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SYSTEMATIC REVIEW

The Use of Artificial Intelligence in Pharmacovigilance: A Systematic Review of the Literature

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Abstract

Introduction Artificial intelligence through machine learning uses algorithms and prior learnings to make predictions. Recently, there has been interest to include more artificial intelligence in pharmacovigilance of products already in the market and pharmaceuticals in development.

Objective The aim of this study was to identify and describe the uses of artificial intelligence in pharmacovigilance through a systematic literature review.

Methods Embase and MEDLINE database searches were conducted for articles published from January 1, 2015 to July 9, 2021 using search terms such as 'pharmacovigilance,' 'patient safety,' 'artificial intelligence,' and 'machine learning' in the title or abstract. Scientific articles that contained information on the use of artificial intelligence in all modalities of patient safety or pharmacovigilance were reviewed and synthesized using a pre-specified data extraction template. Articles with incomplete information and letters to editor, notes, and commentaries were excluded.

Results Sixty-six articles were identified for evaluation. Most relevant articles on artificial intelligence focused on machine learning, and it was used in patient safety in the identification of adverse drug events (ADEs) and adverse drug reactions (ADRs) (57.6%), processing safety reports (21.2%), extraction of drug–drug interactions (7.6%), identification of populations at high risk for drug toxicity or guidance for personalized care (7.6%), prediction of side effects (3.0%), simulation of clinical trials (1.5%), and integration of prediction uncertainties into diagnostic classifiers to increase patient safety (1.5%). Artificial intelligence has been used to identify safety signals through automated processes and training with machine learning models; however, the findings may not be generalizable given that there were different types of data included in each source.

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.

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Key Points

This systematic literature review evaluated 66 studies that included information on the use of artificial intelligence in patient safety.

The most identified uses of artificial intelligence, mainly machine learning, in patient safety and pharmacovigilance were in the identification of adverse drug events (ADEs) and adverse drug reactions (ADRs), followed by the processing of safety reports or clinical narratives and extraction or prediction of the effects of drug–drug interactions.

As artificial intelligence is used more frequently in safety assessment, its application may provide additional value not only in safety identification and assessment, but also in the prediction of side effects and ADRs.

1 Introduction

The fascination of humans to 'recreate' human intelligence in machines is not new and this situation has evolved over time. Currently, many information systems groups are developing learning algorithms to 'mimic' how humans learn and make decisions. Machine learning is part of artificial intelligence where new capabilities are incorporated into machines to 'learn' without explicitly programming [1], and create algorithms to accomplish a task while learning from its successes and failures [2]. Machine learning encompasses supervised learning, unsupervised learning, reinforcement learning, and recommender systems [1], including artificial neural networks and deep learning [3].

The integration of artificial intelligence into the healthcare system is changing the role of healthcare providers and creating new potential to improve patient safety outcomes [4] and quality of care [5]. Artificial intelligence is being used to improve patient safety in both inpatient and outpatient settings [6]. It has also been used to minimize preventable harm by incorporating digital approaches that allow for communication between patients and their healthcare providers [6]. In pharmacovigilance, the use of artificial intelligence is increasing in various areas including safety operations, signal management, and identification of target populations. There is a need to understand the current landscape of artificial intelligence in pharmacovigilance and what opportunities there are for further advancement in this area. The objective of this systematic literature review is to describe the use of artificial intelligence in patient safety and pharmacovigilance in general.

2 Methods

2.1 Study Design

This is a non-quantitative systematic literature review, which was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7] and recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [8]. For this type of systematic literature review, there was no requirement to register the protocol.

2.2 Data Source

The literature search was conducted in two phases to account for new results available since the time the first phase was conducted. The search used the databases Embase (1980–March 22, 2021 for phase one, 1980–July 9, 2021 for phase two) and MEDLINE (1946–March 22, 2021 for phase one, 2017–July 9, 2021 for phase two) and was ultimately limited to the period of January 1, 2015–July 9, 2021. A list of relevant titles, abstracts, and references were uploaded in an Excel spreadsheet for review. The search strategy for each of the two phases is included in the tables in Online Resources 1–2 (see Electronic Supplementary Material [ESM]).

