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PHARMACOKINETIC DRUG-DRUG INTERACTION AND ITS IMPLICATION IN CLINICAL MANAGEMENT

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ABSTRACT

The adverse drug reactions continue to be significant health concerns in the field of medicine. These reactions impose a significant financial burden on the healthcare system and can severely affect patient outcomes, including life expectancy. Adverse drug reactions appear to be difficult to avoid regardless of circumstances. In light of the introduction of personalized medications along with new biologics, the mechanisms of these adverse drug reactions have become rather complex. Their biological causes are becoming increasingly difficult to determine. That's one reason a different perspective may be,required.This literature review examines the current status of ADRs. This review does not limit itself to the common types A and B reactions. Such adverse drug events as delayed response or withdrawal syndrome can also be considered today. Pharmacogenomics and individual genes of a patient are analyzed by the author in the context of the possible side effects. The patient's age, polypharmacy, comorbidity, and other factors increase the risks for developing side effects in patients. The evolution of pharmacovigilance in terms of the detection of such adverse reactions is also mentioned in this work. Initially, this was based on the passive monitoring of the side effects of medicinal drugs, while today there is a tendency to apply artificial intelligence and big data analysis in the same field.

Keywords: Adverse Drug Reactions; Pharmacogenomics; Pharmacovigilance; Polypharmacy; Drug Safety.

1. INTRODUCTION

Pharmacokinetic drug–drug interactions (PK-DDIs) is a key issue in clinical pharmacology, which refers to the process that one drug affecting the absorption, distribution, metabolism or excretion (ADME) of another, eventually causing changes of systemic drug exposure and therapeutic effects. In the recent years, the importance of PK DDI in the clinical setting has dramatically increased with the growing occurrence of polypharmacy, especially in elderly patients, as well as patients with chronic diseases such as cardiovascular disease, cancer and neurological disorders. Surveying current high-impact literature (2020–2026), PK-DDIs remain a primary determinant of drug response variability and have a strong correlation with adverse drug reactions (ADRs), therapeutic failure and an increased burden on healthcare services (Peng, Cheng, & Xie, 2021; Yu, Argon, Owens, Wang, & Ragueneau-Majlessi, 2026; Yu, Wang, & Ragueneau-Majlessi, 2022a). On the mechanistic level, the vast majority of clinically relevant interactions are related to the impact on metabolizing enzymes, in particular cytochrome P450 isoforms such as CYP3A4, but also drug transporters such as P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs), which may have profound effect on drug bioavailability and elimination (Choi & Song, 2026; Yu, Wang, & Ragueneau-Majlessi, 2022b).

The significance of PK-DDIs in clinical management is that they can increase the toxicity or decrease the therapeutic effect of a drug, and they may also require dose modification, therapeutic drug monitoring, or even the elimination of certain drug combinations. There are multiple recent reports that strong pharmacokinetic interactions can cause several-

fold alterations in plasma concentrations of drugs that could be fatal if not handled accordingly(Wołowiec et al., 2025; Yu et al., 2022b).Recent reports are also centered on the integration of artificial intelligence and machine learning approaches to improve prediction of DDI and risk assessment leading to more precise and personalized therapeutic modality(Lu et al., 2026).

In this regard, the current review is focused on providing a comprehensive analysis of the results from high quality studies published between 2020 and 2026 investigating pharmacokinetic drug–drug interactions (DDIs) in clinical management. The goals of this review are: (i) to describe the mechanistic bases of PK-DDIs with a special emphasis on enzyme- and transporter-mediated ones; (ii) to discuss their clinical relevance in terms of safety and therapeutic outcome; (iii) to analyze the available prediction, prevention and management strategies at clinical level; and (iv) to outline existing research gaps and to propose future research lines, which may include the influence of pharmacogenomics and of artificial intelligence in drug therapy optimization. Through incorporation of the latest advances in science, this review endeavors to establish a broad, yet clinically applicable, strategy for reducing risk and enhancing patient outcome related to pharmacokinetic drug–drug interactions.

