JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2025, VOL 8, NO 4

Drug–Drug Interactions In Poly-Pharmacy Patients: Updated Evidence

Hussain M. Maashi[1] , Faisal Musaad Shutayfi[2] , Abdulaziz Saeed Alshahrani[3] , Abdullah Saadi Alghamdi[4] , Hind Makki Alotaibi[5] , Dina Fareed Qrunfulah[6] , Manal Awad Altalhi[7] , Adnan Hasan Alqurashi[8] , Khalid Sulaiman Masmali[9] , Fatimah Raja Alharbi[10] , Ahmed Abdulsamad Mohamed[11] , Mohammed Hamed Alotaibi[12]

[1]Cardiology Clinical Pharmacist Specialist, Armed Forces Hospitals,Taif-Saudi Arabia , Dr.Hussain.M.M.M@Gmail.Com
[2]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Faisal2009rl@Gmail.Com
[3]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia , Azzoz-2012@Hotmail.Com
[4]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Pharm.D.Ab@Gmail.Com
[5]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia , Phd.Hind12@Gmail.Com
[6]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Dina.Qurunfulah@Gmail.Com
[7]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia , Manal-Altalhi@Hotmail.Com
[8]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Alkomandoz258@Hotmail.Com
[9]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia , Khaled-S2010@Hotmail.Com
[10]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Fatimahalharbi15@Gmail.Com
[11]Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Dr.Ahmedabdulsamad@Hotmail.Com
[12]Clinical Pharmacist, Armed Forces Hospitals,Taif-Saudi Arabia, Abohameed1410@Gmail.Com

ABSTRACT

Background: Polypharmacy, which refers to taking several drugs at the same time, is becoming an increasingly widespread phenomenon because of aging populations and the increase in multimorbidity. The practice increases the chances of drug-drug interactions (DDIs) that may interfere with the effectiveness of the therapy, trigger adverse drug reactions, and raise hospitalization. DDIs can be caused by the pharmacokinetic mechanisms (absorption, distribution, metabolism, or excretion) and by the pharmacodynamic mechanisms (additive, synergistic, or antagonistic), only the number and type of medications prescribed increase their complexity.

Aim of Work: The purpose of this review is to establish recent evidences concerning the prevalence, pathophysiology, and clinical consequences of DDIs in polypharmacy patients. It also investigates high-risk population, drug classes with most frequent implications, and approaches to the prevention and management of DDIs in clinical practice.

Methods: The search through the literature in PubMed, Google scholar, and MEDLINE was carried out to find articles published between 2016 and 2025. The keywords incorporated were polypharmacy, drug-drug interactions, adverse drug reactions, elderly, multimorbidity, and chronic diseases. Articles were filtered based on relevancy and duplicates, case reports, non-full-text articles, and irrelevant articles were filtered out. The review takes into consideration studies that include observational studies, clinical trials, systematic reviews, and meta-

analyses that tackle the epidemiology, mechanisms, and treatment of DDIs in polypharmacy.

Results: The results indicate that DDIs are very common among patients taking a combination of drugs, more so among older individuals and in chronic illnesses. Common medicines implicated by this would include cardiovascular medicines, anticoagulants, psychotropics, and non-steroidal anti-inflammatory drugs. Both the pharmacodynamics and pharmacokinetic interplay in enhancing adverse events, therapeutic failure, and hospitalization. Computational and clinical decision-support tools that are being developed can be useful in predicting and managing DDIs.

Conclusion: DDIs continue to pose a significant issue in polypharmacy patients particularly in patients at high risk. The prompt identification, drug evaluation, patient tracking, and predictive mechanisms are necessary in minimizing the negative outcome. A combination of clinical pharmacology and technology can streamline patient safety in managing polypharmacy through a multidisciplinary approach.

Keywords: Polypharmacy, Drug–Drug Interactions, Pharmacokinetics, Pharmacodynamics, Elderly, Multimorbidity, Chronic Diseases, AI-Based Prediction, Medication Review, Clinical Decision Support.

INTRODUCTION

Polypharmacy (a multi-medicinal usage of five or more drugs) has become a common characteristic of contemporary medicine with the ageing population and increasing multi-morbidity. The elderly are among the special populations especially because physiologic shifts in absorption, distribution, metabolism and excretion, combined with multiple prescribers and divides of care, both exacerbate the likelihood and the clinical outcomes of drug-drug interactions (DDIs). These reactions can vary in the extent of the mild, subclinical change in drug concentration to extreme adverse drug events (ADEs), hospitalizations, dysfunction, or even mortality; thus DDIs contributes significantly, preventable, to medication-related harm among polypharmacy patients [1].

Recent systematic reviews and meta-analyses have measured the extent of the issue: DDI prevalence increases exponentially with number of drugs and population studies have shown high and increasing rates of potentially clinically significant DDIs in both community and hospital practice. Predictable subsets of high-risk combinations, such as anticoagulants and anti-platelets, or some antimicrobials, polypharmacy involving cardiovascular, psychotropic and analgesic drugs are also reviewed and predictors of serious ADEs. In settings, exposure to potentially interacting regimens is correlated with observational evidence of exposure to increased emergency visits, longer stay at the hospital, worse health-related quality of life, and higher health-care expenditure [2].

DDIs are facilitated mechanistically by both pharmacokinetic (alterations in absorption, enzyme-mediated metabolism, transporter, or elimination) and pharmacodynamic mechanisms (additive or antagonistic at the same or a related physiologic target). These mechanisms are maximized by age-related impaired renal and hepatic excretion, body composition, and comorbid disease states, which ensure that older and multi-morbid patients are uniquely vulnerable even to interaction that is insignificant in young age groups. In addition, the increased consumption of over-the-counter medications, supplements and herbal preparations pose additional, in most cases, unreported, risks of interaction [3].

To address this issue, recent literature has proposed systems-level and patient-centered approaches: regular medication handoff, routine medication reconciliation, systemized medication reviews and de-prescribing models, the integration of clinical pharmacists into care teams, and the application of

validated communication screening tools embedded in electronic health records (EHRs). Experimental studies and partial implementation indicate that intensive interventions, in particular, those involving a combination of pharmacist review, clinician decision support, and patient engagement can decrease inappropriate prescribing and the cost of risky combinations, but translation into sustained changes in hard clinical outcomes has been inconsistent across health systems [4].

