iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 14 **Issue:** V **Month of publication:** May 2026

DOI: https://doi.org/10.22214/ijraset.2026.82887

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 14 Issue V May 2026- Available at www.ijraset.com

Machine Learning Approaches for Predicting NSAID-Induced Multi-System Adverse Drug Reactions in Orthopaedic Patients: A Review

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Abstract*— Adverse Drug Reactions (ADRs) associated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) remain a clinical concern in orthopaedic care due to their association with complications affecting multiple organ systems, including gastrointestinal, renal, cardiovascular, hepatic, and neurological functions. The major concern is that the traditional approaches fail to recognize the disorders and ADRs, which get worse for the patients; hence, with the modern approach of Machine Learning, Artificial Intelligence, Graph Neural Networks and Deep Learning, the predictions have become easier with all the possessed clinical data. This review explores how computational methods are used to predict adverse drug reactions, keeping in mind the techniques applied, datasets used, evaluation measures, and the predictive performance from various carried on studies. Although many studies have worked on predicting adverse drug reactions, there are still gaps. The big issue is that not much importance is given to orthopaedic patients who use NSAIDs for a prolonged duration. Also, most existing models are not good at predicting multiple system-related problems. To make predictions still better here, more attention should be given to each patient's treatment pattern and models that clinicians can interpret. At last, this framework and model discussed in this survey aim at helping clinicians prescribe NSAIDs more safely purely based on analysed patients' patterns and personal nature, spot risks before itself, and make the full treatment process a very useful and effective one thereby.

Keywords*— Adverse Drug Reactions, NSAIDs, Orthopaedic Patients, Machine Learning, Deep Learning, Pharmacovigilance, Graph Neural Networks, Drug-Drug Interaction Prediction, Artificial Intelligence, Clinical Decision Support Systems

I. INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly prescribed to orthopaedic patients to reduce inflammation, pain and treat musculoskeletal disorders. Some of the day-to-day used NSAIDs are Ibuprofen, Diclofenac, Naproxen, and Celecoxib, which are prescribed for conditions such as arthritis, fractures and other long-term orthopaedic complications. Prolonged consumption of these NSAIDs can lead to Adverse Drug Reactions (ARDs) where, rather than affecting a single organ system, Multiple organ systems can also be affected, such as the Gastrointestinal System, Renal System, Cardiovascular, Hepatic and Neurological Systems. NSAID-related ADRs are very serious because they can lead to increased hospitalisation, treatment-related complications and higher medical risks for patients. The main problem is the difficulty involved in early detection of ADRs because of clinical monitoring limitations, delayed appearance of any symptoms and even patient unawareness related to this matter. The complexity of patient medical histories in older adults and other factors increases the likelihood of overlapping drug effects and medication interactions. Most clinicians often cannot easily determine symptoms due to disease progression or medication-related complications. In order to handle this problem, researchers use approaches of collecting clinical records and patient outcome reports, which are used to train Machine and Deep Learning models. Some of the AI methods used in ADR prediction are NLP, graph-based learning models, etc. The limitations of the existing research are that most of them mainly focus on general methods like broad drug safety monitoring and do not go into domain specificity. Orthopaedic patients are most of the time overlooked in spite of being high risk because prolonged usage of NSAIDs can cause Gastrointestinal bleeding, Renal dysfunction, Cardiovascular complications and delayed recovery. As a limitation, most systems have a dataset imbalance problem, which may result in poor prediction. Therefore, this review paper aims to analyse existing machine learning and deep learning approaches for ADR prediction. Identify research gaps, especially related to NSAID-associated multisystem adverse reactions and their effects on orthopaedic patients. The final motive of this research is to improve ADR prediction, enable earlier risk detection and support safer NSAID prescribing in orthopaedics.

II. LITERATURE REVIEW

A. Traditional Machine Learning-Based ADR Prediction

Traditional machine learning techniques have been extensively utilized for adverse drug reaction (ADR) prediction and pharmacovigilance applications [4], [5], [9]. Algorithms such as Support Vector Machines (SVM), Random Forest (RF), Naive Bayes (NB), Logistic Regression (LR), Decision Trees (DT), and XGBoost have demonstrated effective performance in identifying drug-related side effects from structured clinical datasets and textual pharmacovigilance data [5], [9]. Studies employing datasets such as CADEC, ADE, and custom patient databases achieved promising classification accuracy and predictive capability for ADR detection [5], [9]. In particular, Naive Bayes and LinearSVC models showed strong performance in text-based ADR classification and sentiment analysis tasks [4], [9]. Despite their effectiveness, traditional machine learning approaches face limitations including poor handling of highly imbalanced datasets, reduced contextual understanding, and limited capability in modeling complex biological relationships among drugs, genes, and side effects [5], [9].

