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ARTIFICIAL INTELLIGENCE–BASED PREDICTION OF DRUG–DRUG INTERACTIONS IN POLYPHARMACY PATIENTS: CURRENT ADVANCES AND FUTURE PERSPECTIVES

Mrs. S. Mahalakshmi*[1], Dr. G. Tulja Rani[2], Ganapuram Meghana[3], Manuva Keerthana[4]

[1]Department of Pharmacology, Malla Reddy Pharmacy College, Maisammaguda, Dhulapally, Secundrabad, Telangana, India.

[2]Department of Analysis, Malla Reddy Pharmacy College, Maisammaguda, Dhulapally, Secundrabad, Telangana, India.

[3,4]Department of Pharmacy, Malla Reddy Pharmacy College, Maisammaguda, Dhulapally, Secundrabad, Telangana, India.

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***Corresponding Author**

Mrs. S. Mahalakshmi

Department of Pharmacology, Malla Reddy Pharmacy College, Maisammaguda, Dhulapally, Secundrabad, Telangana, India.

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ABSTRACT

Polypharmacy, typically defined as the concurrent use of five or more medications, is increasingly prevalent among elderly and multi-morbid populations, substantially elevating the risk of drug–drug interactions (DDIs), adverse drug reactions, hospitalization, and therapeutic failure. Traditional DDI detection strategies, largely dependent on retrospective analyses and rule-based alert systems, are inadequate to address the combinatorial complexity and patient-specific variability inherent to modern pharmacotherapy. Artificial intelligence (AI) has emerged as a powerful paradigm for DDI prediction, leveraging large-scale, heterogeneous datasets including electronic health records, pharmacogenomic profiles, and drug interaction databases. This review critically examines current AI-driven methodologies—encompassing machine learning, deep learning, graph neural networks, and natural language processing—for the identification of both established and previously unrecognized DDIs in polypharmacy settings. These approaches enable high-dimensional data integration, facilitate real-time risk stratification, and support personalized therapeutic decision-making. In

addition, the role of real-world evidence, explainable AI (XAI), and hybrid modeling frameworks in improving model interpretability, clinical trust, and translational applicability is discussed. Despite significant advances, key challenges persist, including data heterogeneity, algorithmic bias, limited modeling of multi-drug interactions, and regulatory and ethical constraints. Overall, AI-driven DDI prediction represents a transformative advancement in medication safety for polypharmacy patients. Future efforts should prioritize the development of robust, interpretable, and clinically validated AI systems integrated within decision support platforms to enable safe, scalable, and patient-centric healthcare delivery.

KEYWORDS: Artificial Intelligence; Drug–Drug Interactions; Polypharmacy; Machine Learning; Deep Learning; Graph Neural Networks; Pharmacovigilance; Real-World Evidence.

1. INTRODUCTION

1.1. Polypharmacy prevalence

Chronic diseases, but also has serious implications to DDIs. It is extremely common in the elderly because of several chronic diseases, greater life expectancy and cumbersome treatment Polypharmacy is especially prevalent among the elderly who are especially those who have multiple regimens.[1,2] Research has shown that about 80 percent of elderly patients in tertiary care facilities are on five or more medications, which underscores the important polypharmacy burden in this patient group.[3-5]

1.2.Drug-Drug interactions as major cause of

❖ **Adverse Drug Reaction**: Drug-Drug interactions are the changes in the pharmacodynamics (drug effect) or pharmacokinetics (absorption, metabolism, distribution, excretion) of a drug by another drug, which may have harmful effects. A moderate percentage of ADRs were identified as potentially or likely to be caused by DDIs, in polypharmacy cohorts.[6-7]

❖ **Hospitalization:** Studies with evidence indicate that a significant proportion of ED visits and hospitalizations can be attributed to the interaction of prescribed drugs. Older polypharmacy patients have consistently exhibited increased DDI levels and increased lengths of stay associated with complications related to interactions.[8-10] In addition to

admissions, DDIs can lengthen hospital stay, and raise the acuity of care needed, including ICU admission in case of interactions with serious organ dysfunction.[11,12]