In spite of the better knowledge and technological support, there are still significant gaps. Most interaction alerts result in alert fatigue and low specificity; real-world evidence on the most reliable combinations of things to predict harm is still changing; and low and middle-income areas have other barriers such as poor medication documentation and lack of pharmacy services. Refinement of risk-stratification models incorporating drug, patient, and context; greater ability to enhance clinical relevance of computerized alerts; scaling of practices of feasible de-prescribing and medication-optimization across care settings are thus currently research priorities. This introduction positions drug-drug interactions in polypharmacy as a multifaceted, system-wide concern in safety that requires improved evidence and improved actions should we wish to minimize the occurrence of avoidable medication harm [5].

AIM OF WORK

This review is intended to give a current synthesis of the evidence about drug-drug interactions (DDIs) in polypharmacy patients, especially the aged and multi-morbid populations. In particular, it will: (1) measure the prevalence and patterns of DDIs in recent literature; (2) analyze clinical impacts of DDIs, including adverse drug reactions (ADRs), hospitalization and treatment failure; (3) discuss high-risk drug classes and regimens most commonly involved in clinically important interactions; (4) discuss the current research gaps and recommend better methods to minimize risk in polypharmacy; (5) research gaps and give recommendations about safer prescribing in a polypharmacy setting.

METHODS

This review had been done in a systematic search of scientific literature via the use of major bibliographic databases known as PubMed/MEDLINE, Embase (or equivalent) and Google Scholar. Combinations of search terms and controlled vocabulary (e.g. MeSH) were as follows: drug-drug interaction, polypharmacy, elderly, multiple medications, potential drug interaction, and adverse drug reaction, and synonyms. Terms were connected with the help of Boolean operators (AND/OR), and increased or decreased results were obtained by restricting them to studies published in peer-reviewed journals in English (or in languages understandable by the authors).

Duplicates were eliminated after compilation of all records. Screening was initially done on titles and abstracts to eliminate irrelevant studies. The potential articles were then searched and identified by the full texts and reviews of articles that included original research, observational or interventional studies, or systematic review/meta-analyses addressing DDIs in polypharmacy settings; this determined eligibility as an inclusion/exclusion criterion; that is, case reports, narrative reviews without primary data, non-full-text articles, and studies that did not investigate polypharmacy or drug-drug interactions.

The selected studies were subsequently analyzed thematically: such data as the study design, population (age, comorbidities), types of drugs used, definitions of polypharmacy, type and severity of DDIs, clinical outcomes (e.g., adverse events, hospitalization), and risk-mitigation strategies were extracted. Where possible, data on the method of DDIs identification (clinical and electronic screening tools) and outcome measures were also capturing information. Lastly, the results of the studies were combined to determine regular patterns, risky combinations of drugs, evidence gaps, and recommendations.

RESULTS

The present review comprises articles describing drug drug interactions (DDIs) in polypharmacy, older and multi-morbid patients, and in hospitalized and community environments alongside disease-specific groups (e.g. cancer, chronic kidney disease). It discusses mechanistic research on pharmacokinetic and pharmacodynamic pathways, epidemiological research on quantifying DDI and polypharmacy, research

on high-risk group drugs and popular harmful interactions (such as cardiovascular drugs, antiplatelet drugs, anticoagulant drugs, psychotropic drugs, antimicrobial drugs, and non-steroidal anti-inflammatory drugs), and clinical research of DDIs as causes of adverse drug events, hospitalizations, and treatment failures. Detection and prediction tools (electronic DDI databases, clinical decision support, and emerging AI/ML models) are also evaluated in the review, as well as interventional projects on medication reconciliation, pharmacist-led review, and de-prescribing. The articles included in the review were published in 2016-2025. These themes have structured the findings under the Discussion section, they are: Epidemiology and prevalence patterns; Mechanisms of interaction; High-risk drug classes and combinations; Clinical consequences; Detection and predictive tools and Risk-mitigation and policy/practice interventions.

DISCUSSION

1. Definition and Scope of Polypharmacy.

Polypharmacy is typically described as the use of two or more medications by the same person, most commonly in the literature as the regular use of at least five medications; when the number of medications builds up to ten or more drugs, the term hyper-polypharmacy is frequently used. Definitions are however varied with some papers basing their definition upon length of use (continuous vs. cumulative), whether or not over-the-counter and complementary medicines are also included, or even clinical suitability of an individual prescription as opposed to a fixed number. Conceptualizing polypharmacy as a numerical number thus may overlook clinically appropriate multi-morbidity care as compared to problematic, superfluous prescribing [6].

Population ageing and increased prevalence of multi-morbidity has increased the scope of polypharmacy. Recent large observational studies and systematic reviews report large prevalence ranges by setting and definition: community estimates typically vary between low-20s and more than 40 percent among the elderly; hyper-polypharmacy (taking over 10 medicines) is rising in most countries. These drivers are increased life expectancy; drug cascades of various chronic conditions guided by guidelines, fragmentation of care across specialists, and increased access to pharmacotherapies [7].

Polypharmacy is not always deleterious clinically--appropriate polypharmacy refers to the presence of multiple medicines which are necessary to help a patient and are actually helpful. The issue comes into being because combinations are unneeded, redundant, or contraindicated, which increases risks of adverse drug reactions (ADRs), drug-drug interactions, medication non-adherence, function deterioration, falls, hospitalization, and higher healthcare expenditures. Systematic evidence exists that the number of medications and exposure to potentially inappropriate medications is related to poorer outcomes in older adults, and these harms should be structure medication review and de-prescribing [5].

Regarding the issue of polypharmacy, the following interventions are necessary from a public-health standpoint: (1) standardized operational definitions of surveillance and research, (2) routine medication reconciliation between care transitions, (3) multidisciplinary medication reviews (including the pharmacists,) and (4) shared decision-making, explicitly in terms of life expectancy, patient priorities, and risk-benefit tradeoffs. The global best practices and patient-safety models focus on medication-safety methods and system-level interventions aimed at mitigating preventable harms linked to inappropriate polypharmacy. Due to heterogeneous definitions and different prevalence rates in various settings, in-progress studies ought to combine quantitative surveillance with clinical quality indices with a view of separating proper and counterproductive polypharmacy [8].