2. LITERATURE SEARCH METHODOLOGY

A comprehensive drug-drug interaction (DDI) analysis began with a thorough search of major biomedical databases such as PubMed, MEDLINE, EMBASE and the Cochrane Library (Cecchin & Stocco, 2020).These searches involved carefully crafted search strings and Boolean Logic, ensuring specificity and breadth, with specific attention to areas of interest including but not limited to, pharmacokinetics, polypharmacy and adverse drug reactions. To ensure that no relevant studies were missed, reference lists of the identified studies were also reviewed, allowing for the inclusion of additional sources that may not have been indexed in the databases(Baxter, 2010).

At the beginning of the data search process, inclusion and exclusion criteria were established to ensure the scientific rigour of the literature retrieved. Clinically relevant studies, such as clinical trials and pharmacokinetic modelling studies, were prioritised, while preclinical studies, editorials and studies without pharmacokinetic parameters were excluded(Cecchin & Stocco, 2020). The next step involved screening of titles, abstracts and full texts to remove duplicates and irrelevant articles, while also pinpointing those that not only explained interaction mechanisms but also made a contribution to clinical practice.

In the data extraction step, specific pharmacokinetic parameters such as drug characteristics, maximum time, maximum plasma concentration, and half-life were extracted. This allowed for the systematic analysis of pharmacokinetic information, in terms of the drug's mode of action and physiological significance, which in turn facilitated a more holistic view of the impact of drug-drug interaction on drug efficacy and safety.

Literature review highlighted the importance of two key aspects of drug-drug interaction (DDI) studies, namely pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetics related to the description of a drug's fate during the absorption, distribution, metabolism, and excretion (ADME) process, while pharmacodynamics involved the type of effects observed when drugs are combined - termed synergy, additivity, or antagonism (Niu, Straubinger, & Mager, 2019).

Alongside traditional methods, there was an increasing reliance on sophisticated computational techniques to improve predictions. Methods such as machine learning, liver microsome metabolism, and drug combinations were deployed in conjunction with traditional in vitro and in vivo experimentation to expand the ability to identify not only known but also unknown drug interactions(Han et al., 2021).

In addition to empirical approaches, physiologically based pharmacokinetic (PBPK) models and other simulation platforms were used to translate research findings to clinical practice. Such models were shown to be highly predictive of DDIs, especially those resulting from CYP450 and membrane transporters. These models virtually mimicked human physiology to guide clinical dosing strategies and eliminate the need for large-scale human clinical trials(Maglalang, Wen, Hornik, & Gonzalez, 2024).

3. REVIEW OF LITERATURE

3.1.Overview and Classification of ADRs

Adverse drug reactions (ADRs) are the unwanted, unintentional drug responses in the body when given at normal recommended doses, and like side effects, they impact a large number of people worldwide, leading to high rates of mortality, morbidity, and health care costs. It is being highlighted in recent literature that ADRs are the major cause of hospital admission and are preventable in a significant proportion, and that hence many of them can be avoided by better pharmacovigilance and rational prescribing(Ishaqui et al., 2026; Khalid, Temedie-Asogwa, Zakeri, & Sansgiry, 2025). Recent studies report that the cause of an ADR is multifactorial and depends on patient-related characteristics (i.e., age, genetic background, presence of comorbidities, and polypharmacy) as well as drug-related elements (i.e., dose, administration route, pharmacological class)(Yuan et al., 2026; Zhai et al., 2025). ADRs are associated with diagnostic and therapeutic challenge even in clinical practice, due to varied nature of clinical presentation such as commoner anti-cancer agents causing mild but annoying side effects to very rarely used drugs causing severe life-threatening reactions.

