REVIEW

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Drug-drug Interactions with Oral Anticancer Agents: Mechanisms, Clinical Impact, and Management Strategies

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ABSTRACT

Oral anticancer agents (OAAs) have transformed cancer care by enabling at-home treatment; however, they present challenges due to frequent polypharmacy, narrow therapeutic indices, and reliance on metabolic and transporter pathways. OAAs are predominantly metabolized by CYP3A4/5 and transported by proteins such as P-glycoprotein and breast cancer resistance protein, making them vulnerable to inhibitors and inducers that can dramatically alter systemic exposure. While enzyme inducers like rifampin and some anticonvulsants can lower exposure and compromise efficacy, strong CYP3A inhibitors, such as azole antifungals and macrolides, dramatically raise OAA concentrations, increasing the risk of toxicity. Because of overlapping toxicities such as myelosuppression, hepatotoxicity, QT prolongation, and bleeding, pharmacodynamic drug-drug interactions (DDIs) intensify adverse effects even in the absence of changes in drug levels. Older adults, patients with organ impairment, and those undergoing complicated supportive regimens are at the highest risk for these complications. By permitting customized dose adjustments and identifying high-risk interactions, precision-dosing techniques such as therapeutic drug monitoring, pharmacogenomics, physiologically based pharmacokinetic modeling, and model-informed precision dosing provide a way to reduce the harm associated with DDI. Safe prescribing requires multidisciplinary medication reviews an incorporation of decision-support tools. Taken together, optimizing OAA therapy, lowering toxicity, and improving treatment efficacy depend on an understanding of mechanistic pathways, clinical outcomes, and precision-dosing techniques.

Keywords: Oral anticancer agents; drug-drug interactions; tyrosine kinase inhibitors; pharmacokinetics; pharmacodynamics

INTRODUCTION

Oral anticancer agents (OAAs) have transformed oncology by enabling home-based treatment and greater patient independence, but they are frequently associated with clinically significant drug-drug interactions (DDIs).[1] Polypharmacy, age-related changes in drug metabolism, and multiple comorbidities increase patient vulnerability, making proactive DDI management essential.[2] Nearly 90% of patients receiving OAAs experience at least one potential interaction, with consequences ranging from reduced efficacy to increased toxicity.[3] These risks are amplified by the narrow therapeutic ranges and complex elimination pathways of many anticancer drugs.[1,4,5] Most OAAs depend on cytochrome P450 (CYP) enzymes and drug transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein, rendering them particularly susceptible to metabolism- and transporter-mediated DDIs.[6] CYP3A4 activity and P-gp transport are central to the disposition of tyrosine kinase inhibitors (TKIs), including imatinib, erlotinib, and neratinib.[7] Enzyme induction by agents such as rifampin can reduce exposure and efficacy, whereas inhibition by drugs such as ketoconazole may cause drug accumulation and toxicity.[5,8] Acid-reducing agents (ARAs), including proton pump inhibitors (PPIs) and H_2 receptor antagonists, further lower exposure by impairing absorption of weakly basic OAAs such as dasatinib, gefitinib, and erlotinib, and should be avoided when unnecessary.[9] Pharmacodynamic (PD) interactions also contribute substantially to clinical risk.[10] Concomitant use of

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OAAs with QT-prolonging agents increases arrhythmia risk, while coadministration with anticoagulants raises bleeding risk.[8,11] These interactions require close monitoring and dose adjustment when appropriate.[8,9] Polypharmacy further increases the likelihood of CYP- and transporter-mediated DDIs.[2,3] Regular medication review, particularly at treatment initiation or modification, reduces harm, and pharmacist-led interventions have been shown to lower DDI prevalence and improve management through multidisciplinary collaboration.[4,12] DDI prevention programs, electronic decision-support systems, and individualized dosing guided by therapeutic drug monitoring (TDM) have been associated with reduced hospitalizations and improved patient safety.[13] Integration of pharmacogenomic data with TDM supports individualized dosing of selected OAAs, including neratinib.[6,14] Genetic variability in enzymes and transporters such as CYP3A4, CYP2D6, and ABCB1 further modifies DDI risk. During the coronavirus disease-19 pandemic, use of strong CYP3A4 inhibitors such as nirmatrelvir and ritonavir highlighted the potential for severe increases in OAA toxicity.[15] As treatment strategies evolve, continued vigilance is required, since unrecognized DDIs can impair quality of life, adherence, and clinical outcomes, and may result in treatment failure or dose modification.[1,16] Effective DDI prevention relies on patient education, reliable interaction databases, and systematic medication review, with active patient reporting of all concomitant therapies.[13] Although DDIs involving OAAs are clinically important, they remain underrecognized in routine practice. Improved understanding of pharmacokinetics (PKs), PDs, and transporter mechanisms, together with precision-based strategies such as TDM, pharmacogenomics, and individualized dosing, can substantially improve safety and therapeutic outcomes.[17] Given the complexity of oral anticancer therapy, optimal management requires multidisciplinary collaboration, careful monitoring, and ongoing education. Advances in precision dosing, supported by expanding research into PK, PD, and transporter-mediated interactions, provide a framework to enhance the safety and effectiveness of oral anticancer treatment.[18] This review examines drug interactions with OAAs, focusing on mechanistic pathways including transporter effects, pH-dependent absorption, CYP-mediated metabolism, and PD overlap, and on their clinical implications and management strategies. In the setting of increasing polypharmacy, aging populations, and widespread use of enzyme modulators and supportive therapies, DDIs remain common yet underappreciated. By integrating quantitative clinical data, real-world outcomes, and precision-dosing tools, this review offers a practical framework to improve the safety and effectiveness of oral anticancer therapy.

