

# Discordance in Drug–Drug Interaction Alerts for Antidotes: Comparative Analysis of Electronic Databases and Interpretive Insights from AI Tools

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**Background:** Drug-drug interactions (DDIs) are a critical clinical concern, especially when administering multiple medications, including antidotes. Despite their lifesaving potential, antidotes may interact harmfully with other drugs. However, few studies have specifically investigated DDIs involving antidotes.

**Purpose:** This study evaluated potential DDIs between commonly prescribed medications and antidotes using two widely used electronic databases, along with artificial intelligence (AI) to assess the concordance between these platforms.

**Materials and Methods:** A descriptive analysis was conducted using 50 frequently prescribed medications from the ClinCalc DrugStats Database (2022) and major antidotes as reported by California Poison Control Center. Potential interactions were assessed using Micromedex and WebMD as electronic databases, and ChatGPT and Google Gemini as representative AI. DDI severity levels and documentation quality were recorded, and database/AI agreement was analyzed using the kappa statistic.

**Results:** Overall, 154 potential DDI pairs were identified by the databases (Micromedex: 100, WebMD: 118). Nineteen DDIs were classified as severe by both databases. The overall agreement between databases was poor ( $\kappa = -0.126$ ,  $p = 0.008$ ), indicating significant discrepancies in DDI severity classification. The main mechanisms associated with severe DDIs included serotonin syndrome and QT prolongation, with methylene blue and psychiatric medications being major contributors to severe DDIs. When evaluating the 19 severe DDIs from both databases, the AI models generally aligned with the more severe rating in cases of database discordance. The AI models' consensus was often supported by severity-oriented justifications, highlighting this as a conservative approach to resolving discordant DDI information.

**Conclusion:** Numerous potential DDIs between prescribed drugs and antidotes were identified, with notable inconsistencies between the two databases and AI. This underscores the need to harmonize DDI evaluation criteria across drug information systems and promote clinicians' awareness of inter-database variability. Incorporating comprehensive DDI screening and shared decision-making is essential to ensure safe and effective patient care.

**Keywords:** antidote, drug-drug interaction, micromedex, webMD, ChatGPT, google gemini

## Introduction

In recent years, the rising incidence of human poisoning globally has emerged as a significant public health issue.<sup>1–4</sup> Antidotes are essential for managing poisoned or overdosed patients, as their timely administration can be lifesaving.<sup>5,6</sup> Drug–drug interactions (DDIs) are a significant concern in clinical practice, particularly among patients receiving multiple medications concurrently. Such interactions can lead to adverse drug reactions, diminished therapeutic efficacy, or even life-threatening outcomes.<sup>7,8</sup> Although antidotes are generally required in only specific clinical scenarios, they are often co-administered with a wide variety of other drugs, particularly in emergency and critical care settings. Unfortunately, given their specific pharmacodynamic and pharmacokinetic properties, certain antidotes may significantly



alter the absorption and metabolism of other drugs, or antagonize pharmacological effects of comedications, thereby increasing the risk of harmful interactions.<sup>8,9</sup> To the best of our knowledge, while DDIs are widely studied, no studies providing a comprehensive comparative analysis of the interactions between antidotes and commonly prescribed medications have been reported.

Previous evaluations have demonstrated that commercial drug interaction databases often report discordant results, even when assessing the same drug pairs. For instance, Saverno et al (2011) found that clinical decision-support software varied widely in their ability to detect clinically significant DDIs.<sup>10</sup> Similarly, Vitry (2007) observed notable inconsistencies among four major DDI compendia.<sup>11</sup> These discrepancies raise questions about the reliability of electronic resources used to support prescribing decisions and highlight the importance of independent validation using emerging technologies such as AI. Furthermore, many antidotes are used in time-critical scenarios such as poisoning, overdose, or metabolic emergencies. Their administration must occur promptly—often within minutes to hours—to reverse life-threatening effects. Because these agents are typically administered alongside multiple other medications in emergency or intensive care settings, DDI alerts involving antidotes carry heightened clinical significance and may affect the choice or timing of therapy.

Although clinicians have access to numerous DDI identification tools, Micromedex and WebMD are frequently employed in routine clinical practice. Notably, these two databases often present conflicting information. Previous studies indicated that the performance of electronic databases designed to detect drug interactions during medication processing is highly variable, raising concerns about their clinical reliability.<sup>10,12</sup> However, the absence of standardized criteria for evaluating the clinical significance of DDIs across databases poses a major challenge in clinical decision-making. Discrepancies in DDI classification may lead to inconsistent prescribing practices, clinician confusion, and potential patient harm, especially when managing high-risk medications such as antidotes in acute care settings. Computational methods offer promising alternatives for predicting potential DDIs on a large scale.<sup>13,14</sup> To address inconsistencies among DDI resources, this study examines the potential of artificial intelligence (AI), specifically large language models (LLMs) in the form of ChatGPT and Gemini, in analyzing and reconciling drug interaction databases. Such LLMs have emerged as powerful tools in various fields, including healthcare.<sup>15,16</sup> The use of large language models (LLMs) is also applied in biomedical decision support, with applications ranging from medication management to providing real-time clinical recommendations.<sup>17</sup> These AI models have shown potential to assist healthcare providers by flagging potential drug interactions and helping patients make more informed decisions about their medications.<sup>17</sup> It is important to clarify that in this study, the role of the AI is not to clinically validate these drug-drug interactions. Instead, the LLMs are utilized to provide linguistic and semantic interpretability—that is, to analyze and reconcile the conflicting text-based warnings from the two databases and to generate a structured rationale for a potential consensus. This approach is feasible given that AI models are trained on vast datasets of text and can generate human-like text, understand natural language, and perform complex reasoning tasks.<sup>16,18</sup>

Against this background, this study was implemented to investigate the potential DDIs between frequently prescribed medications and selected antidotes, as detected by two established electronic drug interaction databases and two popular LLMs. By comparing the listed DDIs between these two databases and analyzing the outputs of these two LLMs in their efforts to reconcile the databases' discordant data, we seek to highlight critical interactions that may be clinically relevant, thereby supporting safer prescribing practices. We also emphasize the importance of incorporating comprehensive DDI screening into routine prescribing practice.

