

Drug–Drug Interactions in Outpatient Private Clinic Settings vs. Hospital Settings: A Systematic Review and Comparative Analysis

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ABSTRACT: Drug–drug interactions (DDIs) are a major source of adverse drug events (ADEs) that are potentially preventable in the healthcare system worldwide. The present literature lacks a comparative and rigorous synthesis. The objective of our study was to systematically identify, appraise and synthesize evidence on the prevalence, severity, types, and management outcomes of DDIs occurring between the private clinic and hospital settings, and the factors that contribute to the occurrence of DDIs at the patient and system levels are the objective of our study. PubMed, Scopus, Web of Science and Google Scholar were used for literature search from January 2015 to May 2026. Direct or indirect comparative data on DDIs in private clinic versus hospital outpatient or inpatient setting was required for eligibility. Using the Newcastle–Ottawa Scale (NOS) as well as Cochrane RoB 2.0, risk of bias was determined. Narrative synthesis and data extraction in tables were conducted. Forty-two studies (n ≈ 2.1 million patient records) were included. The prevalence of DDI varied from 10.3%–67.4% in settings. The rates of clinically severe DDIs were significantly higher in hospital than in private clinics (mean 28.4% vs. 15.7%) due to the higher prevalence of multimorbidity and older age of inpatients. The detection rate for DDI, pharmacist interventions and integration of CDSS were much lower at private clinics. The conclusion reported that the DDI are common, clinically important, and occur in unique ways in both settings. Patient complexity results in higher severity DDIs in hospitals, while structural limitations in private clinics result in under-detection. The need for targeted pharmacovigilance, mandatory CDSS adoption and cross-setting medication reconciliation are all very much current priorities.

Keywords: Adverse drug events; Clinical decision support systems (CDSS), Drug-drug interactions (DDIs); Medication reconciliation; Pharmacovigilance



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1. INTRODUCTION

1.1 Background and Rationale

Drug–drug interactions (DDIs) are the changes in the pharmacodynamics, pharmacokinetics or both of a drug caused by another drug administered simultaneously, that lead to an unexpected clinical effect, which can be mild or severe, or even life-threatening [1,2]. Worldwide, it is estimated that DDIs cause 3%–6% of all hospital admissions, and are responsible for ~125,000 deaths per year in the United States alone, and represent billions of dollars of preventable healthcare costs [3,4].

The clinical context (where prescriptions are made) significantly influences the risk, detection and management of DDI. There are several structural, human resource and technological differences between hospitals and private clinics, such

as: complexity of patient case-mix, number of clinicians, presence of clinical pharmacists, integration of clinical decision support systems (CDSS), complete history of patients' medications, or extent of monitoring [5–7]. Although these differences in clinical practice are well recognised none of them has yet been fully explored through a systematic review and comparison of DDI profiles in these two archetypal healthcare settings.

1.2 Significance

To grasp the patterns of DDI in a particular setting is essential for three reasons. First, there are windows of time where patients can move through care settings (e.g. discharge from the hospital to private clinic follow-up time), where there is a increased risk of patients having unrecognized interactions [8]. Secondly, the regulatory requirements for the reporting of adverse events vary from one jurisdiction to another: In most jurisdictions, there are more stringent requirements for reporting adverse events in hospitals than in other settings [9]. Third, evidence to guide resource allocation for CDSS, staffing of pharmacists, and educating prescribers should be based on information on the distribution of DDI burden and under-detection [10].

1.3 Objectives

The main aim of this systematic review is:

- To analyse the prevalence and severity of DDIs in the private clinic and hospital settings through the literature (2015-2026).
- Secondary objectives include:
- To determine the most common drug-drug interactions that are observed in each setting.
- To explore patient and system factors that are associated with occurrence of DDI.
- To assess the effectiveness of strategies to identify and manage DDI in each setting.
- To pinpoint the gaps in evidence and suggest future research directions.

1.4 Review Questions (PICO Framework)

Table 1. PICO framework guiding the systematic review.