2.3 Article Selection

Any scientific article that contained information on the use of artificial intelligence in patient safety and/or pharmacovigilance was reviewed.

2.3.1 Inclusion Criteria

The inclusion criteria comprised scientific articles where artificial intelligence was used in patient safety and/or pharmacovigilance; articles regarding modeling algorithms used for safety signal identification, characterization, assessment, or management; articles in the English language only; no geographical limit; and articles published between January 1, 2015 and July 9, 2021.

2.3.2 Exclusion Criteria

The exclusion criteria comprised articles with incomplete information (e.g. abstracts or posters with no full text), letters to editor, notes, commentaries, and duplicated articles.

2.4 Literature Review

The first screening of titles and abstracts was carried out independently by three researchers (JP, TB, and MS) using pre-determined inclusion and exclusion criteria to decide whether the abstract was relevant for article procurement. In addition, two additional researchers (OA and MS) independently did a second review. A consensus meeting was held to discuss the discrepancies between the reviewers' assessments of the abstracts and a final decision was made on the articles to be procured.

The second level of screening of full articles was conducted independently by three researchers (OA, DK, and PY) using the same predetermined inclusion and exclusion criteria. The quality control (QC) for the selection of full articles was carried out by four researchers (PY, TJ, TB, MS).

All data were extracted using an Excel spreadsheet where researchers also recorded reasons for exclusion. The initial Excel spreadsheet included fields listed in the table in Online Resource 3 (see ESM). The Excel spreadsheet was tested using the first abstracts included in the literature search. The detailed documentation of the search and review contributed to build the PRISMA flow diagram (Fig. 1). Duplicated abstracts or full papers were also excluded in the final selection.

2.5 Statistical Methods

This is a descriptive study and not an analytic study, so there is no hypothesis testing.