2. Epidemiology of Drug–Drug Interactions in Polypharmacy

Studies continually reveal that drug-drug interactions are not uncommon in a patient taking more than one type of drugs. A study was conducted in 2023 and presented a typical one, a systematic review and meta-analysis of older community-dwelling adults (65 or older), which combined the data across 33

studies and included more than 17 million participants, showing a pooled DDI prevalence of 28.8% (95% CI 19.340.7) but individual studies also ranged widely (0.890.6) [2]. This high variability is mostly due to the variation in the way DDIs were recognized: even with a single database (Micromedex®), with a different database (Lexi-Interact ®), and with other criteria (American Geriatrics Society (AGS) 2015 Beers criteria ®) there was great difference in pooled prevalences - 57.8% with a single database (Micromedex ®), 30.3% another database (Lexi-Interact ®), and -with other criteria, 16.6% These results highlight the fact that a large number of older adults at a community level are subjected to at least one of a possible drug-drug interaction, but again, which depends on the definition and screening strategy employed by investigators.

DDI risk is also significant when outpatient prescribing practices are not restricted to elderly patients. As an example, one Egyptian cross-sectional study of 5,820 prescriptions identified that 18 percent of prescriptions contained at least one possible DDI (reported by Lexicomp 10 as flagged), including prescriptions with multiple interactions [10]. This indicates that geriatric populations are not the only ones who face DDI risk in polypharmacy but intersect with each age group in accordance with prescription habits and drug interactions.

DDI will be prevalent in inpatient settings. A retrospective study of internal-medicine patients in a Bulgarian hospital revealed that out of 510 patients, 57% experienced polypharmacy and almost 40% of those suffered at least one potential pharmacokinetic DDI; patients who had more than seven drugs were considered to be at high risk [11]. In another recent study, carried out in a hospital environment, this time in elderly inpatients, around 46% were found to have DDIs potentially of clinical significance, and when they were limited to patients ≥ 70 years old and taking ≥ 3 chronic conditions and polypharmacy ≥ 5 medications, the prevalence was found to be 58% [12]. These researchers point out that DDI is significantly more at risk among hospitalized status, illness complexities, and comorbid conditions.

There are certain groups of patients who are particularly susceptible. The elderly as an elderly population in the community, these are at high risk, due to the age-related physiologic changes (renal/hepatic clearance, pharmacodynamics), which tend to augment the impact of interactions; the 2023 meta-analysis indicated that older adults tend to use cardiovascular drugs, diuretics, anticoagulants, and antiarrhythmic agents, are drug classes that are commonly involved in DDIs [2]. Within a hospital setting, older patients- particularly with chronic conditions or where they are undergoing complex treatment- are prescribed many drugs, which further multiplies the interactions among themselves and among the nurse and their caregivers. An example is a cross-sectional study of older patients with COVID-19 admitted to the hospital in 2022-2023, which conducted a polypharmacy prevalence of 77.7% and a DDI prevalence of 61.7% [13].

In another research conducted in Indonesia (20232024), out of 409 older adults admitted to hospitals, 41.9% of the prescriptions contained possible DDI, and major interactions comprised approximately 56.6% of all possible interactions [14]. A 2025 meta-analysis of elderly African patients estimated a pooled prevalence of DDI in patients at 52.5% (95% CI 35.469.7) in polypharmacy and DDIs to reinforce the fact that it is a wide issue in Africa, not limited to high-income nations. These findings are indicative that older age, multi-morbidity, and chronic illnesses, as well as polypharmacy, particularly when coupled with low access to medication review and interaction-checking services, pose a considerable risk of DDI.

Increased research focus and better detection measures may be suggesting an increased spectrum of DDI risk over recent years, but it is still uncertain whether this is a change in incidence or merely an increased awareness. The increasing data on large-scale studies, the 2023 community meta-analysis, 2025 African meta-analysis and most recent 2023-2024 hospital-based studies, indicate that DDIs are now more renowned as a public-health concern. In the meantime, trends of specialized populations (e.g., hospitalized older adults with COVID-19) demonstrate a high rate of DDI prevalence, which means that contemporary multi-morbidity and polypharmacy continue being central contributors [2]. Correspondingly, regional studies (e.g., in Africa) also indicate that local prescribing practices and drug

availability, as well as healthcare infrastructure, impact reported DDI rates, i.e. global estimates could hide high regional variability [15].

3. Drug-Drug Interaction Mechanisms.

Simply, a drug-drug interaction occurs when one drug (the precipitant or interacting drug) changes the behavioral or effect of another (the object drug), changing its concentration, effect, or toxicity [16]. Practically, a wide range of DDIs work by altering drug disposition (pharmacokinetics: absorption, distribution, metabolism, excretion -ADME) or by altering drug effects (pharmacodynamics: action on receptors, physiological pathways) [17].

3.1 Pharmacokinetic Interactions.

Pharmacokinetic DDIs influence the concentration of a drug in the body - by altering the extent of its absorption, localization, metabolism, and elimination [18].

3.1.1 Absorption

Adsorption is commonly the initial process influenced in case two drugs are administered (orally or via other routes) concomitantly. The gastrointestinal (GI) motility, gastrial pH, chelation or complexation with ions or any other molecule, and some even drug-transporter activity, may influence the extent to which a drug reaches systemic circulation [17]. As an example, certain antibiotics (e.g. tetracyclines, fluoroquinolones) are bound (chelate) by divalent or trivalent cations e.g. calcium or magnesium in antacids or dairy products and form insoluble complexes, which cannot be absorbed quickly and become bio-inactive [19]. The GI motility drugs, including opioids or anti-cholinergics, also have the potential to slow gastric emptying or intestinal transit, which alters the rate (as well as the extent) of absorption, potentially postponing the onset of action or lowering its peak levels [20].

Alteration in gastric pH is another process: in drugs whose solubility is determined by an acidic environment (e.g., some antifungals), acid- inhibiting agents such as proton-pump inhibitors or H 2 antagonists can decrease their absorption [21]. Since absorption is a key factor in bioavailability of a drug (fraction reaching the systemic circulation), absorption DDIs can result in sub-therapeutic (ineffective) or less frequently delayed or variable onset of action [22].

3.1.2 Distribution

Some drugs once absorbed are commuted to plasma proteins (e.g., albumin) or to drug-transport proteins; binding by plasma proteins, such as albumin, as well as by drug-transport proteins, is used to determine the amount of free (active) drug taken into tissues. Contacts of this level can change a ratio of free drug. As an example, when Drug A replaces Drug B in binding sites on proteins, the free (unbound) Drug B might rise in concentration - potentially boosting its pharmacologic or toxic action [23].