B. NLP and Social Media-Based ADR Detection

Natural Language Processing (NLP) and social media mining have emerged as important approaches for real-time pharmacovigilance and adverse drug reaction monitoring [8], [9], [10]. Several studies utilized online healthcare forums, social media platforms, and patient review datasets to extract ADR-related information using techniques such as TF-IDF, Word2Vec, sentiment analysis, collaborative filtering, and deep neural networks [4], [8], [9]. Models integrating DNNs, Bi-LSTMs, and attention mechanisms demonstrated improved capability in identifying adverse reactions from noisy and unstructured patient-generated text [8], [10]. Datasets such as TwiMed, TwitterADR, MedHelp, and Drugs.com reviews were widely used for extracting patient experiences and drug-related complaints [4], [8], [10]. Although these systems improved early ADR signal detection, challenges remain in handling informal language, spelling variations, sarcasm, sparse annotations, and geographically dynamic clinical contexts [8], [9], [10].

C. Deep Learning and Graph Neural Network-Based ADR Prediction

Recent advances in deep learning and graph neural networks have significantly improved the predictive performance of adverse drug reaction detection systems [1], [3], [7], [10], [11]. Deep learning frameworks such as Convolutional Neural Networks (CNN), Multi-Layer Perceptrons (MLP), Bi-LSTM architectures, and multimodal neural networks have been employed to integrate chemical structures, SMILES representations, and gene expression profiles for accurate ADR prediction [1], [10]. Furthermore, Graph Neural Networks (GNNs) such as DruGNN and AutoDDI enabled the modeling of complex drug-drug, drug-gene, and gene-gene interaction networks for pharmacovigilance analysis [3], [7]. Reinforcement learning and graph neural architecture search techniques further enhanced automated drug interaction prediction [7]. While these approaches achieved high predictive accuracy and superior relational modeling, they often suffer from high computational complexity, cold-start problems for unseen drugs, lack of tissue-specific biological context, and limited explainability in real-world clinical applications [3], [7], [11].

D. Graph Neural Networks and Drug Interaction Prediction

Graph Neural Networks (GNNs) have emerged as powerful computational models for predicting adverse drug reactions and drug-drug interactions by capturing complex relational information among biological entities [3], [7], [11]. Unlike traditional machine learning models that rely on isolated feature vectors, GNN-based approaches model drugs, genes, proteins, and molecular interactions as interconnected graph structures [3], [11]. Frameworks such as DruGNN and AutoDDI utilized heterogeneous graphs containing drug-drug, drug-gene, and gene-gene interactions to improve ADR prediction accuracy and relational learning capability [3], [7]. Advanced techniques including Graph Convolutional Networks (GCN), GraphSAGE, and reinforcement learning-based Graph Neural Architecture Search (GNAS) enabled automated optimization of graph architectures for pharmacovigilance tasks [3], [7]. These methods demonstrated superior predictive performance on datasets such as DrugBank, Twosides, SIDER, and STITCH [3], [7]. However, GNN-based systems remain computationally intensive and often struggle with cold-start prediction for unseen drugs, insufficient tissue-specific biological information, and limited interpretability for clinical deployment [7], [11].

E. Clinical Pharmacovigilance and Healthcare AI

Artificial Intelligence has increasingly been integrated into clinical pharmacovigilance systems to improve early detection and prevention of adverse drug reactions in healthcare environments [6]. Several studies utilized Electronic Health Records (EHRs), clinical datasets, biomarker information, and patient demographic records to develop AI-driven ADR prediction frameworks [6].

Machine learning and deep learning models including Random Forest, XGBoost, Artificial Neural Networks, Bi-LSTM, and Gradient Boosting demonstrated strong predictive capability in identifying severe adverse reactions among cancer patients and other high-risk populations [6]. Clinical pharmacovigilance systems aim to support healthcare professionals by enabling personalized risk assessment, early intervention, and improved treatment safety [6]. Despite promising results, major challenges remain in clinical integration, including dataset heterogeneity, limited sample sizes, lack of explainable AI mechanisms, and difficulties in deploying these models in real-time hospital decision-support systems [6].