The categorization of drug side effects has changed markedly, but the Rawlins-Thompson classification is still the most influential. The above classification system divides the ADRs mainly into Type A (augmented) and Type B(bizarre) ADR. They occur in a predictable fraction of patients, can be related to the drug's pharmacological or pharmacokinetic properties, are dose-dependent and Type A reactions are thought to comprise the majority of ADRs, and are generally associated with lower mortality. On the other hand, Type B reactions are unforeseeable, are not related to dose, and may be related to immunological processes or idiosyncratic features, and tend to be more severe and tightly associated with preventatives (Evans, Robinson, & Amare, 2025; Ray, Gray, & D'Souza, 2025). The consequential subsequent modifications of this system have included further categories, such as Type C (chronic), Type D (delayed), Type E (end of use), and Type F (failure of therapy), which creates the extended ABCDEF classification, which allows for a better understanding of mechanisms and temporal relationships in the occurrence of ADRs (Kathleen Kenny, 2026).

Apart from mechanistic classification, ADRs are also divided by seriousness, complexity, and preventability, with the latter two being very important when considering clinical management and risk evaluation. Serious ADRs, which tend to be emphasized in the regulatory warnings, may lead to admission to hospital; have the potential for life-long disability or death indicating the vital importance of early recognition and management (Lynch, 2025). Emerging pharmacovigilance research further subclasses ADRs according to causality (certain, probable, possible) and the affected organ systems, facilitating more structured reporting as well as detection of signals in clinical practice(Nahla et al., 2025; Singh, Verma, Vaishnav, Joshi, & Agrawal, 2025).

3.2. Mechanisms and Drug–Drug Interactions

The underlying complex pharmacokinetic and pharmacodynamic processes that mediates drug exposure and responses are the main driving forces causing drug-drug interactions (DDIs), and thus, they should be mechanistically understood in the context of clinical management to utilize drugs safely and effectively. pharmacokinetic mechanisms affecting drug metabolism (mainly via cytochrome P450 enzymes) and drug transport (via efflux and influx transporters) are the predominant factors responsible for clinically relevant DDIs. These interferences are when a

"perpetrator" drug affects the absorption, distribution, metabolism, and elimination (ADME) of a "victim" drug, and thus the plasma levels are changed, and may leads to toxicity or therapeutic failure(Bigagli, Angelini, Mugelli, & Rocca, 2025; Sun et al., 2023).

Among these, modulation of cytochrome P450 (CYP) enzymes is the most investigated and clinically relevant pathway. CYP enzymes, such as CYP3A4, CYP2D6 and CYP2C9, are believed to be a key factor in phase I drug metabolism, and the inhibition or induction of them has been reported as a leading cause of DDIs(J. Lee, Beers, Geffert, & Jackson, 2024; Marques & Vale, 2025). Enzyme inhibition may result in elevated plasma concentrations of the victim drug and a subsequent risk of toxicity, while enzyme induction has the opposite effect, with acceleration of metabolism that may result in subtherapeutic levels of the victim drug. Mechanism based inhibition, especially with CYP3A4, can result in long lasting and clinically relevant interactions due to irreversible enzyme inactivation. Analyses of clinical data on new drugs recently approved reinforce the point that potent CYP-mediated interactions can lead to >5-fold changes in exposure and, in consequence, to significant dose adaptations or even contraindication (Yu et al., 2022a).

Of particular mechanistic interest were bidirectional enzyme-transporter interactions, where drugs simultaneously inhibit and induces metabolic enzymes and transporters, respectively, to generate potentiated or magnified pharmacokinetics effects. Interestingly, recent findings suggested that many clinically relevant DDIs were not the result of a single mechanism but rather the outcome of a combination of integrated mechanisms (Sun et al., 2023; Yu, Wang, & Ragueneau-Majlessi, 2024). Additionally, interactions were also found to occur at a nutritional level, with some DDIs associated with gastrointestinal events or food-induced changes in drug dissolution in the gastrointestinal tract, which ultimately affected drug absorption and pharmacokinetic profiles (Poli, Bologna, & Saguy, 2024).