Also, transporter proteins (e.g., efflux or uptake transporters) may influence distribution in tissues. Other drugs block or stimulate these transporters, thus affecting the amount of a second drug that gets to its target or tissue objections. Nevertheless, protein-binding replacement has rare clinical effects, as compensatory mechanisms (e.g., higher clearance) are likely to counter variations in free drug concentration [17].

3.1.3 Metabolism (CYP450 and Transporters)

One of the most significant and clinically useful types of PK DDIs is metabolic interactions, especially when it comes to the family of cytochrome P450 (CYP) enzymes []. A variety of medications are processed in the liver through the use of CYP enzymes (e.g., CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2). When a co-administered drug is an inhibitor of a particular CYP isoenzyme, there is a chance of a slowdown in metabolism of the intended drug leading to higher plasma concentration, an extended half-life and a possible overdose. On the other hand, the precipitant drug triggers the enzyme

(stimulation of enzyme expression or activity), the object drug should be metabolized more rapidly - bringing its concentration down, which might cause therapeutic failure [16].

Further, drug-carrying proteins (e.g. P-glycoprotein or other uptake/efflux transporters) interact with metabolic enzymes and can also be directed by interacting drugs, impacting metabolism and distribution/excretion of drug substrates. Recent studies can be considered to broaden our knowledge of classical CYP-mediated interactions. Indicatively, non-CYP metabolic enzymes (phase-II enzymes), other metabolic routes, and transporter-mediated clearance have increasingly been identified as also playing a role in clinically relevant DDIs (especially where new or complicated drugs are present) [24]. The risk and magnitude of DDI are further modulated by inter-individual differences which may be genetic polymorphisms in CYP enzymes or transporters, aging (i.e., in older adults), disease conditions (i.e., liver dysfunction), etc. [25].

3.1.4 Excretion

Lastly, clearance can be modified by other drugs which are con-administered, which in turn changes the drug excretion, usually through the renal or biliary pathways. In case a precipitant drug decelerates the excretion of the object drug (by inhibiting the renal tubular secretion system, altering the urine pH or competing with transporters or decreasing the renal blood flow), the object drug accumulated, increasing the chance of toxicity. As an example, classical interaction: co -administration of an inhibitor of tubular secretion (e.g., probenecid) with penicillin decreases the renal excretion of penicillin - increasing and extending plasma levels of penicillin.

Likewise, non- steroid anti-inflammatory drugs (NSAIDs) can also influence the renal clearance of some drugs by affecting their clearance and exposure, raising their toxicity risk [26]. Since excretion is the last stage in the elimination of drugs, impairments in this process can prove especially serious: not only can the concentration of drugs and/or their active metabolites increase, but active metabolites can also rise unexpectedly in case of disruption in this process [16].

3.2 Pharmacodynamics Interactions.

Although the magnitude of an amount of a drug is altered in the light of pharmacokinetic interactions, the nature of the drug is altered in the light of pharmacodynamic (PD) interactions or the way the effect(s) of drugs interact (or interact oppositely) [27]. Pharmacodynamic DDIs occur when two or more drugs behave on the same receptor, physiological pathway or have effects within the same organ system. Such interactions can be additive, synergistic, or antagonistic in nature [21].

3.2.1 Additive and Synergistic Effects.

The interaction between two drugs with a similar effect can be the sum (additive) or more than the sum (synergistic). Additive interaction is typical in drug combination with overlapping therapeutic purposes. As an example, such combination as two analgesics (e.g., an NSAID and an opioid) can also be more effective in pain treatment than each of them individually - effectually adding up their respective analgesic property [17]. Synergy is the possibility of the drug interaction creating a larger than expected effect than any individual drug. Synergy is also used deliberately in certain therapeutic systems, such as the antimicrobial or oncology combination therapy, in which drugs with different mechanisms of action have a greater therapeutic effect as a combination than as individual drugs.

But synergy is a sword two-sided: it may enhance effectiveness but it could also raise toxicity by huge proportions. As one example, CNS depressants used concomitantly (e.g., opioids or benzodiazepines) may both produce excessive sedation, respiratory depression, or even fatal overdose, which is unwanted synergistic PD DDI [21]. On the same note, the risk of adverse life-threatening arrhythmia may be added to the already excessively dangerous changes in cardiac repolarization by two drugs (e.g., two QT-prolonging drugs) in a synergistic manner than either drug would introduce. As the interactions of PbD rely on the influence of pharmacology over concentration, they are not obliged to appear in the change of plasma levels- they can therefore be less noticeable or predictable, particularly without attentive clinical examination [28].

3.2.2 Antagonistic Effects

Antagonistic PD interactions are when one drug inhibits or nullifies the action or action or the other-either by competing at the receptor (competitive antagonism) or by antagonizing downstream actions of the other via alternative pathways [29]. These interactions can be intentional, such as when using a so-called reversal drug to prevent or diminish the effects of a second drug (e.g. an antagonist to reverse overdose effects of an opioid), or accidental, as occurs when the drugs lose therapeutic activity. A case of deleterious antagonistic effect: non-steroidal anti-inflammatory drugs (NSAIDs) used together with low-dose aspirin (as cardio-protective), where NSAIDs can decrease the antiplatelet effect of aspirin by competing with the enzyme activating aspirin, thereby reducing the cardio-protective action [30].

The condition may also occur in antagonistic PD relations where a beta-agonist and beta-blocker co-influence the same physiological system in opposite ways - e.g., when a beta-agonist is used with a beta-blocker, one may dull the effect of either drug, or both, making the therapy ineffective or leading to unsteadiness in disease that depends on a close regulation of receptors. Since the interaction of additive, synergistic, or antagonistic PD effects may occur, sometimes in combination with PK modes of action, it is not always easy in clinical practice to estimate the overall effect of a drug combination. This complexity highlights the significance of attentive drug choice, observation, dose adjustments as well as in suitable cases, de-prescribing [16].

4. High-Risk Drug Classes and Common Interaction Combinations

4.1 Cardiovascular Medications

The most common contributors to DDIs include drugs used to treat cardiovascular (CV) conditions particularly in populations of inpatient care. In a 2023 cross-sectional study of hospitalized cardiac patients, almost all (97.2) had at least one potentially harmful DDI during their hospital stay [31]. Similar 2024-2025 update also corroborates that elderly CVD patients with polypharmacy or hyper-polypharmacy bear an excessive load of serious DDIs - such as multiple CV agents (including 2-blockers, ACE/ARBs, CCBs, diuretics, statins, and digitalis glycosides) [32].