## Materials and Methods

### Drug Selection

This descriptive study included a list of frequently prescribed drugs from ClinCalc DrugStats Database in 2022.<sup>19</sup> The list of antidotes was retrieved from the California Poison Control Center.<sup>5</sup> The list of drugs included in this study is shown in [Tables 1](#) and [2](#). The total number of analyzed medicines was 88, which included 50 commonly prescribed drugs and 38 antidotes. Both electronic databases could recognize all 88 items for the determination of potential DDIs. DDI analysis by both electronic databases was conducted on April 15, 2025.

**Table 1** List of Antidotes Used for Detection of Potential DDIs

<b>Antidotes</b>	
<b>Antidote</b>	<b>Indication</b>
Acetylcysteine	Acetaminophen overdose
Atropine	Organophosphate and carbamate poisoning, bradycardia
Botulinum Antitoxin, heptavalent	Botulism
Calcium chloride	Calcium channel blocker overdose, hyperkalemia
Calcium gluconate	Calcium channel blocker overdose, hyperkalemia
Cyproheptadine	Serotonin syndrome
Dantrolene	Malignant hyperthermia
Deferiprone	Iron overload
Deferoxamine	Iron overdose
Digoxin Immune FAB	Digoxin toxicity
Dimercaprol	Heavy metal poisoning (eg, arsenic, lead, mercury)
Edetate calcium Disodium	Lead poisoning
Ethanol	Methanol or ethylene glycol poisoning
Flumazenil	Benzodiazepine overdose
Fomepizole	Ethylene glycol or methanol poisoning
Glucagon	Beta-blocker or calcium channel blocker overdose
Glucarpidase	Methotrexate toxicity
Hydroxocobalamin	Cyanide poisoning
Idarucizumab	Dabigatran reversal
Insulin Regular Human	Hyperkalemia
Levocarnitine	Valproate overdose
Methylene blue	Methemoglobinemia
Naloxone	Opioid overdose
Octreotide	Sulfonylurea-induced hypoglycemia
Pentetate Calcium Trisodium	Radioactive contamination with plutonium, americium, or curium
Pentetate Zinc Trisodium	Radioactive contamination with plutonium, americium, or curium
Physostigmine	Anticholinergic toxicity
Pralidoxime	Organophosphate poisoning
Protamine	Heparin overdose
Prussian Blue	Radioactive or non-radioactive thallium, cesium, or rubidium poisoning
Pyridoxine	Isoniazid overdose
Sodium bicarbonate	Tricyclic antidepressant overdose, salicylate poisoning

(Continued)

**Table 1** (Continued).

<b>Antidotes</b>	
<b>Antidote</b>	<b>Indication</b>
Sodium Thiosulfate, Sodium nitrite	Cyanide poisoning
Sodium Thiosulfate, Sodium nitrite, Amyl nitrite	Cyanide poisoning
Succimer	Lead poisoning
Sugammadex	Rocuronium or vecuronium reversal
Uridine Triacetate	5-Fluorouracil or capecitabine overdose
Vitamin K1 (phytonadione)	Warfarin overdose, vitamin K deficiency

**Table 2** List of Frequently Prescribed Medications Used for Detection of Potential DDIs

<b>Top 50 Drugs</b>		
<b>Drug Class</b>	<b>Pharmacologic Category</b>	<b>Drug Lists</b>
Analgesic	Non-opioid	Acetaminophen
	Nonsteroidal Anti-inflammatory Drug (NSAID)	Ibuprofen meloxicam
Antibiotic	Penicillin	Amoxicillin
Anticoagulant	Direct Oral Anticoagulant (DOAC)	Apixaban
Antidepressant	Norepinephrine/Dopamine Reuptake Inhibitor (NDRI)	Bupropion
	Serotonin/Norepinephrine Reuptake Inhibitor (SNRI)	Duloxetine venlafaxine
	Serotonin Receptor Antagonist and Reuptake Inhibitor (SARI)	Trazodone
	Selective serotonin reuptake inhibitor (SSRI)	Citalopram escitalopram fluoxetine sertraline
Antidiabetic drugs	Biguanides	Metformin
	Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist	Semaglutide
	Insulin	Glargine
	Sulfonylurea	Glipizide
Antigout Agent	Xanthine Oxidase Inhibitor	Allopurinol
Anti-inflammatory drug	Corticosteroid	Fluticasone prednisolone
Antihypertensive drug	Angiotensin converting enzyme	Lisinopril
	Angiotensin receptor blocker	Losartan
	Beta blocker	Carvedilol metoprolol
	Calcium channel blocker	Amlodipine
	Diuretic	Hydrochlorothiazide furosemide
Antilipemic drugs	HMG-CoA Reductase Inhibitor (Statins)	Atorvastatin pravastatin rosuvastatin simvastatin

(Continued)

**Table 2** (Continued).

Top 50 Drugs		
Drug Class	Pharmacologic Category	Drug Lists
Antiplatelet Agent	Thienopyridine	Clopidogrel
	Salicylate group	Aspirin
Antiseizure Agent	Gaba Analog	Gabapentin
Bronchodilator	Beta-2 agonist	Albuterol
Drugs used in ADHD	Central Nervous System Stimulant	Dextroamphetamine methylphenidate
Drugs used in asthma and allergy	Leukotriene receptor antagonists	Monteluklast
	Antihistamine	Cetirizine hydroxyzine
Drugs used in Benign Prostatic Hypertrophy	Alpha <sub>1B</sub> blocker	Tamsulosin
Drugs used in Peptic Ulcer and Gastro-Oesophageal Reflux Disease (Gord)	Histamine H <sub>2</sub> Antagonist	Famotidine
	Proton pump inhibitors	Omeprazole pantoprazole
Hormone supplement	Estrogen Derivative	Estradiol
Hypnotic drugs	Benzodiazepine	Alprazolam
Muscle Relaxant	Centrally Acting Agents	Cyclobenzaprine
Thyroid agents	Thyroid hormone	Levothyroxine
Vitamin and Mineral	Electrolyte Supplement	Potassium chloride
	Vitamin D analog	Ergocalciferol

To identify commonly co-prescribed medications for analysis, we retrieved the list of the top 50 most frequently prescribed outpatient drugs from the ClinCalc DrugStats Database (2022). This publicly accessible and literature-based database compiles prescription data from the Medical Expenditure Panel Survey (MEPS), a comprehensive dataset representative of the US outpatient population. We chose this database due to its systematic methodology, reproducibility, and relevance in pharmacoepidemiologic studies. It should be noted that we did not rely on manual selection or specific EMR datasets to avoid selection bias.