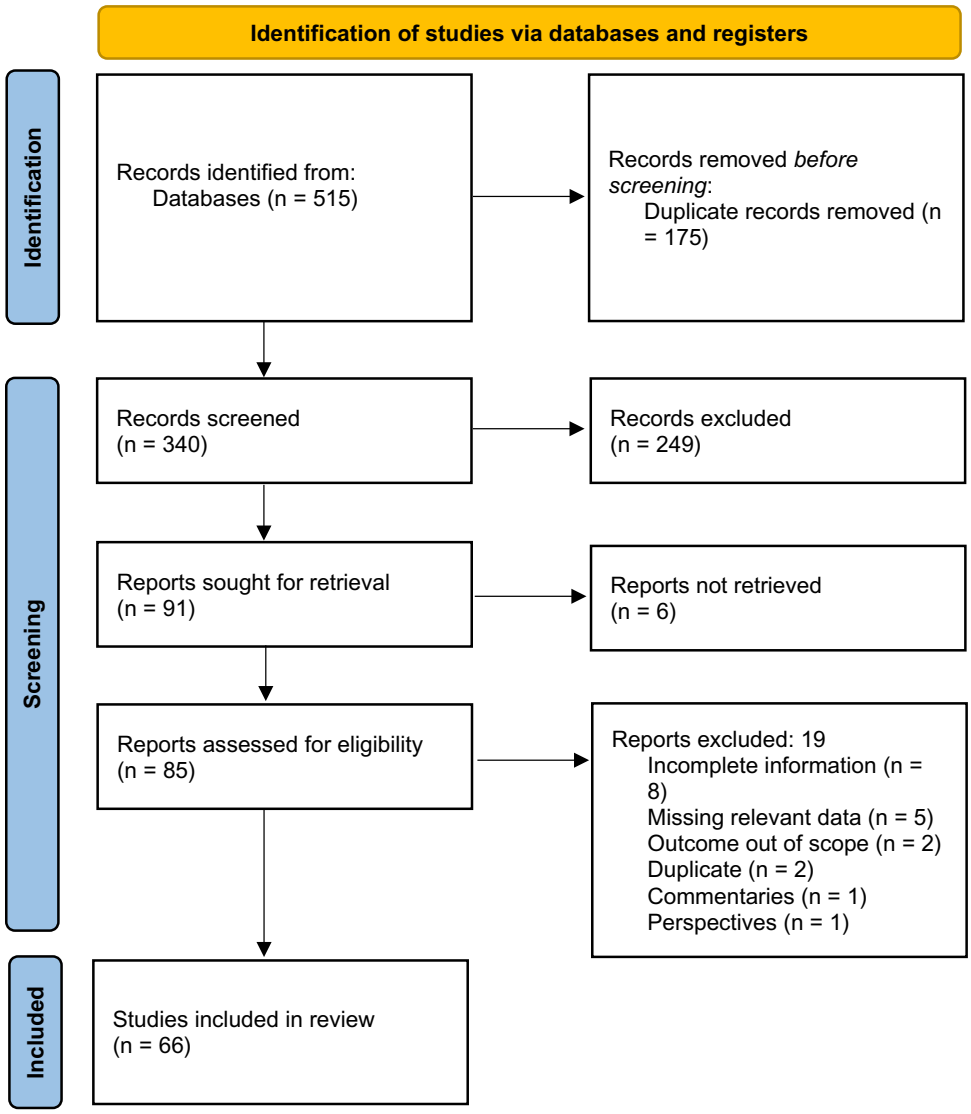

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing documentation of the literature search process [81]

3 Results

3.1 Article Selection

The literature search resulted in 340 articles which were evaluated for relevancy based on their titles and abstracts. Following the title and abstract review, 91 articles were sought for retrieval. After the subsequent review of full texts, 66 articles were ultimately included in the final review [9–74]. The reasons for exclusion of some of the articles were due to incomplete information ($n = 8$), the article was missing relevant data ($n = 5$), outcome out of scope ($n = 2$), duplicate articles ($n = 2$), commentaries ($n = 1$), and perspectives ($n = 1$). The details are documented in the PRISMA flow diagram (Fig. 1).

3.2 Sample Characteristics

Most articles had study locations from the United States of America ($n = 19$), followed by multiple locations ($n = 6$), France ($n = 4$), United Kingdom ($n = 3$), Sweden ($n = 2$), China ($n = 2$), Europe ($n = 1$), Canada ($n = 1$), Austria ($n = 1$), Morocco ($n = 1$), Japan ($n = 1$), and Taiwan ($n = 1$). Some of the databases included MEDLINE ($n = 8$), the United States Food and Drug Administration Adverse Event Reporting System (FAERS) ($n = 6$), Side Effect Resource (SIDER) ($n = 6$), social media platforms ($n = 6$), DrugBank ($n = 4$), drug safety databases of individual companies ($n = 2$), VigiBase ($n = 2$), OrientDB ($n = 1$), EudraVigilance ($n = 1$), Japanese Adverse Drug Event Report (JADER) ($n = 1$), Canada Drug Adverse Reaction Online Database (MedEffect) ($n = 1$), EU-ADR ($n = 1$), and French Spontaneous Reporting Database ($n = 1$). Most studies evaluated all diseases; however, some were specific to certain conditions such as cancer ($n = 4$), diabetes mellitus ($n = 1$), cardiovascular conditions ($n = 1$), and dihydropyrimidine dehydrogenase (DPD) deficiency ($n = 1$). The most identified uses of artificial intelligence in pharmacovigilance and patient safety included the identification of adverse drug events (ADEs) and adverse drug reactions (ADRs) (57.6%), processing safety reports (21.2%), extraction of drug–drug interactions (7.6%), identification of populations at high risk for drug toxicity or guidance for personalized care (7.6%), prediction of side effects (3.0%), simulation of clinical trials (1.5%), and integration of prediction uncertainties into diagnostic classifiers to increase patient safety (1.5%). These percentages refer to the percentage of studies using exclusive categories that were selected based on the main aspect of each article.

