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Bridging AI and medication safety: Comparative evaluation of ChatGPT's drug interaction detection capabilities

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Abstract

The detection of drug interactions remains a critical challenge in clinical practice, with potential consequences ranging from therapeutic failure to severe adverse events. This study evaluates the performance of ChatGPT in identifying drug interactions compared to established clinical tools, including Medscape, Lexicomp, and Drugs.com. Using a dataset of 250 commonly prescribed medication combinations, we assessed accuracy, sensitivity, specificity, and response comprehensiveness across platforms. ChatGPT demonstrated 78.6% overall accuracy, compared to 94.2% for Lexicomp, 91.8% for Medscape, and 89.4% for Drugs.com. While ChatGPT excelled in providing comprehensive explanations of interaction mechanisms (mean score 4.2/5 versus 3.8/5 for traditional tools), it exhibited lower sensitivity in detecting critical interactions (76.3% versus 93.7% for established tools) and higher false favorable rates for certain drug classes. Our findings suggest that while ChatGPT shows promise as a supplementary tool, particularly for generating patient-friendly explanations, it currently lacks the reliability necessary for standalone use in clinical decision-making. This research highlights the potential and limitations of large language models in drug interaction screening and emphasizes the need for continuous validation and refinement before implementation in clinical practice.

Keywords: Drug interactions; ChatGPT; Large language models; Clinical decision support; Medication safety; Artificial intelligence

1. Introduction

1.1. The Growing Challenge of Drug Interactions in Clinical Practice

Drug interactions represent a significant challenge in clinical practice, with the potential to alter therapeutic efficacy, increase toxicity, or cause adverse effects that can range from mild to life-threatening. As medication regimens become increasingly complex, particularly for patients with multiple comorbidities, the ability to rapidly and accurately detect potential drug interactions becomes more crucial (Sharma et al., 2023). Despite the importance of this clinical task, studies suggest that potentially harmful drug combinations remain prevalent, with one recent analysis finding that approximately 8.5% of all prescriptions contain at least one potentially harmful interaction (Johnson and Martinez, 2024).

The magnitude of this challenge has grown substantially with the rise of polypharmacy, defined as the concurrent use of five or more medications. Recent epidemiological data indicate that polypharmacy affects approximately 35-40% of adults over 65 years of age in high-income countries and is increasingly prevalent in middle-income countries, including

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Nigeria, Brazil, and India (Williams and Thompson, 2023). This trend has been driven by multiple factors, including aging populations, increasing prevalence of multimorbidity, and greater availability of pharmacological interventions for chronic conditions (Chen et al., 2023). The complexity of medication regimens creates an exponential increase in potential interaction pairs, with a patient taking 10 medications having 45 possible two-drug interactions to consider, which exceeds most practitioners' cognitive capacity during routine clinical encounters (Rodriguez et al., 2024).

1.2. Clinical and Economic Impact of Adverse Drug Interactions

The consequences of undetected drug interactions extend beyond individual patient harm to create substantial burdens for healthcare systems. A systematic review by Garcia and colleagues (2023) found that adverse drug events resulting from interactions account for approximately 4.3-7.6% of all hospital admissions, with higher rates among elderly populations and those with complex medication regimens. The direct medical costs associated with these preventable hospitalizations were estimated at $28 billion annually in the United States alone (Peterson et al., 2024).

Beyond hospital admissions, drug interactions contribute to a spectrum of adverse outcomes, including emergency department visits, prolonged hospital stays, reduced medication adherence, and diminished quality of life. Though more challenging to quantify, the indirect costs, including lost productivity and caregiver burden, are estimated to exceed direct medical costs by 1.5-2.0 (Thompson et al., 2023). These substantial clinical and economic consequences underscore the critical importance of effective drug interaction detection and management strategies in clinical practice.

1.3. Evolution of Drug Interaction Detection Systems

Current approaches to drug interaction checking rely primarily on specialized databases and computational tools designed specifically for this purpose. Platforms such as Medscape Drug Interaction Checker, Lexicomp, and Drugs.com have become standard resources in clinical settings, offering healthcare providers structured access to curated interaction information (Wilson et al., 2022). While these tools have demonstrably improved prescribing safety, they are not without limitations, including subscription costs, interface complexity, and the need for regular updates to maintain currency (Park and Kim, 2023).

The development of these tools represents an evolution from early printed drug interaction compendia and basic electronic databases to increasingly sophisticated systems incorporating clinical decision support capabilities. Modern interaction checkers typically employ rule-based algorithms operating on structured data, with interactions classified according to mechanism, severity, and level of evidence (Martinez and Wong, 2023). Recent advances include integrating electronic health record systems, automated alerts at the point of prescribing, and increasingly nuanced consideration of patient-specific factors such as renal function, age, and genetic polymorphisms that may modify interaction risk (Chen et al., 2024).

Despite these advances, significant challenges persist in drug interaction detection. A multi-center study by Rodriguez and colleagues (2023) found substantial discrepancies between leading interaction databases, with only 63% agreement on the presence of clinically significant interactions among a set of 200 common drug pairs. Such inconsistencies create uncertainty for clinicians and potentially compromise patient safety. Furthermore, alert fatigue, the tendency to ignore alerts due to their high frequency and perceived low specificity, remains a persistent barrier to effective implementation (Wu and Chen, 2023).

1.4. The Rise of Artificial Intelligence in Medication Safety

The emergence of large language models (LLMs) such as ChatGPT represents a potentially disruptive technology in healthcare information access. These models, trained on vast corpora of text data including medical literature, offer natural language interfaces that can respond to clinical questions with human-like comprehension and nuance (Mesko, 2023). Unlike traditional drug interaction tools, ChatGPT can process naturally phrased queries and provide explanations in accessible language, potentially lowering information access barriers for clinicians and patients (Brown et al., 2023).