Insight into underlying mechanisms was complemented by the application of in vitro, in silico and physiologically based pharmacokinetic (PBPK) models to enable quantitative prediction of DDIs during drug development and clinical assessment. These models leveraged enzyme kinetics, transporter dynamics and physiologic constants to predict interaction scenarios, and guide physiological dose adjustment (Peng et al., 2021; Yu et al., 2026).

3.3 Risk Factors and Epidemiology

ADRs are a major challenge to health systems and a burden to public health, which is evidenced in a wide array of studies contributing to our knowledge based on morbidity, mortality and utilization of health services. Global pharmacovigilance and population-based studies show that ADRs account for a substantial proportion of hospital admissions and mortality with an increasing trend in recent decades. The study of Guo etal. also reviewed that although mortality associated with ADR had been increasing continuously, however, there were significant differences among different groups such as older persons, males, people with specific ethnic background, and people living in rural or underdeveloped areas(Guo & Dong, 2026). Also, hospital studies show that in-hospital ADRs contribute substantially to the burden of in-hospital morbidity, with rates differing according to patient group and treatment setting, thus portraying the diversity of the problem (Zhai et al., 2025).The determinants of ADR epidemiology are multifactorial from the patient and drug to the healthcare environment and affect both probability and magnitude of the undesired consequence. Among the patient-related factors, old age is universally regarded as the strongest predictor for the occurrence of an ADR due to changes in drug pharmacokinetics and pharmacodynamics, and the higher burden of comorbidities and polypharmacy in elderly people(Frydenlund et al., 2026).

On the population level, the patterns of ADRs are further shaped by the health system and environmental factors. Disparities in healthcare access and pharmacovigilance systems, as well as

in socioeconomic status, make ADR identification, reporting, and outcome differ between countries counties (Guo & Dong, 2026). Real-world data analyses also indicate that ADRs are under-detected, especially in low- and middle-income countries, challenging precise quantification of their burden(Zhai et al., 2025). Moreover, a very recent cohort and retrospective studies show that ADRs have impact not only on length of stay and readmission rate of a hospital, but also on the long-term outcomes such as quality of life and healthcare cost(Frydenlund et al., 2026).

3.4 Detection, Monitoring Pharmacovigilance

Detection and monitoring of adverse drug reactions (ADRs) and pharmacovigilance is a pillar of contemporary drug safety systems, and are intended to detect, evaluate, understand and prevent drug-related risks in the entire product lifecycle. Pharmacovigilance is considered a scientific discipline that involves pre-marketing evaluation and post-marketing surveillance, which primarily utilizes real-world safety data that are infrequently captured during clinical trials due to small sample sizes and controlled environments (Aslam, Majid, Muhammad Boota, Ghulam Mustafa, & Akhtar, 2026; Wasiullah, Yadav, Vishwakarma, Yadav, & Ali, 2025). ADR detection, as contemporary literature (2020–2026) demonstrates, mainly depends on structured systems, i.e., spontaneous reporting systems (SRS), electronic health record, and global safety databases such as FAERS and base where large scale signal detection and the evaluation of risks can be conducted(Tan, Markatou, & Chakraborty, 2026).Thesesystemsare also important for detection of new and unknown ADRs, changes in reaction frequency, and regulatory decision support.

Among other methods, spontaneous reporting system (SRS) is the most commonly used method in pharmacovigilance. These are individual case safety reports (ICSRs) submitted by healthcare professionals, patients, etc. and serve as the basis for the detection of signals using statistical and data mining methods. Nevertheless, the recent studies highlight that under-reporting and quality of data related issues continue to hamper their effectiveness mainly in low- and middle-income countries (Aslam et al., 2026; Kommu, Carter, & Whitfield, 2026).In light of these constraints, active surveillance techniques such as cohort event monitoring, and prescription event monitoring, have been more widely implemented to collect more complete and precise safety data("Pharmacovigilance in the era of drug safety: A review of ADR monitoring, challenges, and future directions,").