❖ **Treatment Failure**: DDIs may facilitate the antidrug effect of the treatment regimen by lowering the concentration of the drug at the site of action (e.g. by inducing enzymes) or by antagonistic pharmacodynamic effects. These types of clinically important interactions frequently require dose adjustments, substitution with other therapies, or adjunctive treatments to regain efficacy, which implies safety and therapeutic issues.[13]

1.3. Limitations of Traditional DDIs detecting systems

Conventionally, DDIs have been identified through retrospective approaches, such as clinical observations, post-marketing surveillance and spontaneous reporting of adverse events as shown in Table 1.[14]

Table 1: Limitations of traditional DDI detecting system and its impact on polypharmacy management.

Limitation	Impact on Polypharmacy Management
Retrospective data & fragmented reporting	Missed rare or population-specific DDIs
Combinatorial complexity	Cannot handle multi-drug interactions efficiently
Lack of patient-specific factors	Reduced accuracy in individualized risk assessment
Limited coverage for herb-drug interactions	Some ADRs remain undetected
Static alerts & lack of real-time feedback	Alert fatigue or missed dynamic interactions
Poor mechanistic explainability	Decreases clinician trust and understanding
Novel/emerging drug integration gaps	Fails to capture latest risk profiles

Existing traditional DDI Detection systems are not adequately prepared to deal with the multidimensional complexities of polypharmacy. Their retroactive makeup, restricted scalability, absence of customized integration, and inadequate coverage of herbal and newly-developed drugs, all lead to under-detection of clinically significant interactions. To enhance performance, AI-based methods by using machine learning and informed notifications with a higher predictive accuracy and interpretability.[15]

2. Drug – drug interactions in polypharmacy patients

Drug-drug interactions (DDIs) in polypharmacy patients are the modifications in the effects of one drug by the presence of another drug, which may result in decreased therapeutic efficacy, toxicity or adverse drug reactions.

Polypharmacy is usually described as the simultaneous administration of five or more drugs, which is especially common in older patients and with chronic diseases.[16]

2.1. DRUG-DRUG INTERACTIONS: CLASSIFICATION

1. Pharmacodynamic interactions: Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action resulting in additive or opposing effects. The drugs sometimes compete directly with specific receptors but in many instances the effect is more indirect, and entails interference with physiological processes.[17]

2. Pharmacokinetic Interactions: Pharmacokinetic interactions are those which may influence the drug absorption or distribution, metabolism or excretion processes; these are called ADME interactions.

a. Absorption: The absorption of most drugs taken orally takes place in the small intestine. Other drugs via, e.g. alteration in intestinal motility or gastric PH can change the rate and/or the amount that is absorbed. The vast majority of these interactions give rise to reduced absorption as opposed to increased absorption.[18,19]

b. Distribution: There are various processes which can influence the distribution of drugs in the body. It dictates the way of the distribution of drugs in tissues and this largely depends on blood flow, lipid solubility and plasma protein binding and eventually affects the onset and duration of action of the drug.[20]

c. Metabolism: Though some drugs are cleared by the body due to excretion of the drug through the urine unchanged, most drugs are chemically modified in the body to less lipid-soluble forms, which are more easily excreted by the kidneys. The greatest proportion of metabolism is carried out by the liver.[21]

d. Excretion: The excretion of drugs is primarily through the kidney. Any disruption of renal tubular fluid pH caused by the drugs or the blood flow to the kidney may cause changes in the excretion of other drugs. The same interactions may also take place when two drugs are in competition with each other in terms of the active transport system, which may slow down the excretion of a certain drug.[22]