This is often associated with co-administration of diuretics (e.g., loan or thiazide diuretics) with other CV medications. As an example, in a retrospective study of geriatric patients with congestive heart failure (CHF), the most common interacting pair was furosemide + bisoprolol [33]. These interactions are commonly pharmacodynamic, e.g., overlapping effects on blood pressure, electrolytes, renal activity, heart rate, but can be aggravated by comorbidities, e.g., diabetes, renal dysfunction or old age. Such interactions may cause compromised therapeutic effectiveness (e.g., poor blood-pressure control), the risk of adverse effects (e.g., electrolyte imbalances, renal failure, hypotension), or the worsening of heart failure [34].

4.2 Anticoagulants and Antiplatelets

Another category at high risk of intraoperative DDI is represented by anticoagulants and antiplatelet agents (e.g., Warfarin, novel oral anticoagulants, Aspirin, Clopidogrel). A 2024 prospective cohort study in an older community-dwelling population showed that DDIs with anticoagulant, cardiovascular, and antimicrobial medications were some of the most frequent and that DDIs being associated with increased adverse drug events (ADEs) and diminished health-related quality of life (HRQoL) in two-year follow-ups [35]. In a realistic pharmacovigilance study (as of April 2024), anticoagulants (especially warfarin) had been one of the most common drugs mentioned in DDI-related adverse event reports, and a significant percentage of the result of interactions involved serious effects, including death [36].

The interaction of anticoagulants / antiplatelets with other medications, in particular non-steroidal anti-inflammatory drugs (NSAIDs) or anti-coagulative medications has a significant risk of bleeding. As an example, the co-administration of NSAIDs and oral anticoagulants greatly predisposes any bleeding and gastrointestinal bleeding relative to the anticoagulant therapy itself [37]. Furthermore, antiplatelet

+ anticoagulant combinations may also be present in severe DDIs in cardiovascular patients, in the 2023 cardiac patient cohort; approximately 80% of all identified DDIs used at least one antiplatelet medication [31]. Therefore, anticoagulant/antiplatelet therapy and anticoagulant/antiplatelet therapy combined with other drugs, OTCs, or in older/comorbid patients requires close monitoring, prescription review and risk/benefit evaluation.

4.3 CNS and Psychotropic Drugs

The central nervous system (CNS)-acting drugs, such as antidepressants, sedatives, anxiolytics, antipsychotics, and other psychotropics, are also a risk factor of DDI drug interactions, particularly in polypharmacy. Despite a relative lack of recent epidemiological studies on CNS DDIs on a large scale, based on pharmacovigilance data CNS acting agents are represented in the list of most frequently used drugs that have become involved in severe adverse events attributed to DDIs. As an example, antidepressants, like Sertraline and Fluoxetine, were ranked among the leading drugs implicated in the 2025 FAERS analysis [36].

Combination of CNS suppressants (e.g., benzodiazepines, opioids) or combining serotonergic medications (e.g., SSRIs, SNRI) mechanistically raises the likelihood of additive/synergistic effects (sedation, respiratory depression, or serotonin syndrome). However, most of these interactions are pharmacodynamic and not pharmacokinetic, their presence is of considerable clinical risk, particularly in the elderly or in patients taking a combination of CNS-active agents. These are identified as high-alert medications in clinical reviews [38].

In addition, polypharmacy with CNS drugs, anticoagulants and analgesic is of particular importance: the effects of CNS medication on bleeding risk (e.g., SSRIs reducing platelet aggregation and platelet clotting) with anticoagulants or NSAID on the risk of gastrointestinal or intracranial bleeding. Under these dangers, prescription use of psychotropics must proceed being careful in patients with various comorbidities with the occurrence of other high-risk drugs. It is prescribed to conduct regular medication review and de-prescribe where feasible [38].

4.4 Antimicrobials (Antibiotics and Others)

Antimicrobials (and especially antibiotics) frequently overlap with the risk of polypharmacy and DDI, especially in patients with chronic disease or comorbidity. A 20232024 study of ADR reports among the elderly revealed that the most frequently implicated pharmacological group of adverse events in pDDI was antimicrobial agents [39].

Particular combinations are striking: co-trimoxazole (trimethoprim-sulfamethoxazole) - a common antibiotic - in combination with ACE-inhibitors (or ARBs), potassium-sparing diuretics, other drugs that influence renal activity or potassium status potentially increased the risk of hyperkalemia as a result of additive effects. Additionally, specific antibiotics (e.g., some fluoroquinolones or sulfonamides) can increase the effect of anticoagulants, such as warfarin, increase bleeding risk; therefore, they should be closely monitored in combination.

Another problem: the elderly or chronically ill population can have several medications (e.g., cardiovascular, antidiabetic, immunosuppressants), which may lead to destabilization of regular regimens through DDIs by antimicrobial therapy (which may be short-term but pressing). The 2024 study of older patients undergoing chemotherapy also demonstrates the role of antimicrobials in cumulative DDI load in the complex regimens [40]. These findings underline the importance of antimicrobial stewardship, both to address resistance, as well as to reduce the risk of DDI, particularly in at-risk groups.

4.5 Analgesics and Anti-inflammatories (NSAIDs).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as those found over-the-counter are also the most problematic in polypharmacy, and are often part of the serious reactions. A 2025 review underscored that the interaction of antiplatelet factors or anticoagulants with NSAIDs can be highly

prone to causing bleeding specifically gastrointestinal bleeding [41]. Furthermore, NSAIDs can potentially overcome the effect of some cardiovascular medications (e.g., diuretics, ACE inhibitors, ARBs, beta-blockers), by blocking the production of prostaglandins in the kidney, leading to sodium and fluid retention, elevation of blood pressure, or heart failure aggravation [42].

NSAIDs can also interact with renal excretion of other drugs (e.g., lithium, methotrexate) and exacerbate renal insufficiency - especially in the geriatric, diabetic, hypertensive, or heart-failure patients. Clinical effects: risk of bleeding, renal dysfunction, hypertension or heart failure aggravation, and loss of the CV drugs efficacy. Indicatively, an observational report of 2025 cautions that habitual or unmonitored use of NSAIDs can increase the chances of recurrent myocardial infarction amongst persons with a history of heart attack attacks. As an example of an OTC risk, NSAIDs are a major "ADD-ON risk in polypharmacy CVD, pre-renal or GIT comorbidity is also a risk that consumes a significant role: moreover, hidden lay in polypharmacy due to OTC access (NSAIDs) [43].