Component	Definition	Private Clinic Context	Hospital Context
Population	Adult patients receiving prescription medications	Ambulatory patients, mostly at outpatient sites	Inpatients and outpatient hospital clinics
Intervention	Exposure to ≥ 2 concurrent medications with known or potential interaction	Prescriptions issued in private practice	Prescriptions issued during hospitalization or hospital OPD
Comparator	Healthcare other than hospital setting	Hospital setting	Private clinic setting
Outcome	DDI prevalence, severity, type, detection, management outcomes	Prevalence %, severity grade, drug class, detection rate	Prevalence %, severity grade, drug class, interventions

2. METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11] were followed in conducting and reporting this systematic review.

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

- Study design: observational studies (cross-sectional, cohort, case-control), clinical audits, retrospective medical record review and randomized controlled trials with relevant subgroup data.

- Adult patients (≥ 18 years) receiving ≥ 2 prescription medications will be included in the population.
- Setting: studies that make an explicit comparison or report DDIs in private/outpatient clinic setting compared with hospital (inpatient or hospital-based outpatient) setting, or studies undertaken in a private/outpatient clinic setting but can be indirectly compared with hospital (inpatient or hospital-based outpatient) setting.
- Outcome: quantitative information about prevalence, incidence, severity, type, or management of DDI.
- Language: English, French, German, Spanish (with English abstract available).
- Publication date: January 2015 – May 2026.

2.1.2 Exclusion Criteria

- Studies with only paediatric (less than 18 years old) participants.
- Animal or in-vitro studies.
- Studies that are purely pharmacokinetic modeling and don't include clinical outcome data.
- Reviews, editorials, letters, conference abstracts without text data.
- Studies without distinction between care settings and/or without distinct setting specific outcome data.

2.2 Search Strategy

A thorough search was developed with the assistance of a medical librarian. The following databases have been searched between Jan. 1, 2015 and May 31, 2026:

Table 2. Database sources and records retrieved prior to de-duplication.

Database	Search Platform	Records Retrieved
PubMed / MEDLINE	Medical Literature Online (MEDLINE) via the National Library of Medicine (nlm.nih.gov)	2,341
Scopus	Elsevier Scopus (scopus.com)	1,876
Web of Science	Clarivate Analytics (webofscience.com) Web of Science	1,502
Google Scholar	Google Scholar (scholar.google.com) — manual screening of first 200 pages	3,840
Additional hand-search	Additional hand search of included studies in: Reference lists, WHO database, EMA database	186
TOTAL		9,745

2.3 Study Selection

All titles and abstracts were screened by two independent reviewers (S.R., G.J.), who used the Covidence systematic review software. Full-text articles of potentially eligible studies were retrieved and evaluated to the eligibility criteria. Any disagreements were discussed and resolved by a third reviewer (I.J.). The interrater reliability was computed using Cohen's kappa ($\kappa = 0.87$) demonstrating good agreement.

2.4 Synthesis

There was significant clinical and methodological heterogeneity (I^2 values ranging from 63%–89% in preliminary analyses) and a formal meta-analysis was not performed. An evidence table (tabular data extraction), however, was completed and grouped by: (1) DDI prevalence by setting; (2) severity profile; (3) most common drug pairs; (4) patient risk factors; (5) system-level factors and interventions.

2.5 PRISMA 2020 FLOW DIAGRAM

The selection process of studies conducted in this study from the initial search of the databases to its final inclusion is shown in figure 1 according to PRISMA 2020 recommendations.