2.2 Clinical Burden

Polypharmacy, which is usually defined as the use of five or more drugs at a time, is a significant clinical problem, especially in older and multi-morbid patients. There is much evidence that an increase in medication load can greatly enhance the likelihood of drug-drug

interactions (DDIs), adverse drug reactions (ADRs), medication non-adherence, and therapeutic duplication, which can, in turn, result in poorer clinical outcomes.[23]

a) Elderly clinical burden: The clinical burden of polypharmacy on elderly patients exposed to polypharmacy is disproportionately large because of drug-drug interactions (DDIs), which has been consistently shown in various observational reviews. Interaction-related toxicity and therapeutic failure are further aggravated by potentially inappropriate medications when used in combination with polypharmacy.[24]

b) ICU clinical burden: Polypharmacy is very common among intensive care unit (ICU) patients and has high clinical burden due to the concomitant use of several high-risk drugs including antimicrobials, sedatives, vasopressors, anticoagulants, and cardiovascular drugs.[25]

c) Oncology clinical burden: There is a high prevalence of polypharmacy among oncology patients because of the comorbid conditions and the use of anticancer agents, supportive care drugs, over-the-counter drugs, and comorbid conditions, which cause a large clinical burden in drug-drug interactions (DDIs).[26]

d) Psychiatric polypharmacy: The polypharmacy of the psychiatric medication is extremely common in patients with severe mental disorders and it is always linked with a high clinical burden because of the drug-drug interactions(DDIs) as it is shown by numerous observational studies and systemic reviews.[27]

3. Rationale for AI in Drug–Drug Interaction Prediction

3.1. Increasing complexity of polypharmacy and combinatorial explosion

The growing complexity of polypharmacy, referred to as simultaneous administration of five or more drugs, has brought a so-called combinatorial explosion of possible drug-drug interactions (DDIs) and a significant, frequently so-called wicked public health problem. This increase is mainly caused by an ageing population, increasing multimorbidity and the rigorous implementation of disease-specific guidelines which exert exponentially, not linearly, high risks of adverse drug reactions (ADRs) and hospitalizations.[28,29]

3.2. Exponential Risk Interaction

As the number of drugs, a patient is taking increases, the risk of drug-drug interaction also increases, with a patient taking seven drugs having a 100% chance of having a significant drug-drug interaction.

Hyper-Polypharmacy: The taking of 10 or more drugs (hyper-polypharmacy) increases the likelihood of death more than 2-fold that of non-user.

Drivers of Increasing Complexity

- **Multimorbidity & Aging:** Aged patients usually experience a number of chronic diseases that need to be treated by various specialists, resulting in fragmented care.
- **Deprescribing:** It is important to proactively decrease inappropriate, unnecessary, or harmful medications, particularly when patients transfer between care settings.
- **Medication Reviews:** Have patients undergo medication reviews, such as the STOPP/START criteria (Screening Tool of Older Person Prescriptions) or 7-step medication reviews to streamline regimens.[30,31]

3.3. Exponential growth of drug combinations

The exponential increase in drug combinations is a mathematical fact due to the fact that the number of possible combinations (or multi-drug cocktails) of drugs increases exponentially, rather than linearly, as the number of drugs available increases. Exponential increase in drug combinations under AI-driven polypharmacy is due to the combinatorial explosion of possible combinations of drugs with the number of drugs prescribed, which is currently being addressed by sophisticated machine learning models.[32]

3.4. Link to impracticality of experimental validation

The inherent infeasibility of experimental validation of Drug-Drug Interaction (DDI) prediction in Artificial Intelligence (AI) is due to the enormous amount of potential drug combinations, making extensive, real-world laboratory testing (in vitro/in vivo) prohibitively costly and time-consuming.[33]

3.5. Artificial Intelligence as a Remedy to the Bottlenecks in validation

Rather than trying all combinations, AI is also becoming increasingly applied in prioritizing the interactions that should be experimentally tested in order to optimize resources.[34]

3.6. Key Reasons for Impracticality of Experimental Validation

a) Combinatorial Explosion: There are thousands of FDA approved drugs that means that the number of possible pairs, triplets, or other interactions are astronomical, making it impossible to physically test all of them.

b) Expensive and Time Consuming: Conventional in vitro (laboratory) and in vivo (animal/human) experiments needed to validate interactions are labor-intensive, slow and costly.[35-37]

3.6. Hidden and latent drug-drug interactions

Unintended, undocumented pharmacological interactions between two or more drugs at a time are known as hidden and latent drug-drug interactions (DDIs), and may lead to either reduced efficacy or toxicity.