4.6 Polypharmacy in Chronic Diseases (Diabetes, Heart Failure, COPD)

Drug combinations consisting of more than two drug classes are regularly prescribed to patients with chronic illnesses like diabetes mellitus, chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD) and others. This raises the number of drugs, as well as the risk of DDIs and adverse events [44]. A 2025 clinical review pointed out that polypharmacy in heart failure often results in lower adherence, greater adverse drug events (ADEs), and the risk of drug-drug and drug-disease interactions [34].

A single 25-year-old yet informative study of hospitalized patients with chronic heart failure and/or COPD indicated a median of 67 medications per patient. An average of 6.5-7.2 potential DDIs per patient was identified and the number of DDIs was rising (with a greater number of more serious examples of interactions) between admission and discharge. DDIs were particularly common in patients using both HF and COPD, where regimens included the use of nonselective 2-blockers and 2-agonists, which can be clinically justified, yet are risky; this was one of the most frequent level-X (high-risk) interactions to be seen [44].

The interaction risk is further complicated in patients with diabetes and cardiovascular disease (two highly comorbid chronic conditions) where interaction is possible among the antihypertensives, lipid-lowering agents, antiplatelets/anticoagulants, analgesics/NSAID, and other supportive drugs (e.g., to support neuropathy, renal protection). A study carried out in a cardiology-ward in 2023 discovered that comorbidity of diabetes predisposed many potential DDIs [31].

Polypharmacy under such situations requires close monitoring - routine review of medications, de-prescribing when feasible, ADEs (particularly renal, bleeding, and cardiac) monitoring, and patient education due to the complexity of chronic disease management. The patient-centered approach based on benefit vs. risk is crucial as suggested in recent heart-failure recommendations [34].

5. Detection, Prediction, and Assessment Tools

5.1 Clinical Decision Support Systems (CDSS)

Clinical decision support systems (CDSS) are tools designed to assist physicians in determining the correct action based on patient data.<|human|>6.1 Clinical Decision Support Systems (CDSS) The CDSS is a set of tools that help a physician make the right decision based on patient information.

One of the first systems to be used to identify potential DDIs in real time are clinical decision support systems (CDSS) built into prescribing systems or electronic health systems. As an example, a 2022 study of a DDI-CDSS in a large teaching hospital evaluated both alerts issued between 2019 -2021, as well as user (prescriber) satisfaction. The analysis determined that even though prescribers appreciated the value quantity of the system, a considerable constraint was a high number of false positive alerts and alert fatigue.

In particular, that analysis revealed that most alerts were too general, especially because they were based on a lack of patient-specific data (e.g., organ functionality, comorbidities) or timed by screening instead of dynamic checking. These constraints are likely to lower clinical adoption and performance: a recent stepped-wedge randomized-trial in ICU units reported that, with DDI alerts conditioned to intensive-care-specific combinations, CDSS efficacy increased by an average of 12% [46].

However, a larger systematic review released in 2025 has found out that in general, with the current extensive implementation of CDSS-DI, no convincing evidence of significant positives regarding patient-important outcomes, including adverse events, hospitalized, or death, was found [47]. These observations indicate that the current form of CDSS is a valuable initial step toward DDI detection, but their design requires improvements to ensure the highest clinical value.

5.2 Electronic DDI Screening Databases

DDI databases of either the standalone or web based nature are kept in central location where prescribers, pharmacists or researchers can screen or check drug interactions by hand. A well-known tool is DDInter 2.0 an extensive current DDI knowledge base that over recent years has added a new 28% of reported interactions to get a current total of more than 302,500 documented DDIs in pharmacodynamic (PD) and pharmacokinetic (PK) categories. DDInter 2.0 also introduced other interaction types than those previously present in PK/PD such as drug-disease interactions, drug-food interactions and therapeutic duplication and thus enhanced comprehensiveness and clinical relevance of screening. These databases are particularly helpful in an environment without an advanced hospital-based CDSS: these databases serve inexpensive, updated sources of clinician or pharmacist cross-checking of possible interactions and then prescribing or dispensing [48].

5.3 AI- and Machine Learning–Based Prediction Models

Considering the weaknesses of rule-based platforms and the inability to experimentally validate every potential drug combination, scientists are turning to techniques of artificial intelligence (AI) and machine-learning (ML) to predict unfamiliar or novel drug-to-drug interactions. A recent systematic review (2025) proposed the way combined molecular, pharmacological and real-world data (including patient record, genomics, etc.) can yield that data-driven predictions are scalable further [49]. A representative model HyGNN (a hypergraph neural network): The only type of information utilized in the model is the chemical structure (drug SMILES strings), leading to high interaction predictions (ROC-AUC of up to 97.9) [50].

A recent work applied a deep-learning-based CDSS which used a multilabel Long Short-Term Memory autoencoder to indicate potential DDIs and this research recommends that the application of ML-based tools could lower the rate of false-positive alerts relative to classical rule-based CDSS [51]. In a clinical study, in 2024, an assessment of a ML-based CDSS (named MedGuard) ascertained that more than 1.2 billion prescriptions elicited just about 2.36% alerts, many of which were clinically justifiable DDIs; the research demonstrated interception of incorrect-drug errors and significant clinician approval, which indicates that such systems can circumvent alert clammage and enhance particularity [52].

These developments suggest a highly promising future of AI-driven prediction to detect DDI more effectively, particularly in novel drug interactions, infrequent interactions, or the individual-specific likelihoods of adverse effects, to permit tailored and accurate medication safety.

CONCLUSION

Polypharmacy poses a major danger on drug-drug interactions, especially in aged, multimorbid, and chronic patients. Pharmacodynamics and pharmacokinetics mechanisms result in the increase of adverse event rates and alterations in drug activity, and the commonly impacted systems include CYP450 metabolism, renal excretion, and additive or antagonistic pharmacologic effects. To reduce DDI-related complications, it is critical to be aware of high-risk drug classes, conduct a close review of medications, and use predictive tools. Further research and clinical decision support system integration can also promote further improvement of patient safety during polypharmacy management.

