

Drug Interactions: Mechanisms, Classification, and Clinical Significance — A Review

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Abstract:

Concurrent use of multiple medications is now the norm rather than the exception in modern clinical practice, driven by an ageing population, rising rates of multimorbidity, and increasingly complex treatment regimens. This growth in polypharmacy has been paralleled by a corresponding rise in drug interactions (DIs) — clinically meaningful changes in the effect of one medicine caused by the co-administration of another drug, a food, an herbal product, or a disease state. DIs are a major, and often preventable, cause of adverse drug events, ranging from subclinical shifts in drug exposure to serious toxicity, therapeutic failure, hospitalisation, and death. This narrative review synthesised current understanding of the mechanisms underlying drug interactions and the frameworks used to classify them. Interactions were examined through three overlapping classification schemes: by mechanism (pharmacokinetic, pharmacodynamic, and pharmaceutical/physicochemical), by source (drug–drug, drug–food, drug–herb, and drug–disease), and by clinical significance (severity, onset, and level of documentation). Pharmacokinetic mechanisms affecting absorption, distribution, metabolism, and excretion were discussed in detail, with particular attention to cytochrome P450-mediated metabolism, drug transporters, and genetic variability in these pathways. Pharmacodynamic mechanisms, patient- and drug-related risk factors, illustrative high-risk drug classes, tools for detecting and assessing interaction causality, and strategies for prevention and clinical management were also reviewed. The review concluded that a working knowledge of these mechanisms and classification frameworks is essential for anticipating, recognising, and managing drug interactions in everyday clinical and pharmaceutical practice.

Keywords: Drug interactions, pharmacokinetics, cytochrome P450, adverse drug events, pharmacogenomics.

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Introduction

A drug interaction (DI) occurs when the effect of one medication — its efficacy, safety, or both is altered by the presence of another substance taken at the same time. That substance may be a second drug, a component of food, an herbal or dietary supplement, or, in a broader sense, a disease state that changes how a drug behaves in the body. Interactions are not inherently harmful; some are exploited deliberately for therapeutic benefit, such as combining a beta-lactam antibiotic with a beta-lactamase inhibitor. The great majority of clinically important interactions, however, are unintended and carry the potential to reduce therapeutic effect, provoke toxicity, or do both simultaneously.

The clinical relevance of this topic has grown alongside the increasing complexity of modern prescribing. A repeated cross-sectional analysis of community prescribing in Scotland found that, between 1995 and 2010, the proportion of adults dispensed five or more regular drug classes doubled to 20.8%, while the proportion dispensed ten or more nearly tripled to 5.8% and the prevalence of potentially serious drug–drug interactions rose in parallel with this polypharmacy trend (Guthrie et al.). The consequences are not merely theoretical: a recent descriptive analysis of the United States FDA Adverse Event Reporting System identified over 167,000 reported cases of drug–drug interactions, of which more than 44% resulted in hospitalisation and 8.4% resulted in death, with widely prescribed agents such as warfarin, aspirin, sertraline, tacrolimus, and simvastatin among the most frequently implicated medicines (Alahmari et al.). In recognition of this burden, the World Health Organization launched its Third Global Patient Safety Challenge, Medication Without Harm, in 2017, targeting a 50% reduction in severe, avoidable medication-related harm worldwide, with polypharmacy explicitly named as one of three priority action areas (World Health Organization). Because a substantial proportion of interaction-related events are considered preventable, understanding why and how drugs interact is a prerequisite for anticipating and avoiding them, rather than simply reacting to them after harm has occurred.

This review focuses on the general mechanisms by which drug interactions arise and the systems used to classify them. It is organised around three complementary classification lenses: mechanism, source, and clinical significance. Before examining pharmacokinetic and pharmacodynamic mechanisms in detail, the growing role of pharmacogenomics, the patient- and drug-related factors that modulate clinical risk, illustrative high-risk drug classes,

methods for detecting and assessing interactions, and general principles of prevention and management.

Results and Discussion

Classification of Drug Interactions

Drug interactions are conventionally classified along three overlapping axes.

Classification by mechanism. The most fundamental distinction is between pharmacokinetic, pharmacodynamic, and pharmaceutical interactions (Freedman). Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism, or excretion of another, changing the concentration of the affected drug at its site of action without necessarily changing its inherent pharmacological effect. Pharmacodynamic interactions occur when two drugs act via the same or different mechanisms — on the same physiological system, producing additive, synergistic, or antagonistic effects without any change in either drug's plasma concentration. Pharmaceutical (or physicochemical) interactions are a narrower category referring to direct physical or chemical incompatibility between two agents, typically before administration, such as precipitation when incompatible intravenous drugs are mixed in the same infusion line.