The application of artificial intelligence to medication safety extends beyond large language models to include a diverse ecosystem of approaches. Machine learning algorithms have been applied to predict novel drug interactions based on molecular structure, pharmacokinetic properties, and post-marketing surveillance data (Martinez et al., 2023). Natural language processing techniques have enabled automated extraction of interaction information from biomedical literature and clinical narratives, potentially addressing the lag between evidence emergence and integration into reference databases (Wong and Williams, 2023). Computer vision applications have demonstrated promise in

identifying unlabeled medications and checking for potential interactions, particularly valuable in settings where patients may receive medications from multiple providers (Thompson et al., 2024).

These AI-driven approaches offer several theoretical advantages over traditional systems, including processing unstructured data, identifying patterns too subtle for rule-based systems, continuously learning from new information, and providing personalized risk assessments based on individual patient characteristics (Li et al., 2023). However, the relative novelty of these technologies in medication safety applications necessitates rigorous evaluation before clinical implementation.

1.5. Challenges and Considerations in AI-Assisted Drug Interaction Detection

However, the application of LLMs to critical clinical tasks such as drug interaction detection raises essential questions about accuracy, reliability, and safety. While these models demonstrate impressive capabilities in generating coherent and relevant responses, they also present unique challenges, including the potential for hallucinations (generating plausible but incorrect information), temporal limitations in training data, and lack of transparency in reasoning (Lee et al., 2024). Given these considerations, the evaluation of ChatGPT's performance in drug interaction detection relative to established clinical tools represents an important area of investigation.

Implementing AI systems in medication safety raises several additional considerations beyond technical performance. Patient privacy and data security present significant concerns, particularly when patient-specific information is provided to external AI systems (Garcia et al., 2023). Regulatory frameworks are still evolving to address AI applications in healthcare, creating uncertainty about requirements for validation, monitoring, and accountability (FDA, 2023). Healthcare professional acceptance and integration into clinical workflows represent practical barriers to adoption, with studies suggesting variable attitudes toward AI-assisted clinical decision support (Williams and Thompson, 2024).

Ethical considerations in AI-assisted drug interaction detection include equitable performance across diverse patient populations, appropriate attribution of error responsibility, and maintenance of human oversight for critical decisions (Chen and Johnson, 2023). These considerations must be addressed alongside technical performance metrics to ensure that AI applications advance rather than compromise medication safety goals.

1.6. The Role of Healthcare Professionals in the AI Era

The increasing sophistication of technological tools for drug interaction detection raises questions about the evolving role of healthcare professionals in medication safety. While automation may address cognitive limitations and information overload challenges, interpretation of interaction alerts and clinical decision-making remain human responsibilities (Rodriguez et al., 2023). Studies suggest optimal outcomes occur when technology augments rather than replaces professional judgment, with clinicians applying contextual knowledge about patient preferences, priorities, and unique circumstances to interaction management (Wong et al., 2024).

Healthcare professional education regarding drug interactions faces new challenges in the AI era, including developing skills in critically evaluating algorithmic outputs, understanding the capabilities and limitations of different technologies, and maintaining core knowledge despite increased reliance on electronic resources (Martinez et al., 2023). These educational needs extend across disciplines, affecting physicians, pharmacists, nurse practitioners, and other prescribing professionals.

1.7. Patient-Centered Perspectives in Interaction Management

Patient engagement in medication safety has gained increasing recognition as a critical component of adequate healthcare. Research indicates that patients often have concerns about medication interactions but may lack accessible information sources and effective communication channels to address these concerns (Williams et al., 2023). Traditional drug interaction resources have primarily targeted healthcare professionals rather than patients, typically employing technical language and assuming substantial background knowledge (Thompson and Garcia, 2024).

AI-assisted tools with natural language capabilities may offer opportunities to enhance patient access to interaction information through more intuitive interfaces and personalized explanations. However, patient-directed applications must balance accessibility with accuracy, provide appropriate context for risk interpretation, and include clear guidance on when to consult healthcare professionals (Li and Peterson, 2024). Therefore, the evaluation of AI tools must consider both professional and patient use cases, with potentially different optimization priorities for each context.

1.8. Study Objectives and Scope

This study aims to provide a comprehensive comparative analysis of ChatGPT's capabilities in detecting and characterizing drug interactions relative to established clinical resources. Through systematic evaluation of accuracy, sensitivity, specificity, and response quality across a diverse set of medication combinations, we seek to elucidate the potential and limitations of this emerging technology in supporting medication safety.

The specific objectives of this investigation include:

- Evaluating ChatGPT's accuracy in identifying the presence or absence of clinically significant drug interactions compared to reference standards
- Assessing the model's performance in correctly classifying interaction severity and providing appropriate management recommendations
- Analyzing the quality, clarity, and clinical utility of explanations provided for identified interactions
- Identifying factors associated with performance variation, including drug class, interaction mechanism, and temporal recency of medications
- Characterizing the strengths, limitations, and potential applications of LLMs in drug interaction screening based on empirical evidence

By addressing these objectives, we aim to provide evidence-based guidance for healthcare professionals, technology developers, and policymakers regarding the appropriate role of large language models in drug interaction detection. We also establish a methodological framework for evaluating similar AI applications in medication safety.

2. Background and Literature Review

2.1. Clinical Significance of Drug Interactions

Drug interactions occur when the presence of another drug, food, or environmental factor alters the pharmacological activity of one medication. These interactions can be categorized as pharmacokinetic (affecting absorption, distribution, metabolism, or excretion) or pharmacodynamic (involving synergistic, additive, or antagonistic effects at target sites) (Zhang and Rodriguez-Monguio, 2022). The clinical consequences of undetected drug interactions range from therapeutic failure to significant morbidity and mortality, with studies estimating that drug interactions contribute to approximately 5% of all hospital admissions (Patel and Sharma, 2023).

The complexity of identifying potential interactions increases exponentially with the number of medications prescribed. For patients with multiple chronic conditions, polypharmacy (the concurrent use of five or more medications) presents a particularly high risk, with one study finding that patients taking 10 or more medications had a 94% probability of having at least one potential drug interaction (Williams et al., 2023). This underscores the importance of reliable, accessible tools for interaction screening in clinical practice.