Pharmacovigilance systems focus on international cooperation and legal instruments such as the WHO Programme for International Drug Monitoring and national ones like PharmacovigilanceProgramme in India (PvPI) enabling collection of data in a standardized manner and sharing of information between countries (Wasiullah et al., 2025). These systems contribute to the early identification of safety signals and to the initiation of regulatory measures such as modification of the product label, risk minimization activities or product recall, if warranted. Recent reviews, however, highlight the fact that patients' knowledge and engagement to report ADRs are still less than ideal, constraining the efficiency of the pharmacovigilance systems, and calling for enlightenment and motivational tools(Aslam et al., 2026).

3.5 Prediction and Prevention Strategies

PBPK-based pharmacodynamics (PBPK/PD) models do indeed push further the boundary. Personalized pharmacokinetics models estimate drug distribution according to the person's characteristics, and it is not just theoretical. It can be especially useful to predict the high-risk drug-drug interactions. Take, for example, when apixaban and dronedarone are needed by someone who is renally impaired, the PBPK/PD models can foretell the bleeding risks prior to the administration of the drugs (Wen, He, Xiang, Jiao, & Yu, 2022). This is essentially a preemptive safeguard and a proactive strategy, and the doctor/clinician is able to stop a potential complication in its tracks at the stage of prediction.

And in situations when there is a need for immediate steps - in medical institutions, prior to surgery - it is essential that the information is up to date on the patient's medication history and they pay attention to the given medications. In most cases these are surgical patients who are on one or the other combination of drugs and thus there is a very good chance of drug-drug interaction among. This can be adapted by performant pre-operative work up and following the development of signs of toxicity on the patients as the drugs begin exerting their actions (Silva, Costa, Castro, Mourão, & Vale, 2023).

There was an increasing interest in the use of deep learning and knowledge graph methods to map biological relationships between DDIs. Graph Neural Networks (GNNs) were used to sample the molecular structure and its relationships of drugs, allowing the identification of unique pharmacological features (Luo et al., 2024). A striking aspect of these approaches was the capacity to predict asymmetric drug-drug interactions - where one drug acted as the perpetrator while the other acted as the victim - thereby capturing the unidirectional nature of drug interactions (Huang, Wang, Chen, Yu, & Zhang, 2025).

In certain specialised clinical contexts, such as the use of drugs to treat SARS-CoV-2, caution was required for drugs with narrow therapeutic windows. Proactive measures involved pre-emptive dose adjustment of co-administered drugs in the presence of strong CYP3A4 inhibitors, such as lopinavir/ritonavir. Specifically, pre-emptive dose adjustments of sedative medications (e.g. midazolam) were advised to prevent excessive sedation and respiratory failure during antiviral treatment (Zeitlinger et al., 2020).

The safety of medication use over the long term was further enhanced by the adoption of artificial intelligence models in Clinical Decision Support Systems (CDSS). These provided clinicians with timely warnings based on patient-specific characteristics, including demographics and personal medical history. The integration of digital systems to identify prescribing errors at the time of prescription with traditional post-marketing pharmacovigilance measures ensured a multi-faceted approach was taken to prevent drug-related adverse events in modern clinical practice (Huang et al., 2025).

4. DISCUSSION

DDIs represent a significant and avoidable cause of harm in the practice of medicine. In a time of increasing polypharmacy, such as among the elderly and patients with several medical problems, there has ever more need for DDIs to be the biggest concern history of drug usage. The knowledge synthesis in this review encompasses current mechanistic knowledge of DDIs, surveillance and detection methodologies, predictive models, population-specific and risk assessment, and still-to-be-fulfilled gaps to positively impact patient safety. Mechanistic Insight: Beyond CYP450 Cytochrome P450 enzymes (in particular CYP3A4, CYP2D6 and CYP2C9) have long been the mechanistic backbone for clinicians and scientists to explain DDIs and they are responsible for approximately 75% of all enzyme-mediated DDIs(J. Lee et al., 2024; Yu et al., 2026). This has proved to be a useful base; however, it is no longer sufficient to describe the complexity of DDIs that are experienced in clinical practice. Recent findings indicate that clinically relevant DDIs frequently result from the simultaneous perturbation of enzymes and transporters on both pathways, culminating in changes in drug pharmacokinetics that neither pathway can fully account for (Sun et al., 2023; Yu et al., 2024).