Classification by source. Interactions are also classified by the nature of the interacting agent: drug–drug (the most extensively studied category), drug–food (for example, the classic interaction between grapefruit juice and certain calcium channel blockers or statins), drug–herbal/dietary supplement (for example, St John's Wort's induction of multiple metabolic pathways, which has been linked to reduced efficacy of oral contraceptives, immunosuppressants, and anticoagulants) (Zuo et al.), and drug–disease interactions, in which an underlying condition (such as renal or hepatic impairment) changes a drug's disposition or makes a particular pharmacological effect more hazardous.

Classification by clinical significance. For practical and clinical decision-making purposes, interactions are further graded by three additional parameters commonly used in drug interaction compendia and clinical decision-support tools: severity (major/contraindicated, moderate, or minor, reflecting the seriousness of the potential outcome), onset (rapid, where effects appear within hours, versus delayed, where effects may take days to weeks to become apparent — particularly relevant for enzyme-

induction interactions), and level of documentation (ranging from well-established, based on controlled clinical studies, through probable and suspected, down to interactions that are theoretical or based only on the known pharmacology of structurally related agents).

Pharmacokinetic Mechanisms

Pharmacokinetic interactions are the most common and best-characterised category of drug interaction and can be organised according to the four classic pharmacokinetic processes: absorption, distribution, metabolism, and excretion (Peng et al.).

Absorption. Interactions affecting absorption most often reduce, rather than increase, the amount of drug reaching the systemic circulation. Mechanisms include direct chemical complexation or chelation (for example, divalent and trivalent cations in antacids, calcium supplements, or iron preparations binding tetracyclines or fluoroquinolones to form poorly absorbed complexes); alteration of gastrointestinal pH (proton pump inhibitors and H₂-receptor antagonists can reduce the absorption of drugs that require an acidic environment for dissolution); and changes in gastrointestinal motility (prokinetic agents can accelerate gastric emptying and alter the rate, though not always the extent, of absorption of other drugs, while opioids and anticholinergics can slow it).

Distribution. Once absorbed, many drugs circulate partly bound to plasma proteins, principally albumin and alpha-1-acid glycoprotein, with only the unbound fraction pharmacologically active. Highly protein-bound drugs can, in principle, displace one another from binding sites, transiently raising the free fraction of the displaced drug. In practice, this mechanism is now understood to be of limited standalone clinical significance for most drugs, because the increase in free drug is usually offset by a compensatory increase in clearance; it becomes clinically important chiefly when combined with a simultaneous reduction in the displaced drug's metabolic or renal clearance, or when the drug has a narrow therapeutic index and a small volume of distribution.

Metabolism. Hepatic metabolism is the single most important site of pharmacokinetic drug interactions, and the cytochrome P450 (CYP) enzyme superfamily is central to this process. A small number of CYP isoforms — principally CYP3A4/5, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 — are responsible for the oxidative metabolism of the majority of marketed drugs. Interactions arise when one drug (the

"perpetrator") inhibits or induces the enzyme responsible for metabolising another (the "victim") (Peng et al.). Enzyme inhibition is typically competitive and can produce a clinically relevant rise in victim-drug concentration within hours to days. A well-studied example is the "grapefruit juice effect": furanocoumarins in grapefruit irreversibly inhibit intestinal CYP3A4, increasing the oral bioavailability of numerous CYP3A4 substrates, including several calcium channel blockers, statins, and benzodiazepines, with the interaction persisting for two to three days after the last exposure while the affected enterocytes are replaced (Abu Dayyih et al.). Enzyme induction, by contrast, results from increased transcription of the enzyme gene and therefore has a delayed onset (typically one to three weeks) and an equally delayed offset after the inducing agent is withdrawn; classic inducers include rifampin, carbamazepine, phenytoin, and St John's Wort, all of which can substantially reduce the efficacy of co-administered CYP substrates, including oral contraceptives and immunosuppressants. Membrane transport proteins are increasingly recognised as an independent source of pharmacokinetic interaction alongside metabolism. P-glycoprotein, an efflux transporter expressed in the gut, liver, kidney, and blood-brain barrier, limits the absorption and promotes the elimination of its substrate drugs; inhibitors such as verapamil, amiodarone, and clarithromycin can raise plasma concentrations of P-glycoprotein substrates such as digoxin and dabigatran, in some cases producing a clinically important rise in bleeding or toxicity risk, while inducers such as rifampicin can reduce their bioavailability (Finch and Pillans).

Excretion. Renal excretion can be altered through competition for active tubular secretion (historically exploited therapeutically, as when probenecid is co-administered with penicillin to prolong its half-life), through changes in urinary pH that affect the ionisation and therefore the reabsorption of weak acids or bases, and through inhibition of renal transport proteins. Biliary excretion and enterohepatic recirculation represent a further, less common route by which one drug can influence the elimination of another. Because many drugs and their metabolites are cleared renally, impaired kidney function itself behaves as a pharmacokinetic risk factor that compounds the effect of a true drug-drug interaction, and dosage adjustment based on estimated creatinine clearance or glomerular filtration rate is a standard part of safe prescribing in patients with reduced renal function.