MATERIAL AND METHODS

The published literature on DDIs involving OAAs was systematically evaluated for this narrative review. Major biomedical databases, including PubMed, Scopus, and Web of Science, were searched for peer-reviewed publications, with a focus on English-language studies addressing PK, PD, transporter-mediated, and absorption-related DDIs. Key search terms included combinations of the following: "oral anticancer agents," "drug-drug interactions," "CYP enzymes," "P-glycoprotein," "BCRP," "therapeutic drug monitoring," "pharmacogenomics," "physiologically based pharmacokinetic modelling," and "precision dosing." To ensure clinical relevance, priority was given to clinical trials, observational studies, systematic reviews, regulatory documents, and relevant PK modelling studies. The qualitative synthesis emphasized biological mechanisms, clinical impact, high-risk drug combinations, and contemporary management strategies, including precision-dosing approaches. Empirical evidence and established guidelines were also incorporated to provide a clinically applicable and mechanism-driven perspective on DDI prevention and management in oncology practice.

1. Mechanisms of DDIs

OAAs and concomitant medications are particularly susceptible to PK DDIs mediated by hepatic and intestinal CYP enzymes, as many targeted small-molecule therapies undergo extensive clearance through these pathways. Among the CYP isoforms, CYP3A4 and CYP3A5 are the principal enzymes responsible for the metabolism of most OAAs, while CYP2C19 and CYP1A2 contribute significantly to the clearance of specific agents. Concomitant exposure to strong CYP inhibitors, such as ketoconazole, itraconazole, and ritonavir, or CYP inducers, including rifampicin and carbamazepine, can result in clinically meaningful increases or decreases in OAA exposure, leading to increased toxicity or loss of therapeutic efficacy.[19] At the molecular level, CYP-mediated DDIs arise through three primary mechanisms: competitive inhibition, in which two substrates compete for the same active site; mechanism-based irreversible inhibition, in which the perpetrator permanently inactivates the enzyme; and enzyme induction mediated by nuclear receptor activation, including the pregnane X receptor and the constitutive androstane receptor, in which transcription of CYP genes is increased and metabolic clearance is enhanced. Inhibition of intestinal CYP3A4 is of particular relevance for orally administered drugs with high first-pass metabolism, as even modest changes in intestinal enzyme activity can disproportionately affect oral bioavailability.[20] The clinical relevance of these interactions is amplified in oncology due to the narrow therapeutic indices and exposure-response

relationships characteristic of many OAAs. Enzyme inhibition may result in supratherapeutic plasma concentrations and dose-limiting toxicities, such as severe myelosuppression or hepatotoxicity, whereas enzyme induction can reduce systemic exposure below therapeutic thresholds, leading to treatment failure. Real-world studies and systematic reviews consistently demonstrate that a substantial proportion of patients receiving OAAs are exposed to at least one potential CYP-mediated interaction, underscoring the need for proactive identification and management.[21] Management strategies for CYP-mediated DDIs integrate careful drug selection, clinical monitoring, and precision-dosing approaches. Practical measures include avoidance of strong DDI perpetrators when possible; substitution with non-interacting alternatives; dose modification based on the interaction magnitude reported in clinical DDI studies and regulatory labeling; and use of TDM or model-informed precision dosing (MIPD) when exposure-outcome relationships are established. Current guidelines recommend empiric dose reduction, intensified monitoring, or temporary treatment interruption for CYP3A-metabolized OAAs when potent inhibitors cannot be avoided. Both MIPD and TDM play an important role in mitigating DDI effects and managing interpatient variability.[20] To optimize efficacy and safety in oral anticancer therapy, regulatory resources, such as Food and Drug Administration DDI tables, together with interdisciplinary clinical practices involving oncology pharmacists and TDