaining the safety and effectiveness of medications.

Identifying and capturing medical concepts to assist in drug safety monitoring

Medical concepts can be identified and captured using various methods such as Natural Language Processing (NLP) techniques, ontology-based approaches, and machine learning algorithms. With the aid of these techniques, valuable data can be obtained from unstructured medical data sources like clinical notes, electronic health records (EHRs), and social media posts (Sheikhalishahi et al., 2019; Kimia et al., 2015; Houssein et al., 2021; Luo et al., 2017; Raja & Jonnalagadda, 2015; Shahbazi & Byun, 2021; Prabhakar & Won, 2021).

In 2018, an article was published with a hypothesis about the use of natural language processing in automated extraction and MedDRA mapping of adverse event terms in drug product labels. This study investigated if automated NLP algorithms could extract and map labelled adverse event phrases to MedDRA without human intervention. The study assessed the effectiveness of three NLP techniques (ETHER, I2E, MetaMap) by comparing it to a human-annotated gold standard label dataset to extract and map AE keywords from drug product labels. This technique can reduce the workload in an effective manner. Their results proved that NLP tools can be used in a reasonable way in a regulatory setting and can also be adapted accordingly (Ly et al., 2018).

Meanwhile in early 2018 a study was published regarding the use of Machine Learning (ML) in detection of valid

Individual Case Safety Reports (ICSRs) within social digital media. The models were compared with human experts in pharmacovigilance. The best model achieved good agreement with the experts and performed much faster than humans in analyzing a large amount of data. The results suggested that using these automated machine learning classifiers can be effective and time efficient for detecting important safety information from social media for drug safety monitoring (Comfort et al., 2018). Another study about pharmacovigilance in social media was published in 2015 in which they tried to extract valuable information used in social media posts by a machine learning based approach, this model named ADRMine extracts mentions of ADRs from highly informal text which is prevalent in social media. ADRMine employs conditional random fields (CRFs) and utilizes a range of features, also incorporates a novel technique for capturing semantic similarities between words and this technique has a higher level of accuracy (Nikfarjam et al., 2015).

Machine readable text conversion

Pharmacovigilance involves monitoring and reporting adverse events related to medications (Zhao et al., 2022). Since many reports of adverse events are filed in paper form, Optical Character Recognition (OCR) may be used to digitise these reports and make the data they contain available to automated systems. OCR is a technology that can identify and extract text from pictures and scanned paperwork, such scanned reports or PDFs. This can be especially helpful in pharmacovigilance (Pharmafocus America, n.d.). In 2012 a study published regarding the construction of an open access QT database named Electrocardiogram Vigilance with Electronic Data Warehouse (ECG-ViEW). The purpose of this database is to facilitate the surveillance and monitoring of a marketed drug for potential proarrhythmia effects by assessing the information about the QT interval from electrocardiograms (ECGs) by the conversion of the scanned photos to numerical data using OCR software. This enables physicians and researchers to collect and assess sets of QT interval data (Park et al., 2012).

Automated Disease image classification

Identification and assessment of a specific disease through pictures or medical imaging tests for a pharmacovigilance professional may take more than required time when compared to a clinician. ML and deep learning (DL) algorithms are two common examples of AI techniques that are employed in the prediction and diagnosis of a variety of diseases, particularly those whose diagnosis is based on imaging or signalling analysis (Ghaffar Nia et al., 2023). This will help in further understanding of the disease and the cause which will help in surveillance and monitoring of safety of the drugs. For example a preclinical diagnostic support

system was designed to detect Drug Induced Liver Injury (DILI) where the system used heterogeneity features and automated machine learning (AutoML) models to classify DILI image patterns. Such a diagnostic assistance system may help pharmaceutical firms identify and assess DILI effects early in the medication development process, thereby saving time, money, and resources often used to test for drug efficacy and safety (Puri, 2020). These image classification have many applications in diagnosis and risk assessment, for instance a deep learning method that estimates the likelihood of lung cancer from a patient's most recent and previous computed tomography volumes and an automated classification of skin lesion using a single deep convolutional neural networks to analyse skin cancer are some of those applications (Ardila et al., 2019; Esteva et al., 2017).