## Databases

In this study, we utilized two key databases: IBM Watson's Micromedex and WebMD. Micromedex is a subscription-based resource offering comprehensive information on drugs, literature-based content on pharmaceuticals, disease states, and various tools supporting clinical decision-making. It is widely used by healthcare professionals. Access to Micromedex was facilitated through Mahidol University's institutional license (2025). WebMD, established in 1996, has become one of the most widely used online resources for health information, providing easily accessible, expert-reviewed content on medical conditions, treatments, and preventive care. Articles and tools on this site undergo rigorous peer review by qualified health professionals, ensuring reliability and clinical accuracy. This platform is run by a US-based company that is primarily known for publishing online news and information focused on human health and wellness. WebMD features a drug interaction checker that enables users to cross-reference multiple medications, including herbal supplements and over-the-counter drugs.<sup>20</sup>

In terms of AI models used here, ChatGPT, developed by OpenAI, is a generative pretrained transformer. Its foundation lies in its "transformer architecture" a deep learning technique, and it has been trained on massive datasets sourced from the internet.<sup>16</sup> This extensive training allows ChatGPT to effectively process complex information.<sup>16</sup>

Similarly, Gemini, developed by Google, is an advanced LLM also capable of the understanding of complex natural language, text generation, and delivery of comprehensive, informative answers.<sup>21,22</sup> Both models offer capabilities pertinent to DDI analysis, including the processing of large-scale data, information summarization, and pattern recognition.<sup>23</sup> In this study, the ChatGPT model and Gemini 2.5 Pro model were used, which were chosen because they were the most advanced reasoning models available when the study was performed in May 2025.

## Classification of DDI Severity and Documentation

DDI severity was evaluated using Micromedex and WebMD. Both systems use a four-level classification scheme (*contraindicated/do not use* together as severity level 1, *major/serious* as severity level 2, *moderate/monitor closely* as severity level 3, and *minor* as severity level 4). Specifically, Micromedex categorizes interactions as contraindicated, major (potentially life-threatening and requiring medical intervention to minimize or prevent serious adverse effects), moderate (may worsen the patient's clinical condition and necessitate therapy adjustments), or minor (typically having limited clinical effects; may elevate the incidence or intensity of adverse effects but unlikely to require major modifications to the therapeutic plan).<sup>24</sup> In addition to severity classification, Micromedex also provides documentation ratings to indicate the strength of evidence supporting the assertion that each interaction actually occurs. These include *excellent* (the existence of the interaction has been supported by controlled investigations); *good* (strong support for the interaction, although insufficient well-controlled trials have been performed); *fair* (limited documentation of the interaction, but pharmacological evidence suggests it is likely); and *unavailable* (supporting data not provided). Similarly, WebMD classifies DDIs into four categories: do not use together, serious, monitor closely, and minor.<sup>25</sup> For the first of these, the drugs should not be used together due to the high risk of a potentially dangerous interaction. For *serious interactions*, close medical monitoring of patients administered the two drugs in question is required or alternative therapies should be considered. The category of *monitor closely* denotes a clinically significant interaction that necessitates surveillance by a healthcare provider. Finally, *minor interactions* are unlikely to produce substantial adverse outcomes.

## AI Adjudication and Prompting

### AI Tools and Versions

The specific models utilized were OpenAI's ChatGPT (based on the o3 model) and Google's Gemini (version 2.5 Pro). These models were selected based on their state-of-the-art reasoning capabilities as of May 2025, when the AI analysis was conducted. To simulate a practical clinical workflow, the LLMs will be accessed via their standard, publicly available web-based chat interfaces rather than through an Application Programming Interface (API). The primary web portals used to access the models were <https://chatgpt.com> for ChatGPT and <https://gemini.google.com/app> for Gemini. The models will be provided with specific prompts designs to systematically compare, synthesize, and reconcile the DDI outputs from Micromedex and WebMD.

### Prompting Technique

To ensure consistency and reproducibility, a standardized prompt template was used for all DDI queries. Comparison results from Micromedex and WebMD were compiled in a table format and provided to the LLMs as a PDF file. The following prompt was used:

“You are an AI expert pharmacologist. Your task is to analyze a report containing 19 potential drug-drug interactions (DDIs). For each DDI, you will be provided with severity ratings from two electronic databases: Micromedex and WebMD.

The severity categorizations are as follows:

- **Micromedex:**
  - Level 1: Contraindicated
  - Level 2: Major
  - Level 3: Moderate
  - Level 4: Minor

- **WebMD:**
  - Level 1: Do not use together (considered equivalent to Micromedex Level 1)
  - Level 2: Serious (considered equivalent to Micromedex Level 2)
  - Level 3: Monitor Closely (considered equivalent to Micromedex Level 3)
  - Level 4: Minor Interaction (considered equivalent to Micromedex Level 4)

For each of the 19 DDIs, you are required to:

1. **Identify Concordance/Discordance:** Determine if the severity ratings from Micromedex and WebMD are concordant (ie, they map to the same equivalent level) or discordant (they map to different equivalent levels).
  2. **Establish a Consensus Severity Level:** Assign a single, definitive consensus severity level for the interaction (eg, “Contraindicated” “Major” “Moderate” or “Minor” using the Micromedex terminology or specifying the Level number).
    - If the ratings are concordant, the consensus level should reflect this agreed-upon severity.
    - If the ratings are discordant, apply your expert pharmacological judgment to determine the most clinically appropriate consensus severity level. In cases of uncertainty or differing severities, the more conservative (ie, more severe) rating should generally be prioritized unless a strong mechanistic argument supports a lower severity.
1. **Provide a Brief Mechanism Detail:** Concisely describe the pharmacological mechanism(s) underlying the potential drug-drug interaction.
  2. **Justify Your Consensus Decision:** Clearly explain the rationale for your assigned consensus severity level. This justification is particularly important for discordant cases and should be based on the interaction’s mechanism, potential clinical significance, and the implications of the differing database classifications.