REFERENCES

1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC geriatrics. 2017 Oct 10;17(1):230.
2. Hughes JE, Waldron C, Bennett KE, Cahir C. Prevalence of Drug–Drug Interactions in Older Community-Dwelling Individuals: A Systematic Review and Meta-analysi s. Drugs & Aging. 2023 Feb;40(2):117-34.
3. Zhao D, Huang P, Yu L, He Y. Pharmacokinetics–pharmacodynamics modeling for evaluating drug–drug interactions in polypharmacy: development and challenges. Clinical Pharmacokinetics. 2024 Jul;63(7):919-44.
4. Gavazova E, Staynova R, Grekova-Kafalova D. Managing polypharmacy through medication review tools–pros and cons. Folia Medica. 2024 Apr 30;66(2):161-70.
5. Roncal-Belzunce V, Gutiérrez-Valencia M, Leache L, Saiz LC, Bell JS, Erviti J, Martínez-Velilla N. Systematic review and meta-analysis on the effectiveness of multidisciplinary interventions to address polypharmacy in community-dwelling older adults. Ageing research reviews. 2024 Jul 1;98:102317.
6. Guillot J, Maumus-Robert S, Bezin J. Polypharmacy: a general review of definitions, descriptions and determinants. Therapies. 2020 Sep 1;75(5):407-16.
7. Wang Z, Liu T, Su Q, Luo H, Lou L, Zhao L, Kang X, Pan Y, Nie Y. Prevalence of polypharmacy in elderly population worldwide: a systematic review and meta-analysis. Pharmacoepidemiology and drug safety. 2024 Aug;33(8):e5880.
8. World Health Organization. Medication safety in polypharmacy: technical report. World Health Organization; 2019.
9. Gonzaga de Andrade Santos TN, Mendonça da Cruz Macieira G, Cardoso Sodré Alves BM, Onozato T, Cunha Cardoso G, Ferreira Nascimento MT, Saquete Martins-Filho PR, Pereira de Lyra Jr D, Oliveira Filho AD. Prevalence of clinically manifested drug interactions in hospitalized patients: A systematic review and meta-analysis. PloS one. 2020 Jul 1;15(7):e0235353.
10. Abdelkawy K, Kharouba M, Shendy K, Abdelmagged O, Galal N, Tarek M, Abdelgaied M, Zakaria AY, Mahmoud SH. Prevalence of Drug–Drug Interactions in Primary Care Prescriptions in Egypt: A Cross-Sectional Retrospective Study. Pharmacy. 2023 Jun 18;11(3):106.
11. Georgiev KD, Hvarchanova N, Stoychev E, Kanazirev B. Prevalence of polypharmacy and risk of potential drug-drug interactions among hospitalized patients with emphasis on the pharmacokinetics. Science Progress. 2022 Jan;105(1):00368504211070183.
12. Očovská Z, Maříková M, Vlček J. Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study. Frontiers in Pharmacology. 2023 Feb 2;14:1088900.
13. Chen Z, Tian F, Zeng Y. Polypharmacy, potentially inappropriate medications, and drug-drug interactions in older COVID-19 inpatients. BMC geriatrics. 2023 Nov 25;23(1):774.
14. Faisal S, Khotib J, Wibisono C, Hamidah KF, Utomo FN, Zairina E. Factors contributing to the prevalence of potential drug-drug interactions among hospitalized elderly patients in a tertiary hospital in Eastern Java, Indonesia. Medical Journal of Indonesia. 2025 Sep 30;34(3):174-80.
15. Alemayehu TT, Geremew GW, Tegegne AA, Tadesse G, Getachew D, Ayele HS, Yazie AS, Fentahun S, Abebe TB, Minwagaw T, Wassie YA. Drug-drug interaction among elderly patients in Africa: a systematic review and meta-analysis. BMC Pharmacology and Toxicology. 2025 Dec;26(1):1-6.
16. Roberts AG, Gibbs ME. Mechanisms and the clinical relevance of complex drug–drug interactions. Clinical pharmacology: advances and applications. 2018 Sep 27:123-34.
17. Niu J, Straubinger RM, Mager DE. Pharmacodynamic drug–drug interactions. Clinical Pharmacology & Therapeutics. 2019 Jun;105(6):1395-406.
18. Peng Y, Cheng Z, Xie F. Evaluation of pharmacokinetic drug–drug interactions: a review of the mechanisms, in vitro and in silico approaches. Metabolites. 2021 Jan 27;11(2):75.
19. Walden DM, Khotimchenko M, Hou H, Chakravarty K, Varshney J. Effects of magnesium, calcium, and aluminum chelation on fluoroquinolone absorption rate and bioavailability: a computational study. Pharmaceutics. 2021 Apr 21;13(5):594.