❖ **Unnoticed or infrequent drug-drug interactions:** Unidentified or infrequent drug-drug interactions (DDIs) are a significant, often underrecognized, risk to patient safety, which is often not identified in clinical trials because of insufficient sample size, but only revealed when used in a real-world setting.[38]

❖ **Why DDIs Go Undetected**

1. **Small Sample Sizes in Trials:** Pre-marketing clinical trials are frequently not diverse and do not have the number of responses necessary to identify rare, idiosyncratic reactions.
2. **Non-Specific Symptoms:** Non-specific effects on the central nervous system (CNS) or mild and chronic problems are frequently ignored.[39]

❖ **Rare Interaction Patterns:** It is possible to predict them. The knowledge graphs and graph neural networks (GNNs) based on the complexity of the relationship between drugs, proteins, and biological pathways can be used to predict low-frequency clinical report interactions (rare).[40]

❖ **Post marketing discovery**: AI can be used to quickly and efficiently detect complex and multi-drug interactions in polypharmacy patients, by examining large real-world data (EHRs, omics) to forecast adverse drug reactions that are not observed in clinical trials.[41]

❖ **Key Rationales for AI in Post-Marketing Polypharmacy**

➢ **Complexity and High Dimensionality**

Conventional trials cannot be used to test every combination of drugs. Multidimensional data (genomic, molecular, patient EHR data, etc.) can be analysed with AI algorithms, specifically, deep learning and graph neural networks.[42]

➢ **Real-World Data Mining (Post-Marketing)**

Artificial intelligence (AI) technology, including Natural Language Processing (NLP) and machine learning, is used to analyse Electronic Health Records (EHRs) and social media, as well as medical literature to identify Adverse Drug Reactions (ADRs), which only emerge after a drug has become widely used in the general population.[43]

3.7. Clinical unpredictability

The problem of clinical unpredictability due to polypharmacy, individual patient variability, and the disadvantages of the traditional, manual, and experimental approaches are addressed by the artificial intelligence (AI) in predicting drug-drug interaction (DDI).The reasoning is that AI has the potential to combine large and heterogenous amounts of data, including molecular, genomic, and real-world clinical data, to discover new and complex and hitherto unknown interactions that can enhance patient safety and provide personalized medicine.[44]

The main reasons why AI should be used to handle clinical unpredictability in DDIs are

1. Surpassing the conventional methodologies.
2. □ Working with Complex and Unstructured Data.
3. □ Treating Individualized and Dynamic Risk (Clinical Unpredictability)[45]

3.8. Patient specific variability in drug-drug interaction risk

The rationale for using Artificial Intelligence (AI) to address patient-specific variability in drug-drug interaction (DDI) risk lies is that it is able to go beyond the generic approach to drug labeling based on population to offer real-time, personalized risk assessment.[46]

➢ **Age, Genetics and Organ comorbidities**

Its ability to transcend the population-level drug information to personalized, dynamic risk prediction.

The following are some of the main aspects of patient-specific variability that AI aims to address

1. Genetics (Pharmacogenomics)

AI can process complicated genetic information, including single nucleotide polymorphisms (SNPs) and cytochrome P450 (CYP) gene variations. This enables AI to categorize patients as poor or ultra-rapid metabolizers, how the genetic composition of an individual will influence the rate of drug metabolism and the likelihood of interaction.

2. Organ Comorbidities (Renal/Hepatic Function)

AI models (especially those coupled with Pharmacokinetic (PK) modelling) may be used to model drug disposition in response to organ dysfunction.

3. Age-Related Variability

AI models can differentiate risk profiles between the younger (<60 years) and older (>60 years) populations taking into consideration that age-related changes in liver/kidney performance are more pronounced.[47-49]

Personalised response differences

Individualized prescriptive drug response predictive seeks to prescript with specific patient factors like genetic, clinical, lifestyle, and comorbidity factors in mind.AI has become a potent facilitator of this vision; it can analyse high-dimensional, complex datasets and provide predictive information. It also talks about the data sources, modeling strategies, disease-specific applications, ethical, regulation and practical issues required in the clinical implementation.[50]

3.9. Emergence of big data in healthcare-Growth of

1. Drug databases
2. Omics data
3. Clinical datasets

The main sectors of Big Data Development:

1. Clinical Datasets (EHRs and Imaging): The mainstreaming of Electronic Health Records (EHRs), high-resolution medical images, and lab findings are the foundation of healthcare data. There are now more than 100 million observations in these databases, e.g. Medicare databases, and this enables the data mining and analysis to be done in a large scale.