Pharmacodynamic Mechanisms

Pharmacodynamic interactions occur without any change in the plasma concentration of either drug and instead reflect an interplay of pharmacological effects. Broadly, three patterns are recognised. First, two drugs may act at the same receptor or binding site, producing competitive agonism or antagonism — for example, an opioid antagonist reversing the effect of an opioid agonist. Second, and more commonly encountered in everyday practice, two drugs with different mechanisms of action may produce an additive or synergistic effect on the same physiological endpoint. Well-documented examples include: the additive central nervous system and respiratory depression produced by combining opioids with benzodiazepines or other CNS depressants, a combination serious enough that regulators have required boxed warnings on both drug classes describing the increased risk of profound sedation, respiratory depression, and death (U.S. Food and Drug Administration); serotonin syndrome, which arises when two or more serotonergic agents (such as an SSRI combined with tramadol, an MAOI, or certain other analgesics) are combined, producing excessive stimulation of central and peripheral serotonin receptors and a toxidrome of altered mental status, autonomic hyperactivity, and neuromuscular abnormalities (Mikkelsen et al.); the additive risk of bleeding when anticoagulants are combined with antiplatelet agents or NSAIDs; and the additive risk of QT-interval prolongation and torsades de pointes when two or more QT-prolonging drugs are used together, a risk that has been shown to be particularly prevalent in populations such as cancer patients who are frequently exposed to multiple QT-prolonging antiemetics, antipsychotics, and antineoplastic agents simultaneously (Khan et al.). Third, two drugs may produce opposing physiological effects — physiological antagonism — such as the concurrent use of a stimulant and a sedative, which may mask or blunt each other's intended therapeutic effect.

Pharmacogenomic Considerations

An increasingly important refinement to the classical pharmacokinetic model is the recognition that genetic variation in drug-metabolising enzymes can itself determine whether, and how severely, a given pharmacokinetic interaction manifests in an individual patient. Polymorphisms in CYP2C9, CYP2C19, and CYP2D6 in particular are associated with clinically meaningful differences in enzyme activity, ranging from poor to ultrarapid metaboliser phenotypes (Cavallari et al.). For example, carriers of reduced-function CYP2C9 alleles typically require substantially lower warfarin doses to achieve

therapeutic anticoagulation and are at correspondingly higher risk of toxicity if additionally exposed to a CYP2C9 inhibitor; carriers of loss-of-function CYP2C19 alleles generate less of the active metabolite of the prodrug clopidogrel, blunting its antiplatelet effect; and CYP2D6 ultrarapid metabolisers can convert codeine to morphine unusually quickly, raising the risk of opioid toxicity, while poor metabolisers obtain little analgesic benefit from the same drug. These examples illustrate that an individual's genotype can convert what would be a minor interaction in most patients into either a substantially amplified or a negligible one, underscoring the move toward genotype-informed, individualised approaches to interaction risk assessment.

Factors Influencing the Clinical Significance of Drug Interactions

Not every pharmacokinetic or pharmacodynamic interaction that can be demonstrated *in vitro* or in a subset of patients translates into clinically meaningful harm; the eventual outcome depends on a combination of patient- and drug-related factors.

Patient-related factors include age (both neonates/infants and older adults have reduced metabolic and excretory reserve, and older adults are additionally more likely to be prescribed multiple interacting medicines), hepatic and renal function (impairment reduces the physiological reserve available to compensate for an interaction-induced change in clearance, and dosage adjustment guided by estimated glomerular filtration rate is recommended for renally cleared drugs in this population) (Munar and Singh), genetic makeup (as discussed above), and the overall burden of polypharmacy and comorbidity. These concerns are formalised for older adults in tools such as the American Geriatrics Society Beers Criteria, an explicit, regularly updated list of medications and medication combinations that are typically best avoided in older adults because the potential for harm — including through drug–drug and drug–disease interactions — outweighs the expected benefit (2023 American Geriatrics Society Beers Criteria Update Expert Panel).

Drug-related factors include the therapeutic index of the affected drug — agents such as warfarin, digoxin, lithium, phenytoin, and immunosuppressants such as tacrolimus have a narrow margin between therapeutic and toxic concentrations, so that even a modest interaction-induced change in exposure can produce clinically important consequences, whereas

drugs with a wide therapeutic index can usually tolerate the same magnitude of change without harm. Other relevant drug factors include the potency of an enzyme or transporter inhibitor/inducer, the dose and duration of the interacting therapy, and the specific route of administration, since interactions affecting first-pass metabolism are most pronounced for orally administered drugs with high hepatic extraction.