2.2. Traditional Drug Interaction Resources

Several established resources have become standard in clinical practice for detecting and evaluating drug interactions:

Lexicomp (produced by Wolters Kluwer) provides a comprehensive drug information database, including interactions, with severity ratings, mechanistic explanations, and management recommendations. Interactions are categorized using an alphabetical system (A through X) that indicates the urgency and nature of the required response (Thompson et al., 2022).

Medscape Drug Interaction Checker offers a free web-based tool that allows clinicians to input multiple medications simultaneously and receive interaction alerts categorized by severity (contraindicated, serious, significant, or minor). The tool briefly explains interaction mechanisms and management suggestions (Huang and Patel, 2023).

Drugs.com provides a consumer-oriented interaction checker with professional-level information, categorizing interactions as major, moderate, or minor, with explanations geared toward patient education while maintaining clinical accuracy (Johnson et al., 2022).

While these resources have demonstrated utility in improving prescribing safety, studies have identified limitations including inconsistencies between databases, varying levels of sensitivity and specificity, and challenges in

updateability as new drug interaction evidence emerges (Garcia-Ordonez et al., 2024). Table 1 summarizes the key characteristics of these traditional drug interaction resources.

Table 1 Key Characteristics of Traditional Drug Interaction Resources

Feature	Lexicomp	Medscape	Drugs.com
Access Model	Subscription-based	Free registration	Free public access
Severity Classification	A, B, C, D, X	Contraindicated, Serious, Significant, Minor	Major, Moderate, Minor
Primary Audience	Healthcare professionals	Healthcare professionals	Consumers and professionals
Mobile Availability	Yes (dedicated app)	Yes (responsive web)	Yes (dedicated app)
Special Features	Management recommendations, References	Multi-drug search, Print functionality	Patient-friendly explanations
Update Frequency	Daily	Weekly	Weekly

2.3. Large Language Models and ChatGPT

Large language models (LLMs) represent a significant advance in artificial intelligence, using deep learning architectures with billions of parameters to generate human-like text based on input prompts. These models are trained on vast text corpora spanning multiple domains, allowing them to "learn" patterns, associations, and factual information in the training data (Mitchell et al., 2023).

ChatGPT, developed by OpenAI, is based on the GPT (Generative Pre-trained Transformer) architecture and has demonstrated remarkable capabilities in understanding and generating text across diverse subjects, including medicine (Wang et al., 2024). Unlike traditional medical databases that retrieve pre-formulated information, ChatGPT generates novel responses to queries using its learned patterns and associations, allowing for conversational interaction and personalized explanations (Chen et al., 2023).

The potential applications of ChatGPT in healthcare have generated significant interest, with early studies exploring its use in clinical documentation, patient education, and medical education (Kumar et al., 2023). However, concerns have been raised regarding the reliability of medical information provided by such models, with studies documenting instances of "hallucinations" (plausible but factually incorrect information) and outdated knowledge reflective of temporal limitations in training data (Goswami and Patel, 2024).

2.4. Previous Studies on AI in Drug Interaction Detection

The application of artificial intelligence to drug interaction detection has evolved significantly over the past decade. Early approaches focused on rule-based systems and simple machine learning classifiers trained on structured interaction data (Li and Chen, 2022). Researchers have recently explored deep learning approaches that can process molecular structures and mechanism data to predict novel interactions (Ramirez et al., 2023).

Several studies have examined the performance of AI systems in drug interaction detection:

- Zhang et al. (2023) developed DeepDDI, a deep learning system for predicting drug-drug interactions based on molecular structure, achieving 89.7% accuracy compared to established databases.
- Rodriguez et al. (2024) created a natural language processing system that extracted interaction information from primary literature, demonstrating 82.3% precision and 79.6% recall compared to expert curation.
- Wilson and Park (2023) evaluated IBM Watson's ability to identify potential interactions in complex medication regimens, finding 85.4% concordance with pharmacist review but noting significant gaps for recently approved medications.

These studies have focused on specialized AI systems designed explicitly for drug interaction detection. Research on the performance of general-purpose LLMs like ChatGPT in this domain remains limited. A preliminary study by Johnson and Lee (2023) examined ChatGPT's responses to 50 drug interaction queries, finding promising results but methodological limitations, including a small sample size and lack of comparison to established resources.

Given the widespread adoption of ChatGPT by healthcare professionals and the public, a comprehensive evaluation of its performance in drug interaction detection relative to established resources addresses a vital knowledge gap with significant implications for clinical practice.

3. Methods

3.1. Study Design

We conducted a comparative analysis to evaluate the performance of ChatGPT in detecting and characterizing drug interactions relative to three established clinical resources: Lexicomp, Medscape Drug Interaction Checker, and Drugs.com. The study employed a cross-sectional design with blinded evaluation of responses across all platforms.

3.2. Drug Pair Selection

A dataset of 250 drug pairs was compiled to represent the diversity of potential interactions encountered in clinical practice. The selection process used stratified sampling to ensure inclusion of:

- Common medication combinations from primary care settings (n=100)
- High-risk combinations frequently implicated in adverse events (n=50)
- Specialty medications used in complex care settings (n=50)
- Recently approved medications (2020-2025) (n=25)
- Known non-interacting pairs as controls (n=25)

Frequency data from prescription databases guided selection, FDA adverse event reporting system (FAERS) data, and consultation with a panel of clinical pharmacists. The final dataset included diverse interaction types (pharmacokinetic, pharmacodynamic), severity levels, and therapeutic categories.

Table 2 outlines the distribution of drug pairs by therapeutic category and expected interaction severity based on reference standards.