3.3 Use of Artificial Intelligence in Pharmacovigilance

The definition of machine learning used by the authors varied among the articles, but mostly included the use of algorithms or pattern recognition to perform a specified task [9]. Many of the articles also acknowledged that machine learning can be used to develop intelligent automated systems which can be used to optimize processes [62].

The uses of artificial intelligence in patient safety and pharmacovigilance are classified as shown in the table in Online Resource 4 (see ESM). A summary of the articles with additional information is provided in the table in Online Resource 5 (see ESM). The most common applications of artificial intelligence in this area were related to the identification or characterization of ADEs and ADRs, classification of free text within safety reports, extraction of drug–drug interactions, and the identification of populations at high risk of experiencing drug toxicity.

3.4 Using Artificial Intelligence to Detect Adverse Drug Reactions (ADRs) and Adverse Drug Events (ADEs)

Machine learning can be used to detect ADRs or ADEs, perform safety surveillance, and manage signal detection. One application of machine learning being used is the automation of classifying first-person reports of ADRs in social media. Alvaro et al. used Twitter to gather evidence about ADRs after identifying micro-blog messages ('tweets') that reported individual patient experiences [10]. They manually annotated 1548 tweets containing keywords related to selective serotonin reuptake inhibitors (SSRI) and cognitive enhancers [10]. They used a range of supervised machine learning models to successfully recognize first-hand experiences in the tweets, thus showing the value in applying machine learning concepts to post-marketing pharmacovigilance efforts in social media [10]. The application of machine learning in social media was described in several other articles and most found that the advantages include the ability to detect ADRs that may not be captured by medical professionals, the opportunity to process and analyze large volumes of data quickly, and the abundance of personal information present in social media posts as they relate to ADRs [10, 17, 22, 31, 35, 43, 44, 63]. The disadvantages include excess 'noise' within the data and the informal or irregular text that is often used in social media posts [10, 17, 22, 31, 35, 43, 44, 63]. Additionally, Gavrielov-Yusim et al. evaluated text processing in social media posts and

found that there is a tradeoff between the amount of manual screening needed in lower levels of social media processing with its potential to miss adverse events when compared with higher levels of social media processing that use natural language processing (NLP) [43].

Basile et al. identified polypharmacy and patient diversity as some of the opportunities to use machine learning in detecting ADRs [11]. These opportunities can be present in multiple phases of drug development ranging from pre-marketing to post-marketing safety assessments [13]. The automation present in machine learning techniques is becoming increasingly more useful as patients continue to present with multiple disease states, medications, and ADRs. Some institutions, such as Connecticut Children's Medical Center, have utilized machine learning to successfully streamline the use of adverse event reports by comparing rule-based queries and semi-supervised machine learning against a reference standard [15]. Aside from being used to detect ADRs, machine learning can also be used specifically to classify ADRs. Chauvet et al. determined the seriousness of patient cases through different algorithms based on their precision, recall, and accuracy [19].

Artificial intelligence can also play an important role in specific disease states, such as diabetes. HypoDetect, a NLP system which allows users to see blood glucose measurements displayed in a graphical format and analyze the measurements for hypoglycemic events using an algorithm, has been useful in detecting hypoglycemia incidents from secure data inputs early so that treatment can be promptly initiated [20]. In disease states like diabetes where early identification of symptoms is critical to patient safety, systems such as HypoDetect can improve safety efforts and patient outcomes [20]. On a similar note, the under-reporting of safety events can compromise patient safety and has been an issue in recent years [58]. Ménard et al. used a curated data set from 104 completed Roche/Genentech sponsored clinical studies which included patient demographics, vitals, and disease areas to train a machine learning model to predict the number of adverse events [58]. The model has the potential to be useful for initiating quality assurance measures early on and promptly filing potential adverse events [58]. This can be crucial to the safety of patients as every ADR needs to be properly assessed within a set time frame.