2. Omics Data: The multi-omics technologies, which are advancing rapidly, comprise of genomics, proteomics, transcriptomics, epigenomics and metabolomics, are generating huge volumes of data that can be used to gain a better insight into human diseases and personalized care of the patients.

3. Drug Databases/Pharmaceutical Data: The use of big data in drug development and surveillance is turning drug development and pharmaceutical surveillance faster by analysing clinical trials, enhancing recruitment, and post-market surveillance using real-world data to identify safety concerns.[51,52]

3.10. Role of real world-evidence in drug-drug interaction detection

1. Real-world evidence (RWE): Is an important tool in identifying drug-drug interactions (DDIs), as it is able to analyse patient data in electronic health records (EHRs), claims, and registries, offering insights not available in controlled clinical trials.

2. Electronic Health Records (EHRs): RWE and AI in combination, especially with the help of electronic health records (EHRs), allow to detect drug-drug interactions (DDIs) in polypharmacy patients proactively, in a personalized way, discover new interactions, prevent adverse drug events (ADEs), and offer real-time clinical decision support.

3. Pharmacovigilance Databases: Pharmacovigilance is the science of surveillance of drug safety, which is instrumental in detecting and preventing adverse drug reactions (ADRs).[53,54]

Key Advantages of RWE/AI over Clinical Trials

1. Wider, More Diverse Populations: RWE incorporates real-world patients with multiple comorbidities and polypharmacy as opposed to the exclusion criterion of randomized clinical trials (RCTs).[55]

2. Long-Term and Rare Events: AI examines data over time, revealing rare or longitudinal events that are not detected in RCT, which are often small and short.[56]

3. Real-time Surveillance: AI can provide more rapid, automated safety signalling (e.g. in pharmacies) instead of basing this on post-marketing studies that are slow.[57]

4. Ai Techniques Used for DDI prediction

4.1. Machine Learning Techniques

AI methods, especially machine learning (ML) transform drug-drug interaction (DDI) prediction through the analysis of chemical, biological, and clinical data to predict risks more rapidly than comparable methods. •Important methods are supervised learning (random forests, SVM) to predict interactions by classifying data and improving the understanding of concealed interaction patterns.

- **Supervised Learning:** The models are trained with labelled data (known interactions) to discriminate between interacting and non-interacting pairs of drugs.
- **Random Forests (RF) & Decision Trees:** Useful when there is a lot of data, and when it is necessary to determine which features are important.
- **Support Vector Machines (SVM):** Classification is done by determining the best hyperplane to divide the interaction classes.
- **Logistic Regression:** This is used in the interaction model of causation to sieve the real interaction and eliminate confounding.[58,59,60]

4.2. Deep Learning Techniques

Deep learning (DL) predictive drug-drug interaction (DDI) methods are used to improve drug discovery, by interpreting molecular structure, chemical characteristics, and network data to detect possible, yet frequently concealed, adverse interactions.

➢ **Graph Neural Networks (GNNs):** GNNs are popularly used to predict or analyse molecular structure (atoms/bonds) or interaction networks in which drugs are the nodes and interactions are the edges, akin to high-order structure.

➢ **Convolutional Neural Networks (CNNs):** CNNs are used to analyse chemical properties and other structured data, such as the analysis of molecular graphs.

➢ **Recurrent Neural Networks (RNNs):** Applied to work with sequential data, e.g., SMILES strings (Simplified Molecular Entry System) describing drug structures.

➢ **Multimodal/Multi-view Learning:** It involves the integration of several types of data (molecular structure, text, databases) to gain an in-depth insight into the drug properties.[61,62]

4.3. NLP Methods

NLP-based approaches to drug-drug interactions (DDIs) are aimed at retrieving and categorizing interactions in biomedical literature, electronic health records and drug labeling.