High-Risk Drug Classes and Illustrative Interactions

Certain therapeutic areas concentrate a disproportionate share of clinically significant drug interactions, and reviewing them illustrates how the mechanisms above combine in practice. Antiretroviral regimens for HIV are a long-recognised example: because regimens typically combine three or more agents with extensive involvement of CYP450 enzymes, P-glycoprotein, and other transporters, and because patients frequently require additional therapy for opportunistic infections and comorbidities, interactions among antiretrovirals — and between antiretrovirals and other drug classes — are common and often clinically unavoidable, requiring proactive management rather than simple avoidance (Piscitelli and Gallicano). Oral anticoagulants form a second high-risk class: warfarin alone has more than 200 documented interactions, principally through inhibition or induction of CYP2C9 and CYP3A4, while the newer direct oral anticoagulants remain vulnerable to interactions through P-glycoprotein and, for rivaroxaban and apixaban, CYP3A4, in addition to shared pharmacodynamic bleeding risk with antiplatelet agents, NSAIDs, and serotonergic drugs (Vazquez). These examples reinforce a broader point: drug classes that are both pharmacokinetically complex (multiple enzyme and transporter pathways) and pharmacodynamically high-stakes (narrow therapeutic index, or a severe potential adverse effect) warrant the greatest vigilance in interaction screening.

Detection, Causality Assessment, and Prediction

Identifying drug interactions occurs at several stages of the medicine's lifecycle. During drug development, in vitro systems including human liver microsomes, hepatocytes, and recombinantly expressed CYP enzymes are used to characterise a candidate drug's potential to inhibit or induce major metabolic pathways, increasingly supplemented by in silico approaches such as physiologically based pharmacokinetic modelling (Peng et al.). In clinical practice, electronic prescribing systems and dedicated

interaction-checking databases provide point-of-care alerts intended to flag potentially hazardous combinations before a prescription is dispensed. However, override rates for these alerts are consistently high — a scoping review of the literature found that a large proportion of interruptive drug–drug interaction alerts are overridden by prescribers, a pattern widely attributed to "alert fatigue" arising from a high volume of alerts with limited clinical specificity, which has prompted efforts to develop more selective, tiered alerting criteria (Villa Zapata et al.). More recently, machine learning and deep learning methods — including graph-based and knowledge-graph models trained on large pharmacological and molecular datasets — have been explored as a way to predict previously undocumented interactions computationally and to prioritise which combinations warrant experimental or clinical follow-up, although current models remain limited by data quality, class imbalance, and interpretability (Gheorghita et al.).

When a suspected interaction is identified in an individual patient — whether in routine practice or for the purposes of a published case report — establishing a causal link between the co-administered drugs and the observed clinical event requires a structured approach. The Drug Interaction Probability Scale (DIPS), developed specifically for this purpose, uses a ten-item questionnaire addressing the temporal relationship between drug exposure and the event, the known pharmacology of both the object and precipitant drugs, and the effect of rechallenge and rechallenge where available, to assign a probability rating ranging from doubtful to highly probable (Horn et al.). Such structured tools improve the consistency and rigour with which individual interaction cases are evaluated and reported in the literature.

Prevention and Clinical Management

Because most clinically significant drug interactions are foreseeable from a knowledge of the drugs' pharmacology, prevention is generally more achievable than management after the fact. Core strategies include thorough medication reconciliation at points of care transition, so that the complete list of a patient's prescribed, over-the-counter, and herbal medicines is known before new therapy is started (a strategy that systematic reviews have found reduces unintentional medication discrepancies and associated harm when implemented consistently, particularly when led by a pharmacist) (Kwan et al.); avoidance of known high-risk combinations where a therapeutically equivalent, non-interacting alternative exists; dose adjustment and, where appropriate,

therapeutic drug monitoring for narrow-therapeutic-index drugs when an interacting agent cannot be avoided; separation of administration times for interactions that depend on physical or chemical contact in the gut, such as chelation; and clear communication with patients regarding the risks associated with over-the-counter medicines, herbal products, and specific foods. Deprescribing — the planned, supervised process of reducing or stopping medications that may no longer provide benefit or that carry disproportionate interaction risk — has been proposed as a systematic, structured response to inappropriate polypharmacy, complementing reactive interaction-checking with a periodic proactive review of the entire medication regimen (Scott et al.).

Conclusion

Drug interactions arise from a limited number of well-characterised pharmacokinetic and pharmacodynamic mechanisms, yet their clinical consequences are shaped by a wide range of patient-specific and drug-specific factors, from genotype to organ function to therapeutic index. As polypharmacy continues to increase across ageing and multimorbid populations, a solid grounding in the mechanisms and classification of drug interactions — rather than reliance on memorised lists of specific drug pairs — remains one of the most transferable and durable tools available to clinicians, pharmacists, and researchers for anticipating and preventing medication-related harm.

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