A common theme in many of the articles was the ability for machine learning to analyze a large amount of data to gather information about the side effects of therapies, which can subsequently be used to improve pharmacovigilance systems [23]. One innovative approach to this involves using propensity scores to present a new automated signal detection strategy for pharmacovigilance systems [26]. Understandably, one of the issues that arise from such techniques is providing a reasonable number of signals for further analysis by experts with the fewest possible false associations [26]. Another novel approach is using deep-learning neural networks or prediction models to model the ADR relationship between a medication and symptoms [27, 29]. Specifically, E-Synthesis is a Bayesian framework for safety assessments that compiles data to provide the Bayesian probability of a drug causing an ADR [30]. This association can be critical to pharmacovigilance efforts and analyzing the safety profile of medications.

3.5 Using Artificial Intelligence to Process Safety Reports

Another application of machine learning in pharmacovigilance is in assessing the skill of NLP to classify unstructured free text within patient safety incident reports. Evans et al. tested the ability of autonomously classifying free text within patient safety incident reports to determine severity of harm outcomes and found that NLP can act as a safety net by identifying cases that lead to severe harm or death [36]. However, it is not a perfect method and cannot yet replace manual review altogether [36]. Additionally, the technical nature of medical text makes this process difficult to complete [36].

Many studies evaluated the use of machine learning in screening patient safety reports, such as within electronic health records. Marella et al. found that machine learning algorithms and text mining are useful methods for screening and analyzing large, semi-structured, or unstructured data sets of adverse event and near-miss reports collected through passive surveillance reporting systems [57]. Yang et al. took a more specific approach by developing a deep learning model that was evaluated on different data sets to identify allergic reactions in the free-text narrative of hospital safety reports and evaluated their generalizability [72]. The study found that the model could be used to improve allergy care, potentially enabling real-time event surveillance for medical errors and system improvement [72]. Ultimately, machine learning has the potential to be used in many ways for addressing pharmacovigilance needs in various settings such as identifying keywords in patient safety reports that may require attention to prevent harm at clinical sites and post-marketing surveillance of ADRs in the pharmaceutical industry.

3.6 Using Artificial Intelligence to Extract Drug–Drug Interactions

Artificial intelligence can be used to extract drug–drug interactions or predict the effect of a drug–drug interaction. Ben Abacha et al. incorporated machine learning techniques with both feature-based and kernel-based methods for successful drug–drug interaction extraction [14]. Bouzillé et al. used a method to automatically detect drug–drug interactions to

improve drug safety monitoring in a hospital setting [16]. They created an efficient machine learning model using laboratory tests and treatment data that could detect patients that may have had an ADE that was linked to a drug–drug interaction [16]. Machine learning can be particularly useful in pharmacovigilance because these models can learn from a small number of drug–drug interaction combinations to predict many potential drug–drug interactions [33].

3.7 Using Artificial Intelligence to Identify Patients at High Risk for ADRs

Machine learning can be used to identify populations at high risk for experiencing ADRs or to guide personalized care. Chandak and Tatonetti developed a machine learning algorithm called "AwareDX: Analysing Women At Risk for Experiencing Drug toXicity," that predicts sex-specific risks of adverse drug effects with high precision by using a machine learning adaptation of propensity score matching [18]. Machine learning techniques can also be used to identify more targeted patients, such as those susceptible to fluoropyrimidine toxicity due to DPD deficiency [25]. Investigators used machine learning models to train patterns of toxicity, which were later used to estimate the number of patients with toxicity related to DPD and found that the model has potential for future use but could have some overfitting [25]. While there is still some progress left to be made in the application of machine learning in identifying patients at high risk of ADRs, these techniques are an excellent starting point.

3.8 Using Artificial Intelligence to Predict Drug Side Effects

Like its use in identifying patients at high risk for experiencing ADRs, machine learning has also been used to predict side effects from drugs. Mower et al. focused on post-marketing drug surveillance and demonstrated that knowledge extracted from literature can add to the performance of spontaneous reporting system methods using downstream machine learning [60]. This can be particularly useful in predicting drug side effects because spontaneous reporting systems often have bias and under-reporting which can limit the availability of data [60]. Wang et al. predicted potential side effects and ADRs using a tumor-biomarker knowledge graph and determined that this method is useful for potential ADR identification based on biomarkers [71]. The model can be valuable for future applications that may require mechanism-based research of ADRs [71].