• NLP Methods for DDI Prediction

1. Named Entity Recognition (DNER): Recognizes and classifies drug names in text to create corpora and databases.

2. Relation Extraction: Determines relationships between drug entities, and classifies them as interacting.[63]

4.4. Hybrid Approaches

Hybrid methods of drug-drug interaction (DDI) prediction are a set of deep learning (e.g., Graph Neural Networks, CNNs, Transformers) combined with traditional machine learning (e.g., Random Forests, Gradient Boosting) to obtain more accurate results.

- **Graph-Based Learning:** Graph Attention Networks (GATs) or Graph Convolutional Networks (GCNs) learn structural features of molecular graphs or drug networks.
- **Deep Feature Extraction:** Convolutional Neural Networks and Bi-directional Gated Recurrent Units can be used to process chemical descriptors to detect structural patterns.[64]

4.5. Model Evaluation

Machine learning and deep learning are used to evaluate models to predict Drug-Drug Interactions (DDIs) and these are validated using 5-fold cross-validation using measures such as Accuracy (ACC), Area Under the Receiver Operating Characteristic curve (AUC), Area Under the Precision-Recall Curve (AUPR), precision, and recall. The most frequent methods are Random Forest, Logistic Regression, and Graph Neural Networks (GNNs), and mechanistic/PBPK models can be used to evaluate metabolic inhibition by changing drug concentrations to determine important interactions.[65]

5. Validation of AI Models

Validation ensures that the AI model is accurate, reliable, and generalizes well to new data.

- **Internal Validation:** Testing the model on the same dataset it was trained on.
- **Train-test split:** Dividing the data (e.g., 80% for training, 20% for testing).
- **Cross-validation:** Repeatedly splitting the data into different sets to ensure the model isn't just "memorizing" one specific group of data.
- **External Validation:** Testing the model on completely independent data, such as from a different hospital or a new dataset, to see if it works in different environments.

- **Clinical Validation:** The final step where the model's predictions are compared against real patient outcomes to see if it actually helps doctors make better decisions.[66]

6. DDI Prediction with explainable AI (XAI)

The AI models tend to be black boxes. XAI renders them transparent in order to provide humans with understanding as to why a prediction was made.

6.1. Importance

- **Clinician Trust:** The clinicians will be more inclined to adhere to the suggestion when they can comprehend the rationale.
- **Regulatory Acceptance:** AI-based medical decisions are frequently sought to be explained by the health authorities.[67]

6.2. Methods

- **SHAP & LIME:** Mathematical programs that indicate which characteristics (e.g., the age of a patient or a particular chemical bond) had the greatest impact on the prediction.
- **Attention Mechanisms:** This is a component of deep learning that indicates what aspects of the input data the model paid attention to.[68]

7. Present Problems and Future Research

- **Data Quality Problems:** AI can be as good as the data it is trained on. Lack of medical records or biased medical records may result in incorrect predictions.

- **Need for multi-drug(2Drugs) Interactions:** The majority of research currently is centered on two drug interactions.. The fact is that the number of drugs that patients (in particular, the elderly) use can be five or even more (polypharmacy), and the calculations are even more complicated.

- **Combination with Pharmacogenomics:** It is an examination of the DNA of an individual to understand how a person especially metabolizes drugs, which is an added personalization.

- **Future of Clinical decision support systems:** Shifting away, in favor of intelligent, context-aware systems, which offer actionable advice and do not cause alert fatigue.

➢ **Application of Real time AI in Hospitals:** To prevent adverse events before they occur, the application of AI that monitors patient vitals plus medication administration in real-time is implemented.[69-70]

8. CONCLUSION

Al can greatly enhance DDI prediction: AI can much better predict drug-drug interactions (DDI) by examining large volumes of data, such as molecular-structure data, electronic health records (EHRs), and biological pathways, to find out complex, latent patterns. Specifically, to polypharmacy patients: AI-based DDI prediction systems would be particularly useful with polypharmacy patients (those taking multiple drugs concurrently) who experience increased risk of interacting with each other. Future direction: Future developments will focus on developing AI systems that are personalized to the needs of individual patients, give a clear explanation behind their predictions and being fully integrated into clinical workflows and decision support systems.

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