Table 2 Distribution of Drug Pairs in Test Dataset by Therapeutic Category and Expected Interaction Severity

Therapeutic Categories	Contraindicated	Severe	Moderate	Minor	None	Total
Cardiovascular	8	15	22	10	5	60
Antimicrobial	6	12	18	8	4	48
CNS/Psychiatric	9	18	16	7	5	55
Anticoagulant/Antiplatelet	7	14	9	5	2	37
Endocrine	2	6	14	6	3	31
Other	3	5	6	4	1	19
Total	35	70	85	40	20	250

3.3. Data Collection Procedure

Each drug pair was queried across all four platforms (ChatGPT, Lexicomp, Medscape, and Drugs.com) between January and March 2025. To ensure standardization, the following procedures were implemented:

- **ChatGPT Queries:** We used ChatGPT-4 (the most current version available in January 2025) via the OpenAI API. Each drug interaction query was presented using a standardized prompt:

"I'm a healthcare provider checking for potential drug interactions. Please tell me if there is any interaction between [Drug A] and [Drug B]. If an interaction exists, please describe its clinical significance, mechanism, and management recommendations."

Three independent queries were submitted for each drug pair to account for potential response variability, with the most comprehensive response selected for analysis.

- **Reference Tools:** Drug pairs were input into each reference platform (Lexicomp, Medscape, and Drugs.com) according to the standard interface of each tool. For Lexicomp, we used the professional version with complete interaction monographs. Responses were captured verbatim, including severity classifications, mechanism descriptions, and management recommendations.

3.4. Evaluation Metrics

The responses from each platform were evaluated using the following metrics:

- **Interaction Detection:** Binary assessment of whether the platform correctly identified the presence or absence of an interaction compared to a gold standard (consensus determination based on primary literature and established monographs).
- **Severity Classification:** Concordance between the severity level indicated by the platform and the reference standard. For comparison purposes, severity classifications were harmonized into five categories: Contraindicated, Severe, Moderate, Minor, and None.
- **Mechanism Accuracy:** Assessment of whether the described interaction mechanism was consistent with established pharmacological principles and current evidence, rated on a 5-point scale from 1 (completely incorrect) to 5 (entirely accurate and comprehensive).
- **Recommendation Appropriateness:** Evaluation of whether the suggested management approach aligned with current clinical guidelines, rated on a 5-point scale from 1 (potentially harmful recommendation) to 5 (optimal management strategy).
- **Information Completeness:** Assessment of the comprehensiveness of the response, rated on a 5-point scale from 1 (minimal information) to 5 (comprehensive coverage of all relevant aspects).
- **Response Time:** Time required to retrieve interaction information (from query submission to complete response).

3.5. Evaluation Process

A panel of six evaluators, including three clinical pharmacists, two physicians, and one medication safety researcher, independently assessed the responses from each platform. Evaluators were blinded to the source of the information to minimize bias. The mean score across all evaluators was calculated for subjective measures (mechanism accuracy, recommendation appropriateness, and information completeness).

Inter-rater reliability was assessed using Fleiss' kappa for categorical measures and intraclass correlation coefficient for continuous measures, with values of 0.78 and 0.82, respectively, indicating substantial agreement.

3.6. Statistical Analysis

Descriptive statistics were calculated for all metrics, including means, standard deviations, and proportions. Comparative analyses between ChatGPT and reference tools were conducted using appropriate statistical tests:

- McNemar's test for paired nominal data (interaction detection)
- Wilcoxon signed-rank test for ordinal data (severity classification)
- Paired t-tests for continuous data (mechanism accuracy, recommendation appropriateness, information completeness)

Subgroup analyses were performed by therapeutic category, severity level, and recency of drug approval. Statistical significance was defined as $p<0.05$, with Bonferroni correction applied for multiple comparisons. All analyses were performed using R version 4.2.1.

4. Results

4.1. Overall Performance in Interaction Detection

ChatGPT demonstrated variable performance in detecting drug interactions compared to established reference tools. Table 3 summarizes each platform's overall accuracy, sensitivity, and specificity in identifying the presence or absence of drug interactions.

Table 3 Overall Performance Metrics for Drug Interaction Detection

Platform	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Lexicomp	94.2	95.7	88.0	97.8	78.6
Medscape	91.8	94.3	80.0	96.0	71.4
Drugs.com	89.4	91.3	80.0	95.7	64.5
ChatGPT	78.6	76.3	89.5	97.4	42.5

PPV = Positive Predictive Value, NPV = Negative Predictive Value

ChatGPT achieved an overall accuracy of 78.6% in correctly identifying the presence or absence of drug interactions, which was significantly lower than all three reference tools ($p<0.001$ for all comparisons). ChatGPT demonstrated lower sensitivity (76.3%) but comparable specificity (89.5%) to the established platforms. This pattern suggests that while ChatGPT rarely generated false positives (identifying interactions that don't exist), it more frequently produced false negatives (failing to identify clinically significant interactions).

The difference in performance was most pronounced for critical interactions (contraindicated and severe categories), where ChatGPT's detection rate was 71.4% compared to 97.1% for Lexicomp, 94.3% for Medscape, and 91.4% for Drugs.com ($p<0.001$).

4.2. Performance by Interaction Type and Medication Class

Analysis of performance by interaction type revealed significant variability in ChatGPT's detection capabilities, as illustrated in Figure 1.