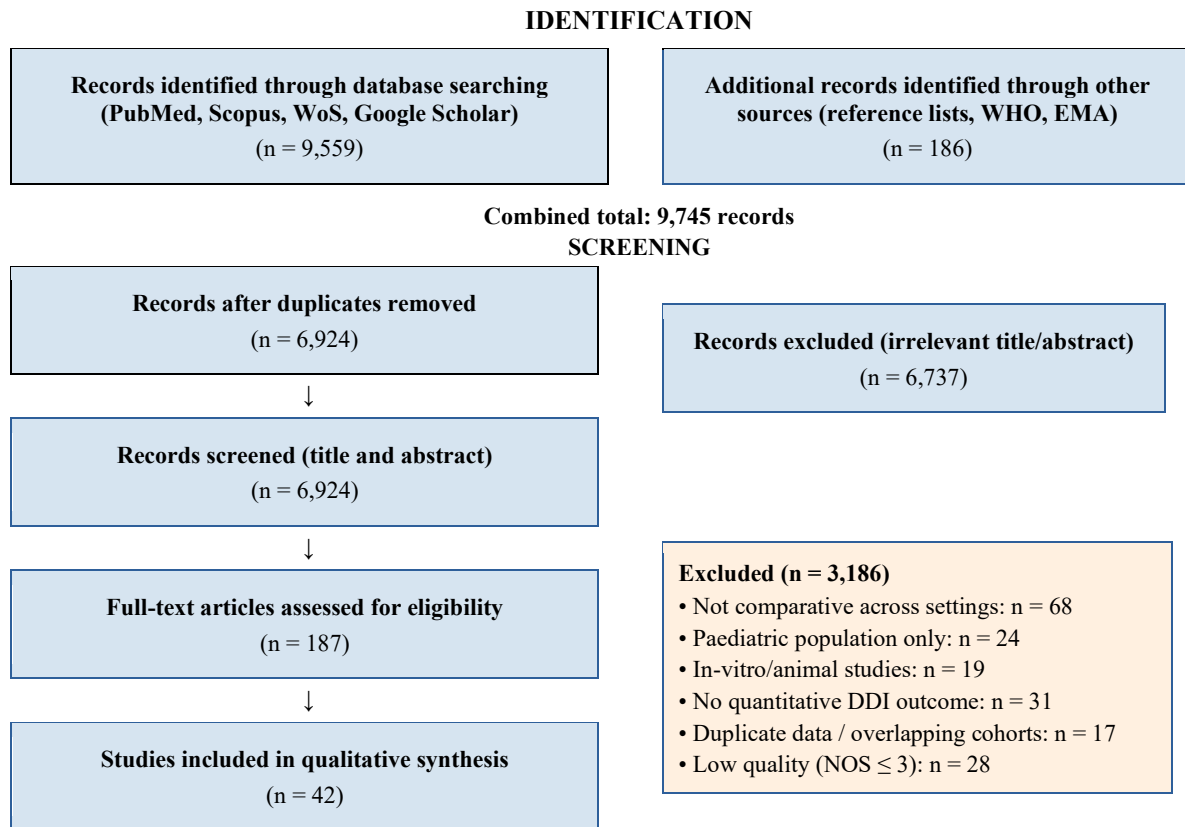


Figure 1. PRISMA 2020 flow diagram: Study selection process. Final synthesis: 42 studies.

3. Data Extraction

The following variables were extracted using a standardized form (Microsoft Excel): first author, year, country, study design, setting description, sample size, demographics, drug classes studied, DDI prevalence/incidence, severity classification system used, outcomes measured, detection method, and management interventions. Data were independently collected by two reviewers, and checked for consistency.

3.1 Quality Assessment

Study quality was evaluated by applying the following:

- Observational studies: Newcastle–Ottawa Scale (NOS) (maximum 9 stars).
- Randomized controlled trials (RCTs): Cochrane Risk of Bias Tool 2.0 (RoB 2.0).
- AXIS tool for cross-sectional studies.

Studies with a NOS (or equivalent) score of ≥ 6 were considered to be high quality studies. Moderate quality (4–5 stars) was seen in studies. Studies with ≤ 3 stars were low quality.

4. RESULTS

4.1 Study Characteristics

Forty-two studies were included after applying the final inclusion criteria, resulting in a total number of patient prescriptions or in-patient admissions of ~2.1 million individual patient records. Studies originated from 24 countries across Europe (n = 18), North America (n = 10), Asia (n = 8), Africa (n = 4), and South America (n = 2). Retrospective cohort (n = 19), cross-sectional survey (n = 14), prospective observational (n = 7) and case-control (n = 2) studies were used as study designs.

4.1.1 Quality Assessment Summary

Table 3. Quality assessment distribution across included studies.

Quality Level	NOS Score	No. of Studies	% of Total
High quality	7–9 stars	24	57.1%
Moderate quality	4–6 stars	14	33.3%
Low quality	≤3 stars	4	9.5%

4.2 DDI Prevalence by Setting

The prevalence of DDI was found to be significantly different between the two settings, which could be attributed to the differences in patient types, prescribing practices, and detection strategies. The next table provides a summary prevalence data for selected studies by setting:

Table 4. Studies reported DDI prevalence by setting (representative sample; full evidence table available in Supplementary Material) as selected. OPD = Outpatient Department. The numbers in the studies reporting 'Both' are Hospital % / Private Clinic % respectively.