Gathering and tracking ADRs

With its creative approaches to the problems of tracking ADR and gathering data from social media, crowdsourcing has emerged as a useful strategy in pharmacovigilance and drug safety. Numerous research have shown that the use of social media data for pharmacovigilance has been investigated. A scoping review on the detection and extraction of adverse medication reactions from social media was carried out by Lardon et al. in 2017. The analysis emphasized how crowdsourcing may be used to gather important ADR data from user-generated content on websites like Twitter (Lardon et al., 2017). According to Nikfarjam et al. (2015), mining ADR mentions from social media with sequence labelling and word embedding cluster characteristics was their main objective. Their research proved how well crowdsourcing worked for collecting social media data for pharmacovigilance (Nikfarjam et al., 2015). A study on crowdsourcing annotations of negative medication reactions in Twitter was presented by Tao et al. in 2017. They investigated the use of crowdsourcing to annotate and categorize tweets about ADR, demonstrating the viability and advantages of enlisting the public data in annotation projects (Tao et al., 2017).

In particular, one study looked at the use of crowdsourcing to provide training data sets for automated systems in pharmacovigilance. A reference dataset of 15,490 social media posts about medications and medical issues was compiled by pharmacovigilance experts. These pieces included a portion that was crowdsourced on Amazon Turk, where Turkers responded to inquiries concerning the medical theories. The efficiency of the crowdsourced curation process in terms of accuracy, price elasticity, and duration was assessed. The findings demonstrated that crowdsourced curation required just around 5% of the time and produced over 90% accuracy relative to the reference dataset. While accuracy was unaffected by pay levels, time efficiency was. Using

numerous Turkers to assess a post through a vote system did not significantly increase accuracy. The use of crowdsourcing to create training datasets for pharmacovigilance automation was shown to be accurate and effective, although more research was required to fully understand its potential, restrictions, and generalizability (Gartland et al., 2021).

In conclusion, crowdsourcing has demonstrated to be an effective strategy for pharmacovigilance and drug safety. It facilitates the extraction of ADR information from social media data and supports data annotation activities by drawing on the collective intelligence of the public. Through crowdsourcing, the general public can participate in effective and scalable analysis, improving monitoring and comprehension of medication safety profiles.

Challenges in Implementing AI in Pharmacovigilance and Drug Safety

There are various huge PV databases or PV systems, such as the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) have been expanding in both developed and developing nations and the Pharmacovigilance database in France, China's pharmacovigilance system, the Vaccine Adverse Event Reporting System (VAERS), and Vigibase in the United States. The Uppsala Monitoring Centre maintains Vigibase, which includes information provided by contributors in more than 150 nations. Underreporting is a basic problem while building a PV database. This is caused by a number of different things, including inadequate reporting system infrastructure, inadequate funding, a lack of human resources, and insufficient regulations. A set of facts illustrates the circumstance: About 70% of the data in Vigibase came from Western nations (the United States, the European Union, etc.), while only 0.9% of ICSRs in Vigibase in 2019 came from Africa (Barry et al., 2020).

In many underdeveloped nations, Pharmacovigilance (PV) guidelines are gradually being established to ensure the safe use of medicinal products. These guidelines outline procedures for detecting, assessing, and preventing adverse effects of drugs. While some countries have implemented PV guidelines, their enforcement and monitoring vary with each other. In cases where guidelines are in place, regulatory authorities and health agencies are responsible for overseeing compliance. This involves conducting audits, inspections, and assessments of PV processes to ensure that healthcare providers, pharmaceutical companies, and other stakeholders adhere to the prescribed procedures. However, the effectiveness of monitoring mechanisms can be limited by factors such as resource constraints, lack of awareness, and inadequate infrastructure. As countries strive to improve their healthcare systems, strengthening PV guidelines and their

enforcement becomes crucial for safeguarding public health. The issue in underdeveloped nations is that they adhere to outdated PV practices and lack the necessary professionals. Traditional PV also needs expertise in several fields of AI, such as engineers for creating NLP and machine learning algorithms, in addition to drug safety supervisors, drug safety physicians, and data/system security administrators (Luo et al., 2017). In these countries, a lack of qualified personnel for AI-based PV is typical. One strategy to increase the number of experts in PV and AI is through education. Introducing AI-based PV in teaching would be the largest step towards educational institutions that offer undergraduate courses to students in relevant majors. In addition to producing more interdisciplinary professionals, education on AI-based PV could raise such professionals' knowledge of PV data. China serves as an illustration of inadequate education; despite recently establishing an online spontaneous self-reporting ADR monitoring system (Zhao et al., 2018). A study of PV in Western China revealed that the ADR reporting rate was incredibly low due to hazy feedback pathways and a lack of awareness of the seriousness of ADRs (Chen et al., 2021).