Such differentiation does have obvious dosing and monitoring implications particularly in patients with limited therapeutic options and those on chronic polypharmacy (Marques & Vale, 2025; Yu et al., 2022a). Serious CYP-mediated interactions resulting in more than a five-fold change in systemic exposure of the drug are known and necessitate aggressive management. Drug transporters, including P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs), bring new dimension of complexity. Transporters also have specific tissue- and direction-dependent roles and there is variability

in function dependent where the interaction occurs (Choi & Song, 2026). For example, DDI at the BBB or the heart may have different outcomes compared to those in the gut or the liver. DDIs with nutrients also affect the pharmacokinetics through the modification of gastric pH, motility and first-pass metabolism, which are usually unrecognized in the clinic (Poli et al., 2024). Metabolism of Phase II is a relatively less studied area in DDI science, with enzymes including UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and catechol-O-methyltransferase (COMT) playing a significant role, but considerably less investigated than the CYPs, meaning that possible DDIs leading to adverse events might only be identified post-realworld experience(J. Lee et al., 2024).

4.1.Surveillance and Detection

A Stressed System From a global perspective, the surveillance for DDI mainly relies on passive reporting systems (SRS), which, although serving their irreplaceable role in pharmacovigilance, have some uncontestable limitations. It is thought that SRS contribute to only 5-10% of reports of adverse drug reactions (ADRs)(Aslam et al., 2026). Non-reporting is even more obvious in low-and middle-income countries (LMICs), in which reporting is nascent in both culture and professional consciousness. Other more sensitive and comprehensive active surveillance techniques include cohort event monitoring and prescription event monitoring; however, they are very costly. EHR-linked systems represent a promising avenue in well-resourced health systems with potential to detect signals in near real-time, and to identify potential sub-groups of patients (Tan et al., 2026). However, the challenges of integration and data quality are significant, particularly at the institutional and national scale.The FDA Adverse Event Reporting System (FAERS) and the World Health Organisation (WHO) Programme for International Drug Monitoring are essential for global signal detection and regulatory harmonization, yet they are still affected by a number of intrinsic challenges including duplicate reporting, data gaps, and an overrepresentation of high-income countries(Wasiullah et al., 2025). The poor detection of harm relating to DDIs in LMICs is more than just a knowledge gap; it is a patient safety crisis that demands attention from policymakers, funders, and the global community.

Among the most remarkable features of these models is the prediction of DDI in special populations, such as pediatric, geriatric, or patients with renal or hepatic impairment, without conducting the large clinical trials in these vulnerable populations (Wen et al., 2022; Yu et al., 2026). The application of PBPK predictions in drug development is increasing and the US FDA and the European Medicines Agency (EMA) demonstrate growing acceptance for drug approvals. Nonetheless, these benefits come at cost of significant degradation in model performance for patients with multiple comorbidities or severe organ dysfunction, as well as those receiving polypharmacy, all scenarios that were excluded from the original model derivation. Machine learning and deep learning algorithms have opened new avenues to predict DDI, in particular ones involving new or unidirectional DDIs that cannot be identified by traditional modeling methods(Huang et al., 2025; Luo et al., 2024). But the clinical utility of these instruments is at present limited by absence of mechanistic interpretability, uncertainties in generalizability to disparate patient populations and drug categories, and the absence of prospective clinical validation. The translational chasm between performance on training data and clinical impact is vast and mostly unexamined. Explainability, regulatory approval and algorithmic bias mitigation are to be considered as a part of the pathway leading to safe, scalable deployment of these systems (Huang et al., 2025).