III. COMPARATIVE ANALYSIS

TABLE I: COMPARATIVE ANALYSIS OF ADR PREDICTION TECHNIQUES

Paper	Technique	Dataset	Strength	Limitation
DeepSide	CNN, MLP, Multimodal Neural Networks	LINCS L1000, SIDER, PubChem	Combines chemical structures and gene expression data for improved ADR prediction	Requires large-scale biological datasets and lacks dosage-specific ADR labels
DruGNN	Graph Neural Networks, GCN, GraphSAGE	SIDER, STITCH, HuRI, PubChem	Modelscomplex drug-gene and drug-drug interactions effectively	Computational complexity and lack of tissue-specific biological context
AutoDDI	Reinforcement Learning + Graph Neural Architecture Search (GNAS)	DrugBank, Twosides	Automatically designs optimized GNN architectures with very high AUROC performance	Cold-start problem for unseen drugs
Quantum BiLSTM	Quantum BiLSTM with Attention Mechanism	TwiMed, TwitterADR	Improved ADR detection from sparse and noisy social media text	High computational complexity and scalability concerns
Predictive Analytics for Anticipating ADRs	Decision Trees, SVM, KNN, Logistic Regression	Custom MongoDB Patient Dataset	Personalized ADR prediction using demographic and clinical features	Limited incorporation of lifestyle and genetic factors
Deep-Learning-Based Drug Recommendation and ADR Detection	DNN, Collaborative Filtering, SVM	MedHelp, SIDER, UMLS	Integrates social media pharmacovigilance with recommendation systems	Lacks dynamic temporal and geographic clinical context

Adverse Drug Reac-tions Detec-tion from Social Media	Naive Bayes, SVM, XGBoost, Random For-est	CADEC, ADE, TwiMed	Comprehensive comparison of classical ML techniques for ADR extraction	Poor handling of highly imbalanced textual datasets
AI in Cancer Pharma-covigil-ance	XGBoost, Random For-est, Bi-LSTM, ANN	EHRs and clin-ical da-tasets from oncolo-gy pa-tients	Strong clinical applicability and real-world ADR prediction capa-bility	High dataset heterogeneity and limited hospital integration

IV. RESEARCH GAPS

Recent studies mainly focus on ADRs related to generic problems and not domain specificity(i.e., orthopaedic). Here, most of them use advanced machine learning or Deep learning algorithms that predict the drug reaction mainly for problems such as Cardiac or cancer-related problems, etc. Orthopaedic system-related ADRs are most of the time ignored because they may not appear that severe at the surface level, but the prolonged use of NSAIDs may lead to adverse drug reactions. This is mainly because orthopaedic patients often take more than one medication, they may be old-aged and can even be unaware of the adverse reactions of the medications. This may not only affect a single system but also multiple systems, such as gastrointestinal, renal, and hepatic. Why most of the models are not orthopaedic-related is that mostly the datasets are not specifically orthopaedic, high computational complexity and scalability concerns, models don't properly understand the complications, there is poor handling of highly imbalanced textual datasets, and mostly the clinicians won't believe predictions by a machine learning model because it may appear like a black box to them. Thus, there should be need of Orthopaedic specific system that properly predicts the adverse drug reaction caused by taking a specific NSAID and its effect on either one or multiple systems, and it should be accurate for a clinician to use it.

V. PROPOSED FRAMEWORK

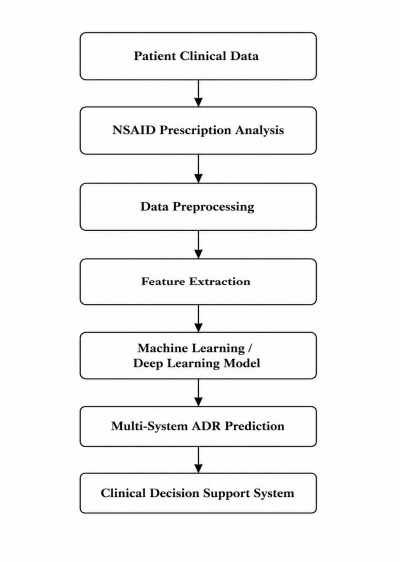

Figure 1: Proposed Framework for NSAID-Induced ADR Prediction in Orthopaedic Patients

For building the model, clinical datasets were collected and examined to identify variables like age, treatment duration, medical history, dosage patterns, and concurrent medication use, which can influence adverse drug reactions. Data cleaning and normalization are done on the dataset to handle missing and inconsistent values. Implementation of the models is carefully done because, instead of going with one specific model which may or may not perform best, comparative model implementation is done based on their actual performances. Logistic Regression and Support Vector Machines were included to establish baseline behaviour between the datasets and determine how simpler models handle structured patient data. Random Forest and Gradient Boosting methods were introduced to capture more complex relationships among prescription data, clinical variables, and other outcomes. Deep learning models play a major role in assessing whether additional interactions arise when larger combinations of patient features are considered. After the model training, the metrics are compared, and the best model is chosen for the ADR Risk Prediction System, which predicts multi-system NSAID ADRs .