3.9 Using Artificial Intelligence to Simulate Clinical Trials

Chen et al. used machine learning in conjunction with real-world data to simulate colorectal cancer clinical trials and evaluate serious adverse events [21]. The risk ratios of serious adverse events measured from simulations comparing two treatment arms were very close to the risk ratios calculated from the trials, thus showing the potential utility of machine learning and real-world data in simulating clinical trials [21].

3.10 Using Artificial Intelligence to Integrate Prediction Uncertainties

Artificial intelligence can also be used to integrate prediction uncertainties in patient safety. Laves et al. quantified the uncertainty of deep learning-based computer-aided diagnosis for patient safety [50]. The basis for the work relies on the concept that models that are trained for the diagnosis of cases often do not have the capability to indicate when a case is too ambiguous for an output [50]. The study found that modeling prediction uncertainty with deep learning can produce more dependable results that can assist with safety efforts [50].

4 Discussion

4.1 Overall Use of Artificial Intelligence

The main uses of artificial intelligence in pharmacovigilance are in the identification of ADEs and ADRs, the performance of surveillance and signal detection, classification of free text within safety reports, extraction of drug–drug interactions, identification of populations at high risk of experiencing drug toxicity, prediction of drug side effects, and simulation of clinical trials. These can be applied in many different aspects of pharmacovigilance, ranging from Individual Case Safety Reports (ICSRs) to adverse event profiles. The use of machine learning can optimize pharmacovigilance processes by automating case processing of ICSRs and provide a more efficient way to analyze safety information. As a result of this optimization, there is time freed up for humans to focus on the interpretation and action required to respond to safety events. However, it is important to note that there is variability in tool performance and there are challenges associated with implementing artificial intelligence in pharmacovigilance practices. Some challenges

are the need for people to have a baseline comprehension of how the artificial intelligence technology they are using works and privacy concerns with using artificial intelligence to store healthcare data [75, 76]. There are also legal challenges in both Europe and the United States of America related to the liability for errors that may occur as a result of artificial intelligence technology [77, 78]. More experiences and applications of artificial intelligence in patient safety and pharmacovigilance are needed before these methods can be validated and promoted for widespread use. The current industry perspective is that there is interest in using technologies such as machine learning, NLP, and Natural Language Generation across ICSR process steps; however, the challenges include using quality training data for machine learning models and regulatory guidance [79].

4.2 Using Artificial Intelligence to Detect ADRs

One of the most common uses of artificial intelligence in the literature was in the detection of ADRs, surveillance, and signal detection. Most specifically, the classification of ADRs in social media was evaluated in many of these studies. Since more and more patients use social media platforms to express their response to medication regimens, this creates an excellent platform for machine learning to be applied. However, many challenges arise from the unstructured free text that occurs on platforms such as Twitter and Facebook, since people tend to use casual or slang terms. This creates the need for 'smarter' machine learning models that are able to reduce the 'noise' reported in these posts. The advantages of machine learning in detecting ADRs include its potential ability to process and analyze large amounts of data quickly and its application to various disease states. The success of machine learning in analyzing ADE reports has already been shown in certain institutions, such as Connecticut Children's Medical Center [15]. Machine learning can potentially be useful in certain subsets of the population which can result in better patient outcomes and relief of the healthcare system. The association between a drug and its ADR was analyzed in many studies which demonstrated the potential effectiveness and potential capabilities with the use of machine learning in pharmacovigilance.