**Input Format Expectation:** Assume you will receive the information for each DDI listing the two drugs involved, the Micromedex rating, and the WebMD rating.

**Output Format Expectation:** For each DDI, please present your analysis clearly, including:

- The drug pair involved in the interaction.
- The Micromedex-assigned severity.
- The WebMD-assigned severity.
- A statement of concordance or discordance.
- Your final consensus severity level.
- A brief description of the interaction mechanism.
- A detailed justification for your consensus decision.”

**Evaluation of AI Outputs** For this initial descriptive study, we directly extracted the severity rating and rationale from the AI’s response to the standardized prompt. A formal scoring rubric or a human consensus review was not part of the methodology, a limitation that should be addressed in future validation studies.

**Example Structured Output:**

“Methylene blue - Bupropion

- **Micromedex Rating:** Contraindicated (Level 1)
- **WebMD Rating:** Serious (Equivalent to Major - Level 2)
- **Concordance/Discordance:** Discordant
- **Consensus Severity Level:** Contraindicated (Level 1)

- **Brief Mechanism Detail:** Methylene blue is a potent monoamine oxidase inhibitor (MAOI). Bupropion inhibits the reuptake of dopamine and norepinephrine and also has some MAOI activity. Co-administration significantly increases the risk of serotonin syndrome and potentially hypertensive crisis.
- **Justification for Consensus Decision:** Although WebMD rates the interaction as Serious (Major), the known potent MAOI activity of methylene blue and the potential for severe, life-threatening serotonin syndrome or hypertensive crisis warrants the more conservative “Contraindicated” rating from Micromedex. The risk of severe adverse events outweighs potential benefits.”

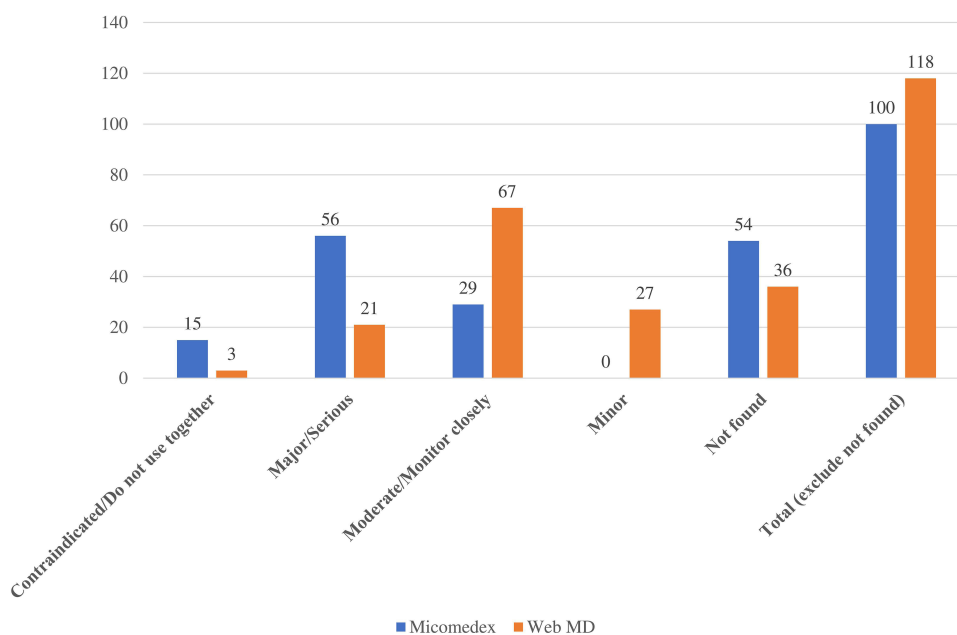
## Data Analysis

The data were analyzed using SPSS version 30 (SPSS Inc., US). To evaluate the consistency between the DDIs detected by the two databases, the kappa statistic was employed. A kappa score ranging from 1.00 to 0.81 represented near-perfect agreement, 0.80 to 0.61 signified substantial agreement, 0.60 to 0.41 denoted moderate agreement, 0.40 to 0.21 reflected fair agreement, 0.20 to 0.00 indicated slight agreement, and values below 0.00 suggested poor agreement.