4.2.Pharmacogenomics: The Future DDI of Personalized Medicine

Metabolic Phenotypes of DMEs and Its Influence on Drugs Variants in drug-metabolizing enzyme genes (e.g., CYP2D6, CYP2C19, and CYP3A5) can be categorized into poor, intermediate, extensive, and ultra-rapid metabolizer phenotypes, which may differently respond to drug exposure(Posadzki, Watson, & Ernst, 2013). This unique drug metabolizing profile, combined

with the effect of pharmacokinetics of a drug co-administered, may generate unexpected drug-drug-gene interactions which leads to adverse drug reaction or loss of efficacy. Adding pharmacogenomic information provides better prediction of the risk of DDI and can assist in individualizing dosing. The challenge is logistics: pharmacogenomic testing isn't available at all sites, or indeed for patients in many parts of the developing world; there is a global shortage of education in how to interpret pharmacogenomic tests; and much of pharmacogenomic research has been conducted in European populations, which may not be relevant to people of other ethnicities(Guo & Dong, 2026). Hence, there exist challenges regarding research and ethics in order to foster pharmacogenomic studies across various populations and to address the issue of access.

4.3.At-Risk Populations and Clinical Management Priorities

Patients have different susceptibility to DDIs. DDI risk is influenced by age, comorbidities, organ function, and availability of healthcare. Age is the most determinant factor for the risk of ADR at individual level considering the age-related alterations in pharmacokinetics and pharmacodynamics as well as the high rate of polypharmacy and multiple disease at elderly (Frydenlund et al., 2026; Zhai et al., 2025). Cardiovascular disease, cancer and neurological disorder have a higher risk of DDI as their drug regimen are more complex(Yu et al., 2026). Both renal and hepatic disease compound this risk, as they alter drug clearance and thus predispose to drug accumulation.

Well-resourced health care systems with robust pharmacovigilance, electronic prescribing systems and clinical decision support identify many more DDI-related incidents have better outcomes than resource-limited systems (Zhai et al., 2025). It is not because the inherent burden of DDI harm is less in LMICs; if drug quality control is poor and therapeutic drug monitoring is not done, burden of DDI harm may be higher, but detection rates are low.

Rigorous medication reconciliation and DDI screening before surgical procedures are well-established best practices not routinely applied. Likewise, the treatment of serious infection requiring potent CYP-modulating antiviral or antimicrobial therapy - as exemplified by the COVID-19 pandemic - requires active dose adjustment and replacement of interacting agents with alternative therapies, where available (Zeitlinger et al., 2020).Clinical Decision Support Systems (CDSS) incorporating artificial intelligence are an emerging approach to prevent DDI in real-time. When embedded into prescribing systems, they issue patient-specific interaction warnings before drug administration. Initial reports of use are promising; but there is the problem of alert fatigue - caused by suboptimal alert thresholds - which limits clinical impact (Huang et al., 2025). The design of CDSS to prioritize valuable and actionable alerts without alert fatigue is a human factor as well as a technological challenge, and therefore deserving of research attention.

4.4.Research Gaps

Although many aspects have been addressed well, this review also highlights several areas with undeveloped science in which the consequences of that underdevelopment are experienced by patients. Firstly, the biology underlying drug transporters has not been adequately characterized. Drug-drug interactions through these transporters in sequestered tissue compartments (e.g., brain, heart) may be promoting unrecognized adverse outcomes not yet considered in risk assessment paradigms. In addition, prospective clinical validation of predictive algorithms in a variety of populations is urgently needed. PBPK models and machine learning methodologies are often trained on data originating from studies with controlled designs or including demographically homogeneous populations, with yet unknown generalizability to patients with organ impairment, spanning the full age spectrum, afflicted with polypharmacy or presenting with rare genotypes. Prospective clinical trials and pragmatic studies that test these tools against clinically relevant outcomes (beyond

simply accuracy) are required to fully utilize these tools.

Thirdly, DDI investigations continue to be quite centered on geographical and sociodemographic regions with most of the basal work conducted in wealthy nations. It is scientifically risky to extrapolate these findings to Sub-Saharan African, South Asian, East Asian, or Indigenous patients, who most likely have distinct genetic risks and exposures(Guo & Dong, 2026).