As discussed above, detection of adverse drug events from social media also presents a number of significant difficulties. First, a variety of phrases, including brand names, active components, slang terms, or generic terms, such "antibiotic," are frequently used to refer to pharmaceuticals. Second, it is possible to refer to ADRs with original idiomatic expressions or words that are not now part of the medical lexicon. Third, because social media is casual, error in language, spelling, abbreviations, and slang are frequently made. Fourth, even if a side effect is present, it may not always be clear what kind of adverse effect was felt. Fifth, talks about a drug may include information on indication, positive outcomes, or worries about negative side effects (Sloane et al., 2015).

Conclusion

In order to manage the growing volume of data and enhance information retrieval, the pharmacovigilance and drug safety sector constantly needs to expand algorithmic development. Data mining, risk prediction, adverse event reporting, decision support systems, and signal validation are just a few of the pharmacovigilance applications and advantages that algorithmic models and artificial intelligence approaches can provide.

The creation of semantic resources like OntoADR, which enhances the retrieval of terms from standardised medical terminologies like MedDRA, might increase the effectiveness of information retrieval. This tool supports pharmacovigilance efforts by making it easier to retrieve reliable and pertinent data regarding adverse drug reactions.

To detect and record medical concepts for medication safety monitoring, AI algorithms can also be used. Automated extraction and mapping of phrases related to adverse events from drug product labels and social media posts is made possible by natural language processing techniques and machine learning algorithms. For pharmacovigilance experts, these automated technologies offer useful data and lighten the effort. The translation of text into machine-readable form using OCR is a critical step in the digitization of adverse event reports and makes the information available to automated systems. OCR technology makes it possible to convert scanned documents into machine-readable formats, which makes data analysis and monitoring more effective.

The diagnosis and evaluation of diseases based on medical imaging is aided by automated disease picture categorization employing AI techniques, such as machine learning and deep learning. By assisting in the early detection of medication-induced side effects, these technologies can help the drug development process save time and resources. Crowdsourcing has become a useful tool for obtaining and monitoring negative medication reactions. Crowdsourcing can be used to extract ADR mentions from social media, analyse tweets, and produce training datasets for automated algorithms. Using collective intelligence to monitor and understand pharmaceutical safety profiles is more effective.

Despite the potential advantages, the industry of pharmacovigilance and drug safety faces difficulties. Due to weak reporting system architecture, scarce resources, and a lack of laws, underreporting in PV databases continues to be a serious problem, particularly in developing countries. Progress is further hampered by the lack of experts in AI-based PV and by out-of-date PV procedures. By creating more trained professionals and increasing awareness of PV data, education and interdisciplinary training can aid in overcoming these difficulties.

In conclusion, the field of pharmacovigilance and drug safety has enormous promise for the further development of algorithms and the incorporation of AI approaches. These developments may improve information retrieval, increase drug safety monitoring, allow for effective data analysis, and make it easier to obtain and monitor adverse drug reactions. Pharmacovigilance can further improve pharmaceutical safety and contribute to better healthcare outcomes by addressing the issues and making use of AI.

Abbreviations

AI - Artificial intelligence

ADE - Adverse event reporting

ADR - Adverse Drug Reactions

AutoML - Automated Machine Learning

DL - Deep Learning

DILI - Drug Induced Liver Injury

ECG-ViEW - Electrocardiogram Vigilance with
Electronic Data Warehouse

ECG – Electrocardiograms

FDA - Food and Drug Administration

PV - Pharmacovigilance

MedDRA - Medical Dictionary for Regulatory Activities

SNOMED-CT - Systematized Nomenclature of Medicine
- Clinical Terms

NLP - Natural Language Processing

ML - Machine Learning

ICSR - Individual Case Safety Reports

OCR - Optical Character Recognition

VAERS - Vaccine Adverse Event Reporting System

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