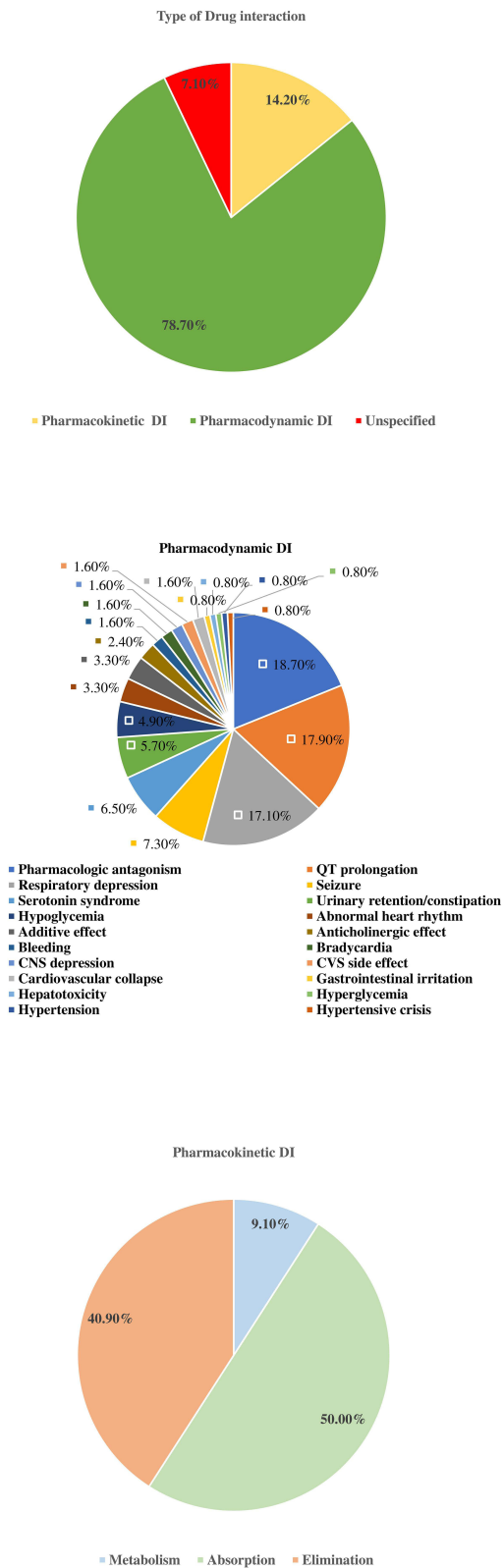
## Results

Among the 50 frequently prescribed medications and antidotes analyzed, a total of 154 potential DDIs were identified. Micromedex detected 100 DDI pairs, classifying their severity as follows: contraindicated, 15; major, 56; moderate, 29; and minor, 0. Meanwhile, WebMD reported 118 DDI pairs, which were categorized as follows: do not use together, 3; serious, 21; monitor closely, 67; and minor interactions, 27 (Figure 1).

Among the DDIs identified by both databases, the predominant mechanisms associated with their effects were as follows: pharmacological antagonism, hypoglycemia, additive central nervous system depression, serotonin syndrome, and QT interval prolongation. Less common mechanisms involved additive anticholinergic effects, increased bleeding risk, impaired drug absorption, and other interactions, as detailed in Figure 2. Interestingly, 19 potential DDIs were consistently classified as severe (contraindicated/major or do not use together/serious) by both databases (Table 3). The documentation levels of potential DDIs as reported by Micromedex were good and fair. Overall, the kappa statistic was  $-0.126$  ( $p$ -value = 0.008), indicating poor agreement in the classification of DDI severity between the two databases (Table 4).



**Figure 1** Comparison of severity classifications of potential drug–drug interactions (DDIs) between Micromedex and WebMD.



**Figure 2** Probable mechanisms of drug–drug interactions (DDIs) between 38 antidotes and 50 commonly prescribed medications.

**Table 3** Severe Drug-Drug Interaction Reported with High Concurrence Between Micromedex and Web MD

No	Drug	Micromedex	Web MD	Effect
1	Methylene blue-Bupropion	Contraindicated	Serious	Increased risk of serotonin syndrome
2	Methylene blue-Dextroamphetamine	Contraindicated	Serious	Increased risk of serotonin syndrome
3	Methylene blue-Citalopram	Contraindicated	Serious	Increased risk of serotonin syndrome
4	Methylene blue-Cyclobenzaprine	Contraindicated	Serious	Increased risk of serotonin syndrome
5	Methylene blue-Cyproheptadine	Contraindicated	Do not use together	Increased risk of CNS depression
6	Methylene blue-Duloxetine	Contraindicated	Serious	Increased risk of serotonin syndrome
7	Methylene blue-Escitalopram	Contraindicated	Serious	Increased risk of serotonin syndrome
8	Methylene blue-Fluoxetine	Contraindicated	Do not use together	Increased risk of serotonin syndrome
9	Methylene blue-Sertraline	Contraindicated	Serious	Increased risk of serotonin syndrome
10	Methylene blue-Trazodone	Contraindicated	Serious	Increased risk of serotonin syndrome
11	Methylene blue-Venlafaxine	Contraindicated	Serious	Increased risk of serotonin syndrome
12	Atropine-Glucagon	Major	Serious	Increased risk of gastrointestinal side effects.
13	Dantrolene-Amlodipine	Major	Do not use together	Severe hyperkalemia with cardiovascular collapse
14	Ethanol-RI	Major	Serious	May result in impaired glucose regulation
15	Ethanol-Glargine	Moderate	Serious	May result in impaired glucose regulation
16	Ethanol-Glulisine	Major	Serious	May result in impaired glucose regulation
17	Ethanol-Metformin	Moderate	Serious	May result in an increased risk of lactic acidosis
18	Ethanol-Glipizide	Major	Serious	May result in prolonged hypoglycemia, disulfiram-like reactions
19	Octreotide-Trazodone	Major	Serious	May result in an increased risk of QT interval prolongation

**Table 4** Assessment of Concordance Between Two Drug Interaction Databases

Category	Kappa	95% CI	p-value	Strength of Agreement
Contraindicated	0.196	-0.205 to 0.598	0.338	Fair agreement
Major	-0.085	-0.281 to 0.110	0.391	Poor agreement
Moderate	-0.046	-0.217 to 0.126	0.602	Poor agreement
Minor	0.000	-0.343 to 0.343	1.000	Slight agreement
Not found	-0.390	-0.575 to -0.205	< 0.001	Poor agreement
Overall	-0.126	-0.218 to -0.033	0.008	Poor agreement

Tables 5 and 6 demonstrate the utility of LLMs, specifically ChatGPT (o3) and Gemini (2.5 Pro), in adjudicating discrepancies identified in DDI severity ratings between the Micromedex and WebMD databases. Table 7 quantifies the alignment of ChatGPT and Gemini with either Micromedex or WebMD in these 19 instances. The findings reveal

**Table 5** Large Language Model (ChatGPT and Gemini) Analysis of Drug-Drug Interaction Severity: Consensus Between Micromedex and Web MD Ratings