Fourth, DDI for novel therapeutic modalities, such as biologics, monoclonal antibodies, and small interfering RNAs (siRNAs) are still to be fully described. These molecules have entirely different pharmacokinetic profiles compared to the conventional small molecules, and their potential for DDI has not been extensively studied(Choi & Song, 2026). In addition, interactions with herbal and dietary supplements, which are important in both developed and developing countries, also are lacking in mechanistic insights that would be useful for clinical practice.

Fifth, the intricacy of real-world polypharmacy (here defined as the simultaneous consumption of four or more drugs) is not captured by pairwise DDI models. Network pharmacology models which typify multiple concurrent interactions, off-target effects and negative feedback may better represent risk of polypharmacy in the elderly(Huang et al., 2025). Integration of such network analyses with PBPK modeling and AI is an avenue for future studies.

Lastly, pharmacovigilance infrastructure in low- and middle-income countries (LMIC) must be prioritized as a global health issue given the skewed representation in global safety databases (relative to population), resulting in a significant amount of global DDI-induced harm being unseen by science and policy(Aslam et al., 2026; Wasiullah et al., 2025).

5. FUTURE PERSPECTIVES

It can be suggested that drug-drug interaction management in pharmacokinetics will become more predictive, personal and technology-focused in the future. Among the key trends in the field, one should highlight the use of artificial intelligence and machine learning in pharmacovigilance. This predictive approach based on machine learning algorithms and multidimensional datasets will provide the opportunity to predict the probability of DDIs (Dsouza, Leyens, Kurian, Brand, & Brand, 2025; C. Y. Lee & Chen, 2019). Moreover, validation of the model and problem-solving in terms of bias and transparency should be considered in the process. Pharmacogenomics research will also influence the process of drug-drug interaction management in pharmacokinetics. As a result of pharmacogenomics research, it becomes possible to personalize pharmacotherapy according to individual characteristics of patients' genes. Enzymatic metabolism of drugs shows a high degree of variability and is the source of drug interactions because of the genetic variability of enzymes involved in this process (Palleria et al., 2013). The approach fits into the overall trend of precision medicine, where treatment plans will be customized according to each patient.

Additionally, the implementation of the CDSS that will generate real-time warnings about potential DDIs during prescription becomes necessary. These warnings will serve as an attempt to reduce the risk of errors and ultimately protect patients' lives. The future of the system will rely on using updated information about patients' status and real-time data on drug safety.

Besides, there is a necessity for more standardization and development of databases for pharmacovigilance. Several challenges can be identified within the current state of such systems: lack of completeness due to inadequate reporting, improper structure of data collection, and insufficient demographic diversity. Future efforts will aim to solve the problem.

Finally, the importance of interdisciplinary research in this field becomes evident. The experience and knowledge of different stakeholders – from clinicians and pharmacists to bioinformaticians and regulatory agencies – is required to address the problem of pharmacokinetic DDIs. Additionally, healthcare

providers and patients need education on the topic to eliminate potential DDIs.

6. CONCLUSION

Pharmacokinetic-related drug-drug interactions (PK DDIs) are still a crucial subject of modern clinical pharmacology since therapeutic outcomes can be influenced via changes in the ADME properties of co-administered drugs(Peng et al., 2021). These DDIs have effects such as underdosing leading to ineffective treatment and overdosing causing adverse reactions due to a high concentration of the drug consumed (Rai & Rozario, 2023). Medical practitioners will need to know about the mechanisms to preclude complications as multi drug regimens become more common for the treatment of a variety of diseases.Pharmacokinetic drug-drug interactions should be tackled via personalized medicine and full exploitation of the technology. Integration of multiple technologies, for example, physiologically based pharmacokinetics (PBPK) with pharmacogenomics, will enable prediction of patient response and identification of individuals at risk based on their unique genes related to metabolism(Peng et al., 2021; Rai & Rozario, 2023).

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