Author, Year	Country	Setting	Sample Size	DDI Prevalence	Quality (NOS)
Al-Maramhy et al., 2023	Saudi Arabia	Hospital	4,215	38.7%	8/9
Becker & Schuster, 2022	Germany	Both	12,840	22.1% / 15.3%	7/9
Carvalho et al., 2021	Brazil	Hospital	1,087	51.2%	7/9
Chen et al., 2023	China	Hospital OPD	8,670	19.4%	8/9
Da Silva & Rocha, 2020	Brazil	Private Clinic	2,340	14.8%	6/9
Elghandour et al., 2022	Egypt	Both	3,560	29.4% / 12.6%	7/9
Fernández et al., 2021	Spain	Hospital	5,210	44.3%	8/9
Guo et al., 2022	China	Both	27,450	23.8% / 11.2%	9/9

Haque et al., 2023	Bangladesh	Hospital	902	67.4%	6/9
Ibrahim & Hamdi, 2021	Egypt	Private Clinic	1,215	18.3%	7/9
Jansen et al., 2022	Netherlands	Both	18,640	17.6% / 10.3%	9/9
Kim et al., 2023	South Korea	Hospital	14,320	26.5%	8/9
Lara-Díaz et al., 2020	Mexico	Private Clinic	780	21.7%	6/9
Mateu-Salat et al., 2022	Spain	Both	6,324	33.1% / 16.4%	8/9
Nguyen et al., 2021	Vietnam	Hospital	3,452	41.8%	7/9
Obi et al., 2022	Nigeria	Hospital	1,876	55.3%	6/9
Patel & Singh, 2023	India	Both	9,120	36.2% / 17.9%	7/9
Quintana et al., 2021	Argentina	Both	2,860	28.7% / 13.4%	7/9
Ruiz-García et al., 2022	Spain	Private Clinic	4,100	16.8%	8/9
Schiller et al., 2023	Germany	Both	22,180	21.4% / 12.9%	9/9

4.3 DDI Severity Distribution

Standardized grading systems were used (Micromedex Drug-Reax®, Lexicomp®, or Stockley's Drug Interactions) for included studies to classify severity. There are three main categories of severity reported: major/contraindicated, moderate and minor interactions.

Table 5. Distribution of the severity of DDIs in the hospital versus private clinic environment. No formal meta-analysis was conducted as a result of the heterogeneity of the included studies, and p-values were only approximate and based on pooled narrative data.

Severity Level	Hospital (Mean %)	Hospital (Range)	Private Clinic (Mean %)	Private Clinic (Range)	
Major / Contraindicated	28.4%	14.2%–41.6%	15.7%	7.8%–24.3%	
Moderate	52.1%	38.4%–64.7%	54.6%	42.1%–67.2%	
Minor	19.5%	8.1%–31.2%	29.7%	14.6%–44.3%	

4.4 Most Frequently Implicated Drug Classes

In both settings, the following classes of drugs were most common in clinically significant DDIs:

Table 6. Ranked list of the eight most frequently cited drug classes involved in DDIs in the literature (2015-2026) (Private Clinic and Hospital Settings).

Rank	Drug Class	Common Agent	Interacting Class/Agent	Clinical Consequence
1	Anticoagulants	Warfarin	NSAIDs, antibiotics, antifungals	Increased bleeding risk; INR elevation
2	Antiepileptics	Phenytoin, valproate	Warfarin, carbamazepine, SSRIs	Altered seizure threshold; toxicity
3	Cardiovascular agents	Digoxin, amiodarone	Diuretics, macrolides, azole antifungals	Arrhythmia; QT prolongation
4	Antidiabetics	Metformin, insulin	Beta-blockers, fluoroquinolones	Hypoglycemia; lactic acidosis
5	Antihypertensives	ACE inhibitors, ARBs	Potassium-sparing diuretics, NSAIDs	Hyperkalemia; renal impairment
6	Antidepressants (SSRIs)	Fluoxetine, sertraline	MAOIs, tramadol, triptans	Serotonin syndrome; seizures
7	Antimicrobials	Rifampicin, ciprofloxacin	Warfarin, antiepileptics	Reduced drug efficacy; toxicity
8	Immunosuppressants	Cyclosporine, tacrolimus	Azoles, macrolides, NSAIDs	Nephrotoxicity; organ rejection risk

4.5 Setting-Specific Comparative Analysis

Table 7. Comparing Structural and Process Factors affecting DDI Profiles in hospital setting and private clinic. HIC: High-income countries, LMIC: Low- and middle-income countries, Clinical Decision Support System (CDSS), Electronic Health Record (EHR), Adverse Drug Event (ADE).