No	Drug-Drug Interactions	Micromedex	Web MD	ChatGPT (o3)	Gemini (2.5 Pro)
1	Methylene blue-Bupropion	1	2	1	1
2	Methylene blue-Dextroamphetamine	1	2	1	1
3	Methylene blue-Citalopram	1	2	1	1
4	Methylene blue-Cyclobenzaprine	1	2	1	1
5	Methylene blue-Duloxetine	1	2	1	1
6	Methylene blue-Escitalopram	1	2	1	1
7	Methylene blue-Sertraline	1	2	1	1
8	Methylene blue-Trazodone	1	2	1	1
9	Methylene blue-Venlafaxine	1	2	1	1
10	Dantrolene-Amlodipine	2	1	1	1
11	Ethanol-Glargine	3	2	2	2
12	Ethanol-Metformin	3	2	2	2
13	Methylene blue-Cyproheptadine	1	1	2	1
14	Methylene blue-Fluoxetine	1	1	1	1
15	Atropine-Glucagon	2	2	2	2
16	Ethanol-RI	2	2	2	2
17	Ethanol-Glulisine	2	2	2	2
18	Ethanol-Glipizide	2	2	2	2
19	Octreotide-Trazodone	2	2	2	2

**Notes:** Severity Level Key; 1 = Contraindicated/ Do not use together, 2 = Major/ Serious, 3 = Moderate / Monitor Closely.

**Table 6** Large Language Model (LLM) Adjudication and Rationale for Discordant DDI Rating

No	Drug-Drug Interactions	Micromedex	Web MD	LLM Consensus Severity	Consensus Aligns with	LLM Rationale for Consensus (As an Example)
1	Methylene blue-Bupropion	Level 1	Level 2	Level 1	Micromedex	Labelled absolute contraindication; hypertensive crisis risk mandates highest level.
2	Methylene blue-Dextroamphetamine	Level 1	Level 2	Level 1	Micromedex	Fatal pressor events reported; FDA requires 14-day wash-out.
3	Methylene blue-Citalopram	Level 1	Level 2	Level 1	Micromedex	Multiple case reports and boxed warnings; must avoid.
4	Methylene blue-Cyclobenzaprine	Level 1	Level 2	Level 1	Micromedex	Pharmacology identical to TCA/MAOI combos; potentially lethal.

(Continued)

**Table 6** (Continued).

No	Drug-Drug Interactions	Micromedex	Web MD	LLM Consensus Severity	Consensus Aligns with	LLM Rationale for Consensus (As an Example)
5	Methylene blue-Duloxetine	Level 1	Level 2	Level 1	Micromedex	Multiple case reports and boxed warnings; must avoid.
6	Methylene blue-Escitalopram	Level 1	Level 2	Level 1	Micromedex	Multiple case reports and boxed warnings; must avoid.
7	Methylene blue-Sertraline	Level 1	Level 2	Level 1	Micromedex	Multiple case reports and boxed warnings; must avoid.
8	Methylene blue-Trazodone	Level 1	Level 2	Level 1	Micromedex	Severe serotonin-syndrome cases exist; safest to avoid.
9	Methylene blue-Venlafaxine	Level 1	Level 2	Level 1	Micromedex	Consensus as above.
10	Dantrolene-Amlodipine	Level 2	Level 1	Level 1	Web MD	Fatalities with CCBs + dantrolene; choose stricter level.
11	Ethanol-Glargine	Level 3	Level 2	Level 2	Web MD	Greater duration pushes risk to Major.
12	Ethanol-Metformin	Level 3	Level 2	Level 2	Web MD	Potentially fatal outcome justifies higher severity.

**Table 7** Summary of LLM Alignment in DDI Cases (N=19)

LLM Analysis	Alignment with Micromedex (Stricter Rating in /19 Cases)	Alignment with WebMD (Stricter Rating in /19 Cases)
ChatGPT (o3)	15 (78.95%)	9 (47.37%)
Gemini (2.5 Pro)	16 (84.21%)	10 (52.63%)
Both LLMs	15 (78.95%)	9 (47.37%)

a consistent pattern: When source database ratings were discordant, these LLMs predominantly established a consensus by aligned with the more severe rating. This is evidenced by their selection of Level 1 (Contraindicated) or Level 2 (Major) severities in such instances. For example, in several methylene blue interactions where Micromedex assigned a rating of “Level 1-Contraindicated” while WebMD assigned “Level 2-Serious” both LLMs defaulted to the “Level 1” classification. Similarly, when WebMD presented a more severe rating for certain ethanol interactions than Micromedex did, the LLM-derived consensus gravitated towards WebMD’s higher severity.

## Discussion

WebMD reported 20% more potential DDIs than Micromedex did which can be explained by it being designed primarily for the general public, with the aim of providing accessible, easy-to-understand information about health and wellness, including drug-related issues. As such, WebMD tends to report a broader range of potential drug interactions, including those with limited clinical significance, to ensure that users are fully informed and exercise caution. However, knowledge of the potential DDIs reported on WebMD may not necessarily be beneficial in clinical practice. For example, the use of pyridoxine with estradiol can lower the former’s level due to changes in metabolism, while the concurrent use of sodium bicarbonate and lisinopril can reduce the latter’s effects, although the exact mechanism is unclear. Such drug interaction pairs are not reported by Micromedex, which can be explained by an excessive number of potential DDI alerts with insufficient documentation potentially resulting in alert fatigue for both healthcare providers and patients. Meanwhile, some significant DDIs were not listed on WebMD. This may be explained by the fact that Micromedex caters mainly to healthcare professionals such as physicians and pharmacists, who require clinically validated, evidence-based

information.<sup>2</sup> Consequently, Micromedex prioritizes interactions that are strongly supported by clinical studies and have clear therapeutic implications. Interestingly, we also observed that the two databases reported varying levels of severity for some potential DDI pairs. This significant finding could lead to drug-related issues in pharmacotherapy and may create conflicts between patients and healthcare providers when these groups have access to different information about the suitability of particular drug pairs. For instance, Micromedex, which is favored by healthcare providers, classified the severity of the potential DDI between flumazenil and alprazolam as *contraindicated*. Meanwhile, in WebMD, which is primarily used by patients, this interaction was not reported. In contrast, Micromedex found no potential DDI between protamine and clopidogrel, while WebMD categorized this potential DDI as *serious*. This is due to Micromedex, commonly used by healthcare providers, reporting no concerns regarding this DDI, while WebMD, typically used by patients, classifies it as a major potential DDI. When discrepancies of this kind occur, it is preferable to prioritize the more severe DDI report from the two databases to prevent patient complications and minimize medical liability.

According to the kappa statistic for severity agreement of potential DDIs, poor agreement was observed between the two electronic databases. This might be due to the measurement parameter of severity ratings in an ordinal scale, and more than half of potential DDIs classified by Micromedex were group 2 (Major/serious, n=56), meanwhile WebMD was group 3 (moderate/monitor closely, n=67). In addition, the discrepancy between Micromedex and WebMD may also stem from differences in documentation practices. Micromedex provides explicit references and evidence ratings (eg, “excellent” “good” “fair”), enabling clinicians to assess the reliability of each DDI alert based on clinical studies or pharmacologic rationale. In contrast, WebMD does not consistently disclose its evidence sources or grading criteria, limiting transparency and scientific appraisal.<sup>11,20</sup> While WebMD’s consumer-oriented design may favor broader inclusion of potential interactions, this does not necessarily reflect a more conservative or safety-driven approach. Instead, its emphasis appears to be on maximizing public awareness, even at the expense of clinical specificity.

We observed that over 80% of the probable mechanisms of potential DDIs between antidotes and commonly used medications were pharmacodynamic, rather than pharmacokinetic. Since antidotes are intended to neutralize or counteract the pharmacological action of harmful agents directly at their site of action (eg, receptor blockade, competitive inhibition, or chemical neutralization), it is reasonable for the interactions in which they are involved to predominantly affect pharmacodynamic processes.<sup>26</sup> Therefore, pharmacological antagonism was found to be the most common mechanism behind the DDIs. The most common serious toxicology-related conditions associated with these interactions were serotonin syndrome and QT prolongation. Serotonin syndrome results from drug interactions between methylene blue and Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), and the evidence supporting this is largely considered to be of good quality. Previously, case reports have described serotonin syndrome caused by methylene blue, with most studies occurring in the field of anesthesiology, so the use of methylene blue as an antidote was not addressed.<sup>27–29</sup> Clinicians should be aware of the potential of drug interactions between methylene blue as an antidote for treating methemoglobinemia and other medications to result in serotonin syndrome. This highlights the need for particular caution given that serotonin syndrome is a relatively common toxicological condition, occurring in approximately 14–16% of toxicological cases,<sup>28</sup> and has a mortality rate of 2%–12%.<sup>30</sup>

While this study focused primarily on pharmacodynamic mechanisms as the dominant contributors to antidote-related DDIs, it is important to recognize that patient-specific factors—particularly pharmacogenomic variability—can significantly influence these interactions. For example, polymorphisms in cytochrome P450 enzymes such as CYP2D6 and CYP2C19, which are involved in the metabolism of many antidepressants, may alter plasma concentrations and increase susceptibility to serotonergic toxicity when combined with methylene blue.<sup>31,32</sup> Similarly, impaired renal or hepatic function, age-related changes in drug clearance, or underlying neurological or cardiovascular conditions may exacerbate the risks associated with QT prolongation or CNS depression.<sup>33</sup> These host-related factors may account for interindividual variability in DDI severity and suggest that static database-based assessments could be complemented by personalized risk stratification in future research.

To enhance clinical utility, the integration of a risk stratification framework may help guide prescribers in managing DDIs involving methylene blue and serotonergic agents. Such a framework could consider factors including: (1) the serotonergic load of the co-prescribed agent (eg, high-potency SSRIs like fluoxetine vs lower-potency agents), (2) the

half-life and accumulation risk of the serotonergic drug, (3) patient-specific vulnerability (eg, genetic polymorphisms affecting drug metabolism or blood-brain barrier function), and (4) documented case reports or severity grading in major databases.<sup>27–29,34</sup> Based on these elements, clinicians may classify the interaction risk into low (eg, short-acting agents with minimal serotonergic activity), moderate (eg, agents with potential interaction but short half-life), and high (eg, long-acting, potent serotonergic agents with boxed warnings). While this stratification is preliminary and hypothesis-generating, it may facilitate safer clinical decisions pending further validation in real-world studies.

Our studies indicate that psychiatric medications, particularly antidepressants, exhibit the highest incidence of DDIs with antidotes among the different drug classes. One possible explanation for this is the complex pharmacodynamic and pharmacokinetic profiles of psychiatric agents. Specifically, psychiatric medications, particularly antidepressants (eg, SSRIs, SNRIs) and antipsychotics, frequently modulate neurotransmitter systems such as those of serotonin, dopamine, and norepinephrine. These neurotransmitter pathways are not only highly interconnected but also involved in numerous physiological processes beyond psychiatric symptoms, making psychiatric drugs inherently prone to interactions with agents exerting systemic physiological effects, such as antidotes.<sup>1,2</sup> Moreover, many psychiatric agents are known to prolong the QT interval, lower the seizure threshold, or alter autonomic regulation.<sup>3</sup> By their nature, antidotes often act on critical pathways (eg, cardiovascular, neurological, or metabolic systems) in acute or emergency settings, which increases the likelihood of additive or synergistic adverse effects when used in combination with psychiatric drugs. In fact, a previous study showed that, among psychiatric outpatients receiving antidepressants, 48.1% were at risk of drug interactions with other psychiatric medications, and 9.2% with non-psychiatric drugs.<sup>35</sup> Elsewhere it was reported that 43.6% of patients on CYP450 enzyme inducers or inhibitors experienced drug interactions involving this enzyme.<sup>36</sup> Additionally, data from US Poison Centers (2016–2023) highlight that antidepressants, especially SNRIs, SSRIs, benzodiazepines, and sedatives, are the most drugs commonly implicated in suicide attempts among elderly individuals.<sup>37</sup> It is thus crucial for healthcare providers to understand the potential drug interactions between psychiatric medications and antidotes to ensure effective and safe patient care.

A previous study demonstrated marked differences in listed DDIs among databases.<sup>12,38</sup> However, to the best of our knowledge there have been no comprehensive evaluations of the accuracy of severity classifications in drug interaction databases for interactions between antidotes and other drugs. To bridge this research gap, here we performed kappa analyses to evaluate the discrepancies in DDIs of this type between two electronic databases. Our results revealed poor agreement in the classification of DDI severity between these databases. Such differences could be attributable to the use of a wide range of information sources, such as publications in languages other than English, and inconsistencies in the inclusion of drug company reports that are not publicly available, national post-marketing surveillance reports, and product information summaries, which often vary between countries and include broad class labels. The clinical importance of this information is often unclear due to the lack of access to the original supporting evidence in its entirety. The limited epidemiological studies on drug interactions are also problematic because such studies frequently use only one drug interaction database, do not sufficiently clarify which interactions are of the greatest concern, and do not adequately control for potential confounding variables.<sup>11</sup> Moreover, the variability in criteria for identifying drug interactions means that some databases might classify drugs with similar or different mechanisms of action as being involved in a drug interaction, while other databases do not consider them to interact. This issue is made worse by the absence of established guidelines for classifying the severity of drug interactions or determining the best method for assessing their clinical relevance. In real-world clinical practice, discrepancies between drug interaction databases present a challenge for healthcare providers. Clinicians often manage conflicting DDI information by consulting multiple resources, applying clinical judgment, or following institutional policies that emphasize patient safety. Patel and Beckett (2016) noted that many practitioners adopt a conservative strategy by defaulting to the most severe interaction classification when faced with discordant database outputs. While this approach may minimize risk, it may also lead to alert fatigue or the unnecessary avoidance of beneficial drug combinations. Thus, the use of AI tools to adjudicate such discrepancies—particularly when aligned with conservative safety principles—may offer a promising adjunct to clinical decision-making.

The application of LLMs for evaluating DDI severity, as demonstrated in this study, reveals a notable inclination towards conservative, safety-oriented decision-making. In our analysis, the Large Language Models (LLMs)

demonstrated a tendency to align with the more severe drug-drug interaction (DDI) classification when presented with discordant information from the databases. It is crucial, however, to frame this finding as a preliminary, study-specific observation rather than a validated, inherent characteristic of these models. We explicitly state that this is a hypothesis-generating finding that requires rigorous statistical support and further validation in future studies before any conclusions can be drawn about a “safety-oriented” inclination. Furthermore, this observation must be contextualized within the significant limitations of using AI in a clinical capacity. The “black box” nature of current LLM reasoning presents a considerable challenge; the inability to scrutinize the algorithmic pathway is a fundamental barrier to clinical trust and error analysis. The AI-adjudicated ratings should be understood as unverified algorithmic outputs, not as clinically validated recommendations. To eventually integrate these models as a support for clinical decision-making, light needs to be shone on the inner workings of LLMs. Specifically, before LLMs can be responsibly adopted for widespread clinical use in managing DDIs, there is a need for extensive research to reveal how they reach their decisions, ensure the reliability of their outputs across diverse scenarios, and confirm their clinical validity and utility in real-world settings.

To the best of our knowledge, this is the first study to focus on DDIs involving antidotes, a drug group of high urgency but limited representation in prior research. The inclusion of real-time AI adjudication to address inter-database discordance is also novel, particularly in the context of high-risk, time-sensitive therapeutic agents. These aspects highlight the clinical relevance and methodological contribution of the current study. However, this study has several limitations that must be acknowledged. First, our findings are based on a limited set of 38 antidotes and 50 co-prescribed medications, and the results may not be generalizable to all drug classes. Second, the study’s reliance on only two databases, Micromedex and WebMD, introduces a potential selection bias, as other authoritative resources like Lexicomp or Stockley’s Drug Interactions were not included and could have altered the findings. Third, the DDI analysis represents a cross-sectional “snapshot” from April-May 2025. While this approach establishes the existence of discordance, the specific data in these dynamic databases will change over time. Finally, and most importantly, this study did not include a formal validation of the AI outputs against expert clinical judgment. The AI’s “consensus” ratings are unverified algorithmic outputs. Key performance metrics such as accuracy, hallucination risk, and reproducibility were not assessed, and these are critical directions for future research. All of the issues raise concerns about the consistency and comprehensiveness of drug interaction reporting across the databases. Therefore, to optimize treatment outcomes while minimizing adverse effects, healthcare professionals should be encouraged to consult multiple databases when evaluating potential DDIs. For future work, it would be valuable to evaluate a broader range of drug interaction resources (eg Medscape, Lexicomp, Stockley’s Drug Interactions) and some subscription-based AIs that were not used in the current study due to subscription constraints or limited availability through the institution’s library system. Additionally, further studies involving more extensive efforts to compare clinical management recommendations across all available resources should be considered.

## Conclusion

In this study, a substantial number of potential DDIs between commonly prescribed medications and antidotes were identified, based on data from Micromedex and WebMD. Serotonin syndrome and QT prolongation emerged as the most common mechanisms associated with serious potential interactions, with methylene blue and psychiatric medications being major contributors to severe DDIs. The low concordance between the two databases underscores the need to harmonize DDI risk evaluation and interpretation, in order to generate standardized information for prescribers. As promising tools to achieve this, AI models preliminarily showed a conservative tendency in resolving DDI discrepancies, aligning with more severe ratings as justified by the need to prioritize patient safety; however, it is critical to emphasize that these AI models are analytical tools and should be viewed as supportive, not substitutive, of expert clinical interpretation and judgment, and essential to perform further validation of the reliability of these models and to shed more light on their inner working. Both patients and healthcare providers should be made aware of discrepancies in presented DDI-related information between resources, and collaborative decision-making should be encouraged when clinically significant DDIs are identified, to minimize potential harm and ensure patient safety. The findings presented are preliminary and must be validated across more diverse drug groups. Future work should focus on actionable steps, such as developing AI-assisted consensus platforms to flag discrepancies for human expert review and creating a multi-phase

study plan to formally validate LLM performance against a gold standard of clinical judgment. These steps are essential to responsibly harness AI to improve the safety and reliability of clinical decision support systems.

## Abbreviations

AI, artificial intelligence; DDIs, drug–drug interactions; eg, *exempli gratia*; LLMs, large language models; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; US, United States.

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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