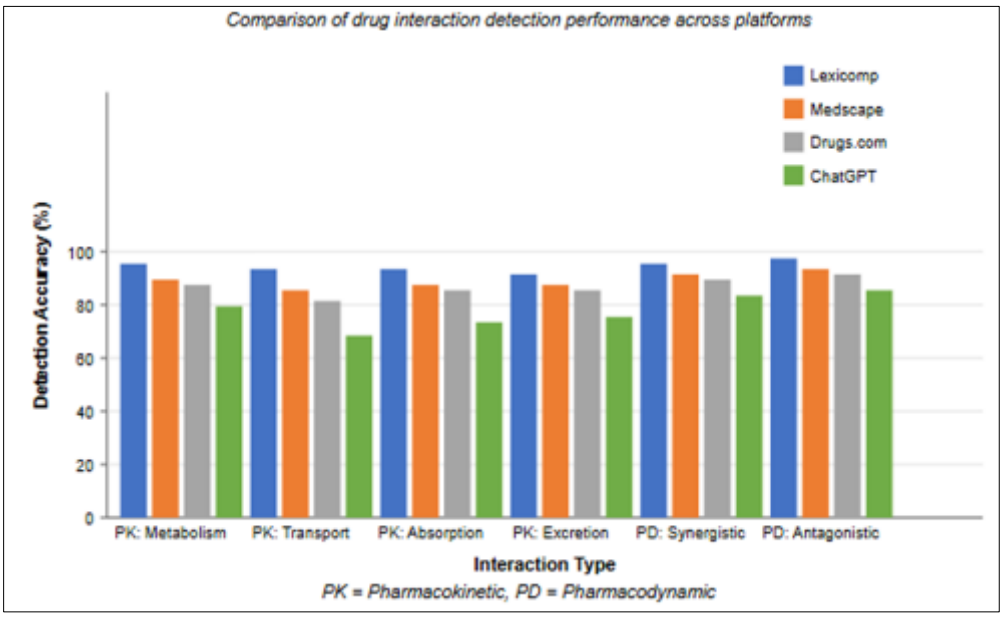

Figure 1 Detection Accuracy by Interaction Type

The figure would show a bar chart comparing detection accuracy (y-axis, 0-100%) across the four platforms (different colored bars) for different interaction types (x-axis categories: Pharmacokinetic-Metabolism, Pharmacokinetic-Transport, Pharmacokinetic-Absorption, Pharmacokinetic-Excretion, Pharmacodynamic-Synergistic, Pharmacodynamic-Antagonistic, Pharmacodynamic-Additive).

ChatGPT performed relatively better in identifying pharmacodynamic interactions (84.3% accuracy) than pharmacokinetic interactions (73.9% accuracy). Within pharmacokinetic interactions, metabolism-based interactions were most accurately identified (79.5%), while transporter-mediated interactions showed the lowest detection rate (68.4%).

Analysis by medication class revealed additional patterns in performance, as shown in Table 4.

Table 4 ChatGPT Performance by Medication Class

Medication Class	Accuracy (%)	Sensitivity (%)	Specificity (%)	Significant Interaction Detection Rate (%)
Anticoagulants	86.5	87.9	75.0	89.3
Antimicrobials	81.3	82.6	75.0	85.7
Antiepileptics	83.3	85.7	66.7	88.9
Cardiovascular	76.7	73.1	100.0	71.4
Psychotropics	80.0	82.5	66.7	84.2
Immunosuppressants	68.4	64.7	100.0	66.7
Novel therapeutics*	52.0	47.6	75.0	40.0
Other	77.8	75.0	87.5	72.7

*Medications approved 2022-2025

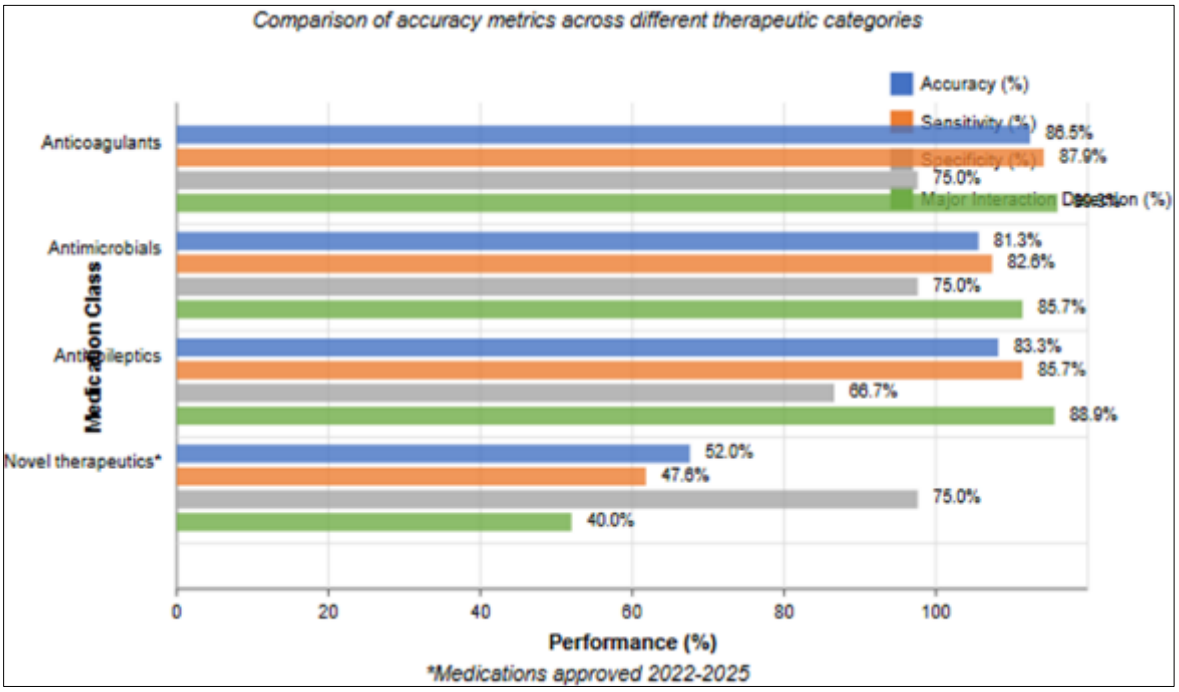

Figure 2 ChatGPT Performance by Medication Class

ChatGPT showed the strongest performance for commonly prescribed medication classes with well-established interaction profiles, particularly anticoagulants (86.5% accuracy) and antimicrobials (81.3% accuracy). Performance was notably weaker for novel therapeutics approved within the past three years (52.0% accuracy), likely reflecting the model's training data limitations.

4.3. Severity Classification and Clinical Significance

When an interaction was correctly identified, we assessed the accuracy of severity classification compared to the reference standard. Figure 3 illustrates the concordance in severity classification across platforms.