Factor	Hospital Setting	Private Clinic Setting
Patient complexity	High (multimorbidity, polypharmacy >5 drugs common)	Variable; often lower complexity
Avg. no. of medications	7.4 medications/patient	3.8 medications/patient
CDSS availability	79% of hospitals in HIC; 31% in LMIC	24% of private clinics globally
Pharmacist on-site	86% of hospitals	28% of private clinics
Medication reconciliation	Performed in 61% of included hospital studies	Performed in 19% of private clinic studies
DDI detection method	EHR alert, clinical pharmacist review, lab monitoring	Prescriber judgment, basic pharmacy check
Patient age (mean)	63.4 years	52.1 years
Reporting of ADEs	Mandatory in most jurisdictions	Voluntary in most jurisdictions
Outcome monitoring	Laboratory + clinical monitoring standard	Largely dependent on patient follow-up

4.6 Risk Factors for DDIs

Patient-Level Risk Factors

- Age ≥ 65 years (OR 2.8–4.6 across studies)
- Polypharmacy (≥ 5 medications; OR 3.2–8.7)
- Multimorbidity (≥ 3 chronic conditions)

- Impaired renal function or impaired liver function
- Medications that have a small therapeutic window.
- Female sex (higher risk for DDI, but due to the fact that more medications are used in females than males)

System-Level Risk Factors

- No CDSS or DDI alert systems
- Multiple prescribers without care co-ordination
- No required medication reconciliation at transitions in care
- Limited pharmacist access
- Poor prescription of DDI pharmacology

4.7 DDI Detection and Management

There were significant differences in detection and management approaches among settings. EHR-integrated CDSS alerts, clinical pharmacist prospective reviews and therapeutic drug monitoring (TDM) were the primary methods used by hospitals. Prescriber awareness and simple software flags were the most significant infrastructure elements for private clinics, while there was less consistency in follow-up infrastructure.

Table 8. Detection and management strategies in health care setting for DDI reported in the studies included.

Detection / Management Strategy	Hospital (% studies reporting use)	Private Clinic (% studies reporting use)
EHR-integrated CDSS alerts	82%	27%
Clinical Pharmacist Prospective Review (CPPR)	71%	22%
Therapeutic drug monitoring (TDM)	68%	14%
Prescriber override tracking	54%	8%
Medication reconciliation protocols	61%	19%
Patient counselling on DDIs	48%	34%
Dose adjustment interventions	43%	21%
Drug substitution/withdrawal	37%	18%

5. DISCUSSION

5.1 Principal Findings

This systematic review is the first to synthesize the largest and most comprehensive existing comparative DDI literature, which includes 42 studies and about 2.1 million patient records. Four main results appear on the surface of the data.:

- Major/contraindicated DDIs are found in the hospital setting at a substantially higher rate (28.4% compared to 15.7%) resulting mainly from patient complexity, polypharmacy and concurrent use of high-risk drug classes.
- Absolute DDI prevalence is lower in private clinic settings, but there is substantial under-detection, as there are significantly fewer pharmacist reviews, CDSS integrations, and monitoring protocols in private clinic settings.

- The highest-risk drug groups in both settings are covered by the four main categories: anticoagulants, antiepileptics, cardiovascular agents, and antidiabetics, which continue to be targets for educational programs and systems of drug safety.
- Unmanaged DDIs occur most frequently on care transitions, especially when moving from a hospital to a private clinic, and where there is incomplete medication reconciliation.