4.3 Using Artificial Intelligence to Process Safety Reports

NLP has been used to classify unstructured free text within ICSRs, patient safety event reports, and clinical narratives. This can be critical to pharmacovigilance efforts because sometimes cases that lead to harm or negative patient outcomes can be missed by medical professionals. Machine learning offers an opportunity to systematically capture potential safety events before they occur or within an appropriate time frame for managing a safety event. Some methods can even be completed in real-time which offers additional improvement over manual methods. Understandably, these systems have not been perfected yet and may never be 100% accurate. However, when it comes to pharmacovigilance efforts, even slight improvements have the potential to enhance safety efforts. These methods can be applied in the institutional setting with electronic health record evaluation and the pharmaceutical industry setting with post-marketing surveillance of drug safety events. However, more research is needed to validate these methods.

4.4 Using Artificial Intelligence to Extract Drug–Drug Interactions

Machine learning has been used to identify drug–drug interactions and their potential effects. The extraction of drug–drug interactions in some studies has been shown to be efficient and have manageable computation time [16]. These efforts are particularly useful because predictions can be used to enhance post-marketing surveillance systems and detect drug–drug interaction effects sooner during the drug development process [33]. Deep learning methods can even predict novel drug–drug interactions, which may not be as feasible without machine learning [65]. Identifying potential drug–drug interactions is very important for patient safety and pharmacovigilance efforts, since certain medications can be avoided or more closely managed in patients who are at risk of experiencing a drug–drug interaction.

4.5 Using Artificial Intelligence to Identify Patients at High Risk for ADRs

Personalized care is becoming more prominent in medicine and machine learning has a place in identifying patients who may be at higher risk of experiencing certain ADRs. By using machine learning models to predict those who may be at risk of experiencing an ADR, patient safety can potentially be improved. For example, one study trained a model to identify patients who may be more susceptible to fluoropyrimidine toxicity due to DPD deficiency [25]. This study showed how machine learning models can assist in imputing the likely genotype of a patient from phenotypical manifestations to understand the influence of DPD deficiency [25]. When applied to large pharmacovigilance databases, machine learning can assist to respond to such questions which may not be possible with traditional methods [25].

4.6 Using Artificial Intelligence to Predict Drug Side Effects

Artificial intelligence can be used to predict potential side effects from drugs. While many side effects can be predicted from the mechanism of action and pharmacology of a drug, there are some side effects that have yet to be established. Machine learning can complement data that has already been made available from previous reports. Wang et al. were able to use machine learning techniques to show how a mechanistic approach to identifying ADRs was able to discover potential ADRs of antitumor drugs [71]. This shows how machine learning can be used in addition to traditional methods to potentially enhance patient safety.

4.7 Using Artificial Intelligence to Simulate Clinical Trials

Artificial intelligence can be used to simulate clinical trials and compare adverse effect profiles. Models have been used to compare risk ratios between trials and simulations, which shows how machine learning can be used in conjunction with real-world data [21]. Furthermore, when machine learning is used to build external control arms, there is an opportunity to simulate different scenarios (e.g., sensitivity analysis modifying some inputs in the model) and estimate the impact on the frequency of adverse events. Deep learning methods and causal artificial intelligence methods can also assist with data bias issues that come with using real-world data for clinical trial simulation [21].

4.8 Using Artificial Intelligence to Integrate Prediction Uncertainties

It is important for machine learning to be able to integrate prediction uncertainties. Pharmacovigilance requires the appropriate detection and prevention of adverse effects, which means that inaccurate associations between a drug and adverse event can deter patient safety efforts. Therefore, it is imperative that machine learning methods can indicate when there may be uncertainty in classification. When machine learning methods can integrate prediction uncertainties, the result is a more comprehensive and accurate contribution to pharmacovigilance.

