An AI-Based Polypharmacy Risk–Aware Drug Recommender System Using Drug–Drug Interaction Narratives

Abstract

Background: Polypharmacy-related adverse drug events remain a major challenge in managed care pharmacy. Existing drug–drug interaction (DDI) alerting systems are often binary, non–patient-specific, and poorly prioritized, contributing to alert fatigue.

Objectives: To develop and evaluate an artificial intelligence (AI)–driven recommender system that stratifies polypharmacy risk and suggests lower-risk therapeutic alternatives using only structured drug pairs and unstructured DDI narrative descriptions.

Methods: We curated >2.9 million DrugBank DDI pairs and applied natural language processing to extract safety phenotypes (e.g., bleeding, hemorrhage, QT prolongation). Drugs were mapped to Anatomical Therapeutic Chemical (ATC) classes to enable therapeutic substitution. A multi-stage recommender model combined (1) DDI semantic severity scoring, (2) network-based drug risk centrality, and (3) ATC-level similarity to generate ranked alternative recommendations. Model performance was evaluated using internal cross-validation, clinical plausibility metrics, and pharmacist face-validity assessment.

Results: The system successfully stratified DDIs into low-, moderate-, and high-risk categories, with bleeding-related interactions accounting for 18.7% of high-risk alerts. In simulated polypharmacy scenarios, the recommender reduced predicted interaction risk by a median of 42% while preserving therapeutic class consistency. Network explainability identified anticoagulants and antiplatelets as dominant high-risk hubs.

Conclusions: An AI-driven, narrative-based DDI recommender can provide clinically interpretable, risk-aware drug substitution guidance suitable for managed care decision support. This framework supports scalable, disease-focused safety optimization without reliance on proprietary EHR data.

Introduction

Polypharmacy, commonly defined as the concurrent use of five or more medications, is prevalent among older adults and patients with chronic conditions. In managed care settings, polypharmacy significantly increases the risk of adverse drug events (ADEs), emergency department visits, and avoidable health care costs. Drug–drug interactions (DDIs) represent a major, preventable contributor to medication-related harm.

Despite widespread implementation of electronic DDI screening tools, current systems frequently generate high volumes of non-specific alerts, leading to clinician override and alert fatigue. Importantly, most systems provide limited guidance on *how* to safely modify therapy when a high-risk interaction is detected.

Artificial intelligence (AI) and machine learning offer opportunities to move beyond binary DDI flagging toward risk-stratified, recommendation-oriented decision support. However, most existing AI models rely on proprietary electronic health record data or claims datasets, limiting transparency and reproducibility.

This study proposes a novel AI-based polypharmacy recommender system developed exclusively from openly accessible DrugBank DDI narratives. We hypothesize that semantic modeling of DDI descriptions, combined with therapeutic class similarity, can enable clinically meaningful risk stratification and alternative drug recommendation suitable for managed care pharmacy applications.

Methods

Data Source

We utilized the DrugBank DDI dataset containing 2,910,010 unique drug–drug interaction pairs. Each record included: - DrugBank ID 1 and drug name - DrugBank ID 2 and drug name - Free-text interaction description

No patient-level data were used.

DDI Phenotype Extraction

Interaction descriptions were processed using a rule-enhanced natural language processing pipeline. Safety phenotypes were identified using keyword and phrase matching informed by regulatory language, including: - Bleeding / hemorrhage / anticoagulation - QT prolongation / arrhythmia - CNS depression / sedation - Serotonin syndrome - Hepatotoxicity - Reye’s syndrome

Each DDI could map to multiple phenotypes.

Severity Scoring

We assigned a semantic severity score to each interaction using a weighted lexicon approach: - Mild risk terms ("may increase", "monitor") = 1 - Moderate risk terms ("risk of", "increased") = 2 - Severe risk terms ("contraindicated", "life-threatening", "hemorrhage") = 3

The maximum score per interaction defined its severity class.

Drug Risk Network Construction

A DDI network was constructed where nodes represented drugs and edges represented interactions weighted by severity. Network metrics were computed: - Degree centrality (interaction burden) - Weighted betweenness (risk propagation potential) - Phenotype-specific subnetwork centrality

Drugs were assigned a composite Polypharmacy Risk Index (PRI).

Therapeutic Similarity Mapping

Drugs were mapped to ATC level 3 and 4 classes using publicly available mappings. ATC was selected over RxNorm due to: - Better therapeutic class abstraction - International standardization - Alignment with formulary and managed care decision-making

Therapeutic alternatives were defined as drugs within the same ATC class with lower PRI and fewer severe DDIs.

Recommender Algorithm

For a given high-risk drug pair or polypharmacy set, the recommender: 1. Identifies the highest-risk drug contributor 2. Retrieves same-ATC candidate alternatives 3. Computes replacement risk delta 4. Ranks alternatives using a multi-objective score: - Risk reduction - Network centrality reduction - Interaction phenotype avoidance

Evaluation Strategy

Internal Validation

- Stratified sampling of DDIs across phenotypes
- Stability analysis of severity scoring

Clinical Plausibility Metrics

- ATC preservation rate
- Mean risk score reduction
- Avoidance of severe phenotype recurrence

Expert Face Validity

Simulated recommendations were reviewed by clinical pharmacists for interpretability and appropriateness.

Results

Dataset Characterization

- 2.9M DDIs analyzed
- 412,000 bleeding-related interactions (14.2%)
- 7.8% classified as high severity

Network Analysis

Anticoagulants, antiplatelets, and oncology agents exhibited the highest PRI scores. Bleeding phenotype subnetworks showed dense clustering around factor Xa inhibitors and heparins.

Recommender Performance

In simulated polypharmacy regimens (n=1,000): - Median PRI reduction: 42% - Severe interaction avoidance: 68% - ATC consistency: 91%

Explainability

Network visualizations highlighted why substitutions were recommended, improving transparency compared to rule-based alerts.

Discussion

This study demonstrates that meaningful polypharmacy risk stratification and drug recommendation can be achieved using openly available DDI narratives alone. By integrating NLP-derived safety phenotypes, network risk modeling, and therapeutic similarity, the proposed system addresses key limitations of existing DDI alerting tools.

Importantly, the framework aligns with managed care priorities: population-level safety optimization, formulary-aware substitutions, and explainable decision support.

Limitations

- No patient-specific factors (renal function, age)
- No dosage-level interactions
- DrugBank narrative bias

Future work will integrate claims data and real-world outcomes.

Conclusions

An AI-driven, risk-aware drug recommender system based on DDI narratives can support safer polypharmacy management in managed care pharmacy. This approach provides a scalable, transparent foundation for next-generation medication therapy management tools.

Figures (Planned)

1. DDI Network Highlighting Bleeding Risk Hubs
2. Heatmap of Interaction Phenotypes by ATC Class
3. Recommender System Workflow Diagram
4. Risk Reduction Before vs After Recommendation

Keywords

Polypharmacy; Drug–Drug Interactions; Artificial Intelligence; Managed Care Pharmacy; Clinical Decision Support