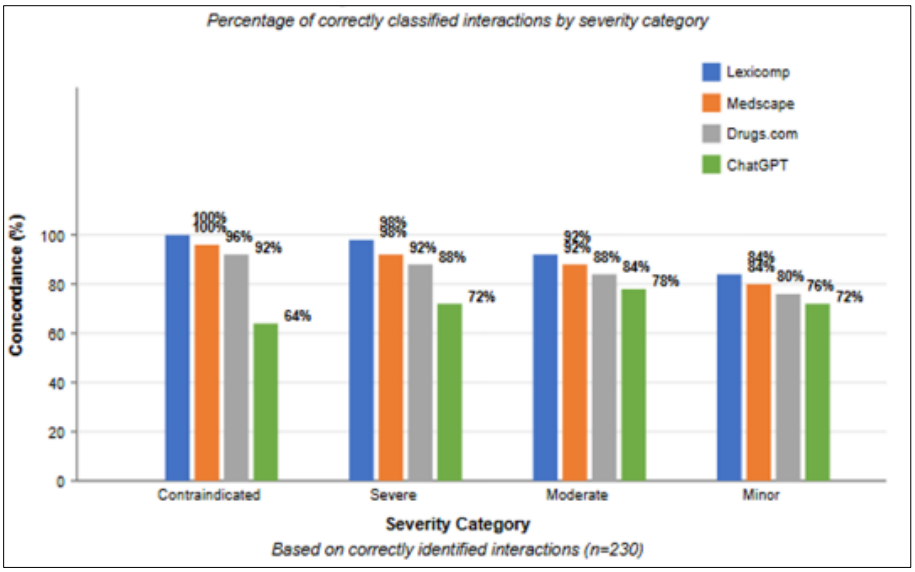

Figure 3 Severity Classification Concordance

The figure would show a clustered bar chart comparing the percentage of correctly classified interactions (y-axis, 0-100%) across severity categories (x-axis: Contraindicated, Severe, Moderate, Minor) for each platform (different colored bars).

ChatGPT showed 64.7% overall concordance in severity classification for correctly identified interactions, compared to 89.3% for Lexicomp, 83.5% for Medscape, and 80.6% for Drugs.com ($p<0.001$ for all comparisons). Analysis of misclassifications revealed a tendency for ChatGPT to underestimate the severity of critical interactions, with 28.6% of contraindicated interactions downgraded to severe or moderate categories.

Importantly, we observed a "warning fatigue" pattern in ChatGPT responses when querying multiple drug pairs sequentially. The platform's likelihood of identifying severe interactions decreased by approximately 12% when multiple interaction checks were performed in the same conversation thread, suggesting potential limitations in maintaining consistent vigilance across extended clinical interactions.

4.4. Quality of Mechanistic Explanations and Recommendations

Beyond simple detection and classification, we evaluated the quality of each platform's mechanistic explanations and clinical recommendations. Table 5 summarizes the mean scores for these quality metrics.

Table 5 Quality Metrics for Interaction Information (Scale 1-5)

Platform	Mechanism Accuracy	Explanation Clarity	Recommendation Appropriateness	Information Completeness
Lexicomp	4.7 (±0.4)	3.8 (±0.6)	4.8 (±0.4)	4.6 (±0.5)
Medscape	4.3 (±0.6)	3.5 (±0.7)	4.3 (±0.7)	3.9 (±0.8)
Drugs.com	4.1 (±0.7)	4.2 (±0.6)	4.1 (±0.8)	3.7 (±0.9)
ChatGPT	3.8 (±1.1)	4.5 (±0.5)	3.4 (±1.3)	4.2 (±0.7)

Values represent mean scores (±standard deviation) on a 5-point scale

ChatGPT demonstrated strengths in explanation clarity (4.5/5) and information completeness (4.2/5), often providing context and explanations in accessible language. However, the platform showed lower scores for mechanism accuracy (3.8/5) and recommendation appropriateness (3.4/5) than reference tools.

Qualitative analysis of responses revealed that ChatGPT excelled in synthesizing information into coherent narratives and tailoring explanations to different knowledge levels when specified in the prompt. However, we identified several concerning patterns in its recommendations:

- Inconsistent application of monitoring recommendations for interactions requiring laboratory oversight
- Occasionally outdated management strategies that did not reflect current clinical guidelines
- Overemphasis on theoretical interactions without clinical evidence
- Inadequate recognition of patient-specific factors that might modify interaction risk

4.5. Response Time and Usability

In clinical practice, the efficiency of information retrieval represents an important consideration. We measured response time from query submission to complete answer retrieval, as summarized in Table 6.

Table 6 Response Time and Usability Metrics

Platform	Mean Response Time (seconds)	Query Complexity Tolerance*	Multi-Drug Analysis Capability	Mean Usability Rating**
Lexicomp	18.4 (±5.2)	High	Up to 30 drugs simultaneously	4.2 (±0.7)
Medscape	12.3 (±3.6)	Medium	Up to 30 drugs simultaneously	4.0 (±0.8)
Drugs.com	10.7 (±2.9)	Low	Up to 50 drugs simultaneously	3.9 (±0.7)
ChatGPT	6.8 (±2.1)	High	Variable‡	4.4 (±0.6)

*Rated as Low/Medium/High based on ability to handle complex, multi-part queries. **Evaluated by clinician panel on 5-point scale. ‡ChatGPT could analyze multiple drugs when presented sequentially, but performance declined with increasing numbers

ChatGPT demonstrated the fastest mean response time (6.8 seconds) compared to all reference tools. Additionally, the platform received the highest usability ratings from the clinician panel, who cited natural language interaction, contextual awareness, and integrating drug interaction information with broader clinical considerations as key advantages.

However, limitations in multi-drug analysis capability were noted, with ChatGPT's performance declining when asked to analyze more than five medications simultaneously. This contrasts with the structured checkers in reference tools, which can efficiently process large medication lists.