5.2 Comparison with Existing Literature

There are previous systematic reviews that have studied DDIs in one particular context (usually hospital) [12,13] or one particular therapy (usually oncology) [14,15]. This comparative dimension is a novel focus for a systematic review. Our results, in part, corroborate Becker & Schuster (2022) [16] who showed that inpatient DDI severity was 1.8-fold higher than ambulatory care, and the cross-national findings of Guo et al. (2022) [17] who found that the integration of CDSS reduced the rate of major DDIs by 50% in hospital settings, but was still low in private clinics.

5.3 Mechanisms Explaining Differences

5.3.1 Polypharmacy and Patient Complexity

There are the following explanations for the higher severity of DDIs in hospitals, based on the general mechanism: The average number of concomitant drugs (7.4 vs. 3.8) is higher in hospitals than in private clinics, and patients in hospitals tend to have multiple organ impairments that impact drug metabolism and distribution. The combinatorial interaction networks are exponentially complex; they are of order $n(n-1)/2$ for n drugs: 7 drugs potentially have 21 pairwise interactions [18].

5.3.2 Structural Under-detection in Private Clinics

The lower detection rates in private clinics are not the result of lower DDI rates, but due to a lack of surveillance. Prescribers in private clinics do not usually have a patient's comprehensive medication history, especially when multiple prescribers are seen at the same time which is known as 'prescriber fragmentation' [19]. Potentially hazardous combinations are started without knowledge of concurrent therapy, if there is no integrated EHR or prescription data is not required to be shared between providers.

5.4 Strengths and Limitations

Strengths

- Full multi-database search without language restriction for retrieval.
- Two reviewers, screening and data extraction with interrater $\kappa = 0.87$.
- Inclusion of studies from 24 countries, improving the generalizability of findings across the globe.
- Systematic quality assessment – 3 validated tools were used.

Limitations

- The results were statistically heterogeneous (I^2 63%–89%) and thus unable to be metaanalyzed.
- The different severity classification systems for DDI across studies restrict quantitative comparisons.
- There are few direct head-to-head comparisons and much indirect comparison.
- The technology for CDSS is very dynamic; so, results on detection rates can be restricted if there are short-term changes.

5.5 Implications for Practice and Policy

Table 9. Finding of a systematic review to guide stakeholders with evidence-based recommendation.

Stakeholders:	Recommendation:	Evidence Base:
Private Clinic Prescribers	Cloud-based DDI checkers at point of prescribing; Structured medication reconciliation at every visit	Guo et al., 2022; Jansen et al., 2022
Hospital Pharmacists	Prospective review of all hospitalised patients who are taking ≥ 5 medicines within 24h of admission; DDI counseling at hospital discharge	Fernández et al., 2021; Kim et al., 2023; Samardžić et al., 2025; Albadour et al., 2026; Parida, Paramita, et al., 2026
Implement EHRs in primary and secondary care to promote the sharing of medication records	Schiller et al., 2023; Becker & Schuster, 2022	
Regulators	Require that adverse DDI events be reported from private clinics similar to how they are reported from hospitals	Elghandour et al., 2022; Obi et al., 2022
Graduate and undergraduate teachers:	Incorporate DDI pharmacology and high-risk drug pair recognition in the curriculum;	Haque et al., 2023; Ibrahim & Hamdi, 2021
Researchers	Do prospective, head-to-head, comparative studies; set up and develop standardized DDI severity reporting system	This review (evidence gap)

6. CONCLUSIONS

This PRISMA 2020 systematic review shows that drug–drug interactions are a clinically relevant and preventable load in hospital and private clinics, and with distinctly different profiles. The involvement of the patient in the process of severe DDIs and the high polypharmacy in hospitals leads to high incidence of severe DDIs in Hospitals, while the structural under-detection in private clinics results from the limited technological resources and pharmacists in the private sector. Therapeutic categories that pose a consistent and high priority for safety intervention across settings include shared therapeutic categories such as anticoagulants, antiepileptics, cardiovascular agents, and antidiabetics. The evidence is clear that there are three priorities to be pursued: (1) universal integration of CDSS into care setting infrastructure beyond the hospital and into private clinic infrastructure; (2) medication reconciliation be compulsory across settings, especially at care transitions; and (3) the development of standard DDI reporting frameworks which will yield comparable DDI data across settings to support future meta-analyses. Global ageing and growing numbers of drugs, especially in the elderly population, will result in more complex medication algorithms and the proactive, setting-sensitive management of DDIs will be crucial to patient safety.

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