20. Nautiyal H, Kazmi I, Kaleem M, Afzal M, Ahmad MM, Zafar A, Kaur R. Mechanism of action of drugs used in gastrointestinal diseases. InHow Synthetic Drugs Work 2023 Jan 1 (pp. 391-419). Academic Press.
21. Devi R, Priya L. The Mechanism of Drug–Drug Interactions: A Systematic Review. Clinical Journal for Medicine, Health and Pharmacy. 2024 Sep 30;2(3):32-41.
22. Reji RS, George A, Vikraman N, Augustine AM, Gayathri L, Kumar P. IDENTIFICATION OF POTENTIAL DRUG-DRUG INTERACTIONS IN CARDIOLOGY DEPARTMENT IN A TERTIARY CARE HOSPITAL.
23. Calzetta L, Page C, Matera MG, Cazzola M, Rogliani P. Drug-drug interactions and synergy: from pharmacological models to clinical application. Pharmacological Reviews. 2024 Nov 1;76(6):1159-220.
24. Li Y, Meng Q, Yang M, Liu D, Hou X, Tang L, Wang X, Lyu Y, Chen X, Liu K, Yu AM. Current trends in drug metabolism and pharmacokinetics. Acta Pharmaceutica Sinica B. 2019 Nov 1;9(6):1113-44.
25. Ruiz A, DiCristina S. Absorption to Excretion: The Aging Body's Take on Drugs–A Review of Pharmacokinetic Changes and their Impact on Medication Management. Current Pharmacology Reports. 2025 Jul 26;11(1):42.
26. Farid A, Altaee R. Clinically Important Pharmacokinetic Drug-Drug Interactions: An Overview of Excretion, Factors Affecting Excretion, and Transporter Mechanisms. Journal of Kerbala University. 2025 Jun 30;22(2):72-81.
27. Niu J, Straubinger RM, Mager DE. Pharmacodynamic drug–drug interactions. Clinical Pharmacology & Therapeutics. 2019 Jun;105(6):1395-406.
28. McQuade BM, Campbell A. Drug prescribing: drug-drug interactions. FP essentials. 2021 Sep 1;508:25-32.
29. Chaachouay N. Synergy, additive effects, and antagonism of drugs with plant bioactive compounds. Drugs and Drug Candidates. 2025 Feb 5;4(1):4.
30. Cascorbi I. Drug interactions—principles, examples and clinical consequences. Deutsches Ärzteblatt International. 2012 Aug 20;109(33-34):546.
31. Kalash A, Abdelrahman A, Al-Zakwani I, Al Suleimani Y. Potentially Harmful Drug–Drug Interactions and Their Associated Factors Among Hospitalized Cardiac Patients: A Cross-Sectional Study. Drugs-real world outcomes. 2023 Sep;10(3):371-81.
32. Sheikh-Taha M, Asmar M. Polypharmacy and severe potential drug-drug interactions among older adults with cardiovascular disease in the United States. BMC geriatrics. 2021 Apr 7;21(1):233.
33. Permatasari DI, Husna NA, Yosmar RA. Potential drug-drug interactions of cardiovascular drugs based on literature in geriatric patients with congestive heart failure at Dr. M. Djamil Padang Hospital. M. Djamil Padang Hosp Interac. 2024;9:10.
34. Stolfo D, Iacoviello M, Chioncel O, Anker MS, Bayes-Genis A, Braunschweig F, Cannata A, El Hadidi S, Filippatos G, Jhund P, Mebazaa A. How to handle polypharmacy in heart failure. A clinical consensus statement of the Heart Failure Association of the ESC. European Journal of Heart Failure. 2025 May;27(5):747-59.
35. Hughes JE, Bennett KE, Cahir C. Drug–drug interactions and their association with adverse health outcomes in the older community-dwelling population: a prospective cohort study. Clinical Drug Investigation. 2024 Jun;44(6):439-53.
36. Alahmari A, Fatani S, Ahmed N. Drug–drug interactions: A descriptive analysis of FDA adverse event reporting system. Medicine. 2025 Sep 19;104(38):e44606.
37. Zheng Y, Zhang N, Tse G, Li G, Lip GY, Liu T. Co-administered oral anticoagulants with nonsteroidal anti-inflammatory drugs and the risk of bleeding: A systematic review and meta-analysis. Thrombosis research. 2023 Dec 1;232:15-26.
38. Alhozim BM, Almutairi ET, Albutyan ZY, Alzahrani NA, Alonizy MM, Albutyan LY, Refaei IA, Al-Otaibi FA, Saleh AM, Khurmi AM, Alsahli MM. The impact of polypharmacy on drug efficacy and safety in geriatric populations. Egyptian Journal of Chemistry. 2024 Dec 1;67(13):1533-40.
39. Jiang H, Lin Y, Ren W, Lu L, Tan X, Lv X, Zhang N. Potential inappropriate medications and drug–drug interactions in adverse drug reactions in the elderly: a retrospective study in a pharmacovigilance database. Frontiers in Pharmacology. 2025 Apr 8;16:1546012.

40. Oliveira RF, Oliveira AI, Cruz AS, Ribeiro O, Afreixo V, Pimentel F. Polypharmacy and drug interactions in older patients with cancer receiving chemotherapy: associated factors. BMC geriatrics. 2024 Jun 25;24(1):557.
41. Dunbar D, Ouanounou A. An update on drug interactions involving anti-inflammatory and analgesic medications in oral and maxillofacial medicine: a narrative review. Frontiers of Oral and Maxillofacial Medicine. 2025 Jun 10;7.
42. Stöllberger C, Finsterer J. Nonsteroidal anti-inflammatory drugs in patients with cardioor cerebrovascular disorders. Zeitschrift für Kardiologie. 2003 Sep;92(9):721-9.
43. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs. Therapeutics and clinical risk management. 2015 Jul 15:1061-75.
44. Roblek T, Trobec K, Mrhar A, Lainscak M. Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. Archives of Medical Science. 2014 Oct 27;10(5):920-32.
45. Van De Sijpe G, Quintens C, Walgraeve K, Van Laer E, Penny J, De Vlieger G, Schrijvers R, De Munter P, Foulon V, Casteels M, Van der Linden L. Overall performance of a drug–drug interaction clinical decision support system: quantitative evaluation and end-user survey. BMC Medical Informatics and Decision Making. 2022 Feb 22;22(1):48.
46. Bakker T, Klopotowska JE, Dongelmans DA, Eslami S, Vermeijden WJ, Hendriks S, Ten Cate J, Karakus A, Purmer IM, van Bree SH, Spronk PE. The effect of computerised decision support alerts tailored to intensive care on the administration of high-risk drug combinations, and their monitoring: a cluster randomised stepped-wedge trial. The Lancet. 2024 Feb 3;403(10425):439-49.
47. Holbrook AM, Silva JM, Faruque JA, Deng J, Schneider T, Jaffer A. Effect of electronic drug-drug interaction alerts on patient and clinician outcomes: a systematic review. Journal of the American Medical Informatics Association. 2025 Oct;32(10):1617-28.
48. Tian Y, Yi J, Wang N, Wu C, Peng J, Liu S, Yang G, Cao D. DDInter 2.0: an enhanced drug interaction resource with expanded data coverage, new interaction types, and improved user interface. Nucleic Acids Research. 2025 Jan 6;53(D1):D1356-62.
49. Huang W, Wang X, Chen Y, Yu C, Zhang S. Advancing drug-drug interactions research: integrating AI-powered prediction, vulnerable populations, and regulatory insights. Frontiers in Pharmacology. 2025 Aug 13;16:1618701.
50. Saifuddin KM, Bumgardner B, Tanvir F, Akbas E. Hygnn: Drug-drug interaction prediction via hypergraph neural network. In2023 IEEE 39th International Conference on Data Engineering (ICDE) 2023 Apr 3 (pp. 1503-1516). IEEE.
51. Alrowais F, Alotaibi SS, Hilal AM, Marzouk R, Mohsen H, Osman AE, Alneil AA, Eldesouki MI. Clinical decision support systems to predict drug–drug interaction using multilabel long short-term memory with an autoencoder. International Journal of Environmental Research and Public Health. 2023 Feb 2;20(3):2696.
52. Chen CY, Chen YL, Scholl J, Yang HC, Li YC. Ability of machine-learning based clinical decision support system to reduce alert fatigue, wrong-drug errors, and alert users about look alike, sound alike medication. Computer Methods and Programs in Biomedicine. 2024 Jan 1;243:107869.