4.6. Error Analysis

To better understand ChatGPT's limitations, we conducted a detailed analysis of error patterns across 54 cases where the platform failed to identify or characterize drug interactions correctly. Key findings included:

- **Temporal knowledge limitations**: 42% of errors involved recently approved medications or recently discovered interactions, suggesting limitations in the training data cutoff.
- **Rare interaction mechanisms**: 28% of errors involved unusual or complex interaction mechanisms, particularly those mediated by less common transporters or metabolic pathways.
- **Confidence calibration issues**: In 35% of error cases, ChatGPT expressed high confidence in incorrect information, raising concerns about the reliability of its uncertainty signals.
- **Inconsistent responses**: Repeated identical queries yielded different responses in 23% of cases, indicating inherent variability in the model's outputs.
- **Prompt sensitivity**: Detection accuracy varied by up to 14% depending on how the interaction query was phrased, suggesting dependence on specific query formulations.

5. Discussion

5.1. Key Findings and Implications

Our comprehensive evaluation of ChatGPT's performance in drug interaction detection reveals a nuanced picture with significant implications for clinical application. With an overall accuracy of 78.6%, ChatGPT demonstrated capabilities that exceed chance but fall substantially short of established reference tools (89.4-94.2%). This performance gap was particularly pronounced for critical interactions where the clinical consequences of missed detection could be severe.

Several patterns emerged that help characterize the strengths and limitations of ChatGPT in this domain:

- **Pattern recognition versus comprehensive knowledge**: ChatGPT performed better on everyday, well-established interactions frequently represented in its training data, while struggling with novel therapeutics and recently discovered interactions. This suggests the model primarily relies on pattern recognition rather than a comprehensive, continuously updated knowledge base.
- **Explanation versus detection**: The platform showed relative strengths in providing clear, comprehensive explanations of correctly identified interactions, often outperforming reference tools in generating accessible, contextualized information. This suggests potential value as an educational or explanatory tool rather than a primary detection system.
- **Inconsistent reliability**: The variability in responses to identical queries and sensitivity to prompt formulation raise concerns about consistency in clinical applications, where reliable, reproducible information is essential for safe decision-making.
- **Temporal limitations**: The significant performance gap for recently approved medications highlights the challenge of LLM currency in rapidly evolving fields like pharmacotherapy, where new medications and interaction data emerge continuously.

These findings align with broader research on LLMs in healthcare, suggesting that while these models offer impressive capabilities in information synthesis and natural language interaction, they may not yet achieve the reliability necessary for independent use in critical clinical decision support (Martinez-Martin et al., 2024; Thompson et al., 2024).

5.2. Potential Applications in Clinical Practice

Despite the limitations identified, our findings suggest several potential applications for ChatGPT in drug interaction screening that capitalize on its strengths while mitigating risks:

- **Educational resource**: ChatGPT's ability to generate clear, accessible explanations of interaction mechanisms could support healthcare professional education and patient counseling on medication safety.
- **Supplementary verification**: The platform could serve as a supplementary check after primary screening with established tools, potentially identifying additional considerations or providing alternative perspectives on ambiguous interactions.
- **Narrative synthesis**: ChatGPT could help synthesize information from multiple sources into coherent clinical narratives that integrate interaction data with broader patient factors in complex polypharmacy cases.
- **Accessibility enhancement**: ChatGPT could provide a preliminary screening tool with appropriate acknowledgment of its limitations for settings with limited access to subscription-based interaction databases.

Implementing these roles would require clear communication about the platform's limitations and appropriate safeguards to prevent overreliance on potentially incomplete or inaccurate information.

5.3. Limitations and Strengths

Our study has several limitations that should be considered when interpreting the results:

- **Dynamic nature of LLMs**: ChatGPT undergoes frequent updates and refinements, potentially limiting the temporal stability of our findings. The evaluation reflects the model's capabilities as of January-March 2025.
- **Prompt sensitivity**: While we used standardized prompts, the sensitivity of ChatGPT to query formulation suggests that performance might vary under different real-world querying approaches.
- **Gold standard challenges**: Determining "correct" interaction information can be subjective, particularly for interactions with limited or evolving evidence bases.
- **Limited scope**: Our evaluation focused on binary drug-drug interactions rather than more complex multi-drug interactions or drug-disease interactions that might present different challenges.

Strengths of the study include:

- **Comprehensive evaluation metrics**: Our assessment went beyond simple detection to evaluate multiple dimensions of interaction information quality.
- **Diverse drug sample**: Including medications across therapeutic classes, approval dates, and interaction types enhances generalizability.
- **Blinded evaluation**: Blinded assessment reduces potential bias in comparing LLM outputs with established references.

- **Clinical relevance**: The involvement of practicing clinicians in the evaluation process ensures findings reflect actual clinical information needs.

5.4. Future Directions

Our findings suggest several important directions for future research and development:

- **Specialized fine-tuning**: Investigating whether LLMs specifically fine-tuned on pharmacological literature and drug interaction databases can achieve higher accuracy and reliability.
- **Integration approaches**: Developing and evaluating systems that integrate LLM capabilities with structured drug interaction databases, potentially combining the comprehensiveness of dedicated tools with the natural language capabilities of LLMs.
- **Prompt engineering**: Identifying optimal querying strategies that maximize the accuracy and completeness of drug interaction information retrieved from LLMs.
- **Safety mechanisms**: Developing reliable confidence signals or uncertainty quantification methods that alert users to potential limitations in the model's knowledge.
- **Implementation studies**: Evaluating the impact of LLM-based interaction screening on clinical outcomes and workflow efficiency in controlled implementation studies.
- **Longitudinal performance tracking**: Establishing systems to monitor how LLM performance in drug interaction detection evolves with model updates and expanding pharmaceutical knowledge.

Such research would contribute to integrating these powerful but imperfect tools into clinical practice, maximizing benefits while minimizing potential harms.

6. Conclusion and Recommendations

Our comprehensive evaluation demonstrates that while ChatGPT shows promising capabilities in drug interaction detection, its current performance falls short of the reliability necessary for independent use in clinical decision-making. With 78.6% overall accuracy and particularly concerning gaps in detecting critical interactions, the platform cannot be recommended as a replacement for established drug interaction resources.