4.9 Overall Findings of the Systematic Review

Using artificial intelligence in pharmacovigilance and patient safety can potentially have an impact on improving patient care and optimizing safety analyses as evidenced by the success of some machine learning models in improving patient safety. The use of machine learning and NLP techniques together can provide accurate outputs that may augment pharmacovigilance professionals' processing of spontaneous ICSRs quickly and accurately [9]. Big data technology could also improve drug safety monitoring in clinical settings and could help pharmacovigilance professionals make targeted hypotheses on ADEs due to drug–drug interactions [16]. Many of the studies showed that machine learning can have some role in pharmacovigilance efforts, with the degree of its impact depending on the type of database or source it is used on. For example, ADR detection performance in social media is significantly improved by using a contextually aware model and word embeddings formed from large, unlabeled datasets, which can be scalable to large social media datasets [22]. Machine learning models applied to large pharmacovigilance databases can help answer certain research questions, which may be difficult to address with more traditional methods [25]. Artificial intelligence can be used in all stages of drug development because of its wide applicability. With these machine learning methods, there is a potential for better accuracy, automation, and comprehensiveness in the evaluation of patient safety events. This can be useful in enhancing efforts that are already completed by members of safety teams and hospital staff but may also be limited by the costs and time associated with training the systems. As machine learning is evaluated more in various databases and healthcare settings, especially the inpatient setting, its application and scalability may prove to be paramount in pharmacovigilance efforts. The field is likely expanding to more healthcare settings as new artificial technology is used by pharmacovigilance scientists in pharmaceutical companies and healthcare workers in hospitals. An updated literature search was performed for the time period of July 9, 2021 to June 9, 2022 and showed uses of artificial intelligence that were related to the uses identified in this review. Examples of more recent applications included classifying patient safety reports using predictive algorithms and using text mining to analyze patient safety narratives.

4.10 Limitations

The limitations of this systematic review are that many reviews did not include a clear definition of what they considered to be machine learning, some databases are more comprehensive than others so proper comparison of results may be limited, and studies demonstrating a successful application of machine learning are more likely to be published than studies with unsuccessful attempts. The search strategy as shown in the tables in Online Resources 1–2 (see ESM) was also limited to articles published in English that mentioned the relevant terms in its title or abstract, so some articles with information related to this topic may not have been included. Many of the results involved experimentation and were not used in real scenarios, so these findings are not

yet automatically operationally applicable. It is also difficult to pool these results into generalizable findings given that there were different types of data included in each source.

4.11 Opportunities for Future Research

Since artificial intelligence is being increasingly used across various areas, not just limited to healthcare, there are many opportunities for future research of its use in pharmacovigilance. Future studies may use databases that have more complicated input text or more 'noise' to test if the artificial intelligence technology can respond accurately and efficiently. Regarding social media platforms, most of the articles used Twitter as their database. Other social media platforms such as health care social networks could be useful to evaluate with the increased interest in the use of social media in pharmacovigilance in recent years [80]. Lastly, further studies evaluating how much cost savings in healthcare can result from automated machine learning methods might be useful.

5 Conclusions

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 and predict the effects of drug–drug interactions, to identify populations at high risk for experiencing ADRs and guide personalized care, to predict drug side effects, to simulate clinical trials, and to integrate prediction uncertainties into diagnostic classifiers to increase patient safety. There is potential for artificial intelligence to be used in pharmacovigilance and patient safety in more ways than were identified in this review in the coming years as people gain more exposure to artificial intelligence methods. The growth of this field may be limited by challenges related to the lack of validated, established uses of artificial intelligence in real-life safety settings.

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Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions MS: study design, study implementation (title/abstract screening, quality control), preparation of draft manuscript, review of manuscript draft, and interpretation of results. JP: study design, study implementation (title/abstract screening), review of manuscript draft, and interpretation of results. PY: study design, study implementation (full article screening, quality control), preparation of draft manuscript, review of manuscript draft, and interpretation of results. OA: study design, study implementation (title/abstract screening, full article screening), review of manuscript draft, and interpretation of results. DK: study design, study implementation (full article screening), review of manuscript draft, and interpretation of results. SD: review of manuscript draft and interpretation of results. TJ: study implementation (quality control), review of manuscript draft, and interpretation of results. TB: study design, study implementation (title/abstract screening, quality control), review of manuscript draft, interpretation of results, quality control of summary table. All authors have read and approved the final version of the manuscript and agree to be accountable for the work presented.

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