VI. CONCLUSION AND FUTURE SCOPE

The reviewed studies demonstrate the effectiveness of using machine learning and deep learning models in predicting ADRs across clinical settings. Still, challenges including data imbalance, limited model interpretability, real-world implementation, and insufficient representation of orthopaedic patients on prolonged medications persist. Future research should focus on diverse, balanced datasets and interpretable models to develop reliable ADR prediction systems that increase patient safety and support clinical decision-making.

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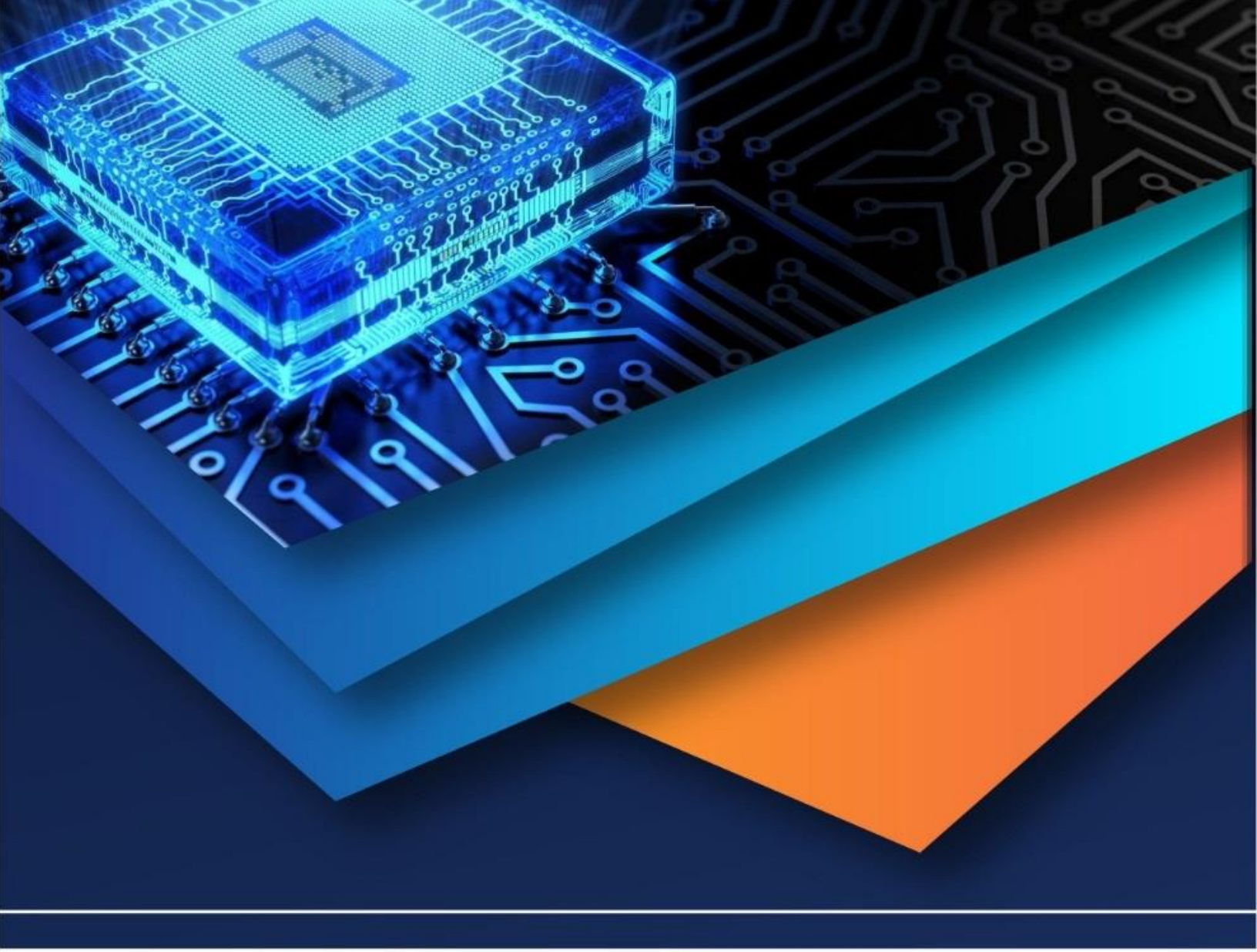

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