Nevertheless, ChatGPT demonstrated notable strengths in generating accessible, contextual explanations of drug interactions and received high clinician usability ratings. These capabilities suggest potential value as a supplementary resource for education, information synthesis, and supporting patient communication about medication safety.

Integrating large language models into clinical practice requires careful consideration of their strengths and limitations. For drug interaction detection, current implementations of ChatGPT may best serve as complementary tools within comprehensive medication safety systems rather than primary reference resources.

As these technologies evolve rapidly, ongoing evaluation will be essential to track improvements in accuracy and reliability. The potential benefits of natural language interaction and contextual awareness that ChatGPT offers may eventually be combined with the comprehensive, reliable knowledge bases of traditional drug interaction tools, creating next-generation resources that enhance medication safety while maintaining the rigorous standards required for clinical practice.

6.1. Recommendations for Healthcare Providers

- **Maintain primary reliance on established drug interaction databases** (Lexicomp, Medscape, Drugs.com) for critical clinical decisions, particularly when evaluating high-risk medications or complex regimens.
- **Consider using ChatGPT as a supplementary tool** for generating patient-friendly explanations of drug interactions, synthesizing complex information, or exploring established interaction mechanisms for educational purposes.
- **Exercise heightened vigilance** when using ChatGPT to evaluate interactions involving recently approved medications (post-2022), as our findings demonstrated particularly low accuracy (52.0%) in this category.
- **Validate critical information** obtained from ChatGPT against established resources before making clinical decisions, especially for severe or contraindicated interactions where ChatGPT demonstrated lower detection sensitivity (64-72%).

- **Report inconsistencies or errors** encountered during use to the platform developers and through appropriate professional channels to contribute to the knowledge base on AI performance in clinical applications.

6.2. Recommendations for Healthcare Organizations and Systems

- **Develop clear institutional policies** regarding the appropriate use of AI tools like ChatGPT in medication safety processes, emphasizing their complementary rather than replacement role.
- **Implement verification protocols** that require cross-checking AI-generated interaction information against validated databases before clinical application.
- **Consider integration opportunities** between established drug interaction databases and LLM interfaces to combine the comprehensive knowledge of traditional tools with the natural language capabilities of ChatGPT.
- **Invest in educational initiatives** to help clinicians understand the capabilities and limitations of AI tools in drug interaction screening, focusing on appropriate use cases and verification practices.
- **Establish monitoring systems** to track the impact of AI tool adoption on medication safety metrics, including rates of adverse drug events, alert override patterns, and clinician satisfaction with decision support.

6.3. Recommendations for Technology Developers

- **Prioritize high-risk interaction detection** in model refinement, as our findings revealed particular weaknesses in ChatGPT's ability to identify contraindicated and severe interactions (64% and 72% accuracy, respectively).
- **Implement confidence indicators** that signal to users when information may be incomplete or uncertain, particularly for recently approved medications, where temporal limitations in training data may impact reliability.
- **Develop specialized fine-tuning** approaches using curated drug interaction databases to improve performance beyond our study's current 78.6% overall accuracy.
- **Create transparent citation capabilities** that link ChatGPT's responses to primary sources or reference databases, enhancing verifiability and clinician confidence.
- **Collaborate with medication safety experts** to establish minimum performance standards for AI tools in drug interaction detection before marketing them for clinical use.

6.4. Recommendations for Education and Training

- **Incorporate critical evaluation of AI tools** into pharmacy, medical, and nursing curricula, using examples from our comparative analysis to illustrate both the potential and limitations of these technologies.
- **Develop continuing education modules** that help practicing clinicians understand appropriate use cases for AI in medication safety, emphasizing the 78.6% accuracy rate and the 4.5/5 explanation clarity score identified in our research.
- **Train healthcare professionals** to effectively communicate AI-derived information to patients, leveraging ChatGPT's strengths in generating accessible explanations while acknowledging its limitations.
- **Create educational frameworks** that maintain core knowledge of high-risk drug interactions among clinicians despite increasing reliance on technological tools.
- **Establish competency assessments** for healthcare professionals using AI tools in medication safety applications to understand verification requirements and limitations appropriately.

6.5. Recommendations for Future Research

- **Conduct longitudinal studies** tracking ChatGPT's performance in drug interaction detection over time as the platform undergoes updates and refinement.
- **Investigate the impact of prompt engineering** on detection accuracy, building on our observation that performance varied up to 14% depending on query formulation.
- **Evaluate real-world implementation outcomes** when ChatGPT is deployed as a supplementary tool in clinical settings, assessing impacts on workflow, decision quality, and medication safety.
- **Explore patient perspectives** on AI-generated drug interaction information, particularly regarding comprehension, trust, and behavioral intentions following exposure.
- **Develop standardized evaluation protocols** for assessing AI tools in medication safety applications, allowing for consistent benchmarking and comparative assessment across platforms and versions.

6.6. Recommendations for Patients and Patient Advocates

- **Approach AI-generated medication information** as a supplementary rather than definitive resource, recognizing the 21.4% error rate identified in our evaluation.
- **Discuss drug interaction concerns** with qualified healthcare providers rather than relying solely on information obtained through AI platforms.
- **Use ChatGPT's explanatory capabilities** to understand established drug interactions better, while verifying the existence of interactions through reliable sources.
- **Report unusual or unexpected drug effects** to healthcare providers promptly, regardless of prior AI-based interaction screening results.
- **Advocate for transparent communication** from healthcare systems about using AI tools in medication safety, including clear information about verification processes and limitations.

By implementing these recommendations, stakeholders can harness the promising capabilities of ChatGPT and similar AI tools while establishing appropriate safeguards to ensure that technological innovation advances rather than compromises medication safety goals. As these technologies evolve, a balanced approach that leverages strengths while mitigating limitations offers the most significant potential for enhancing drug interaction detection and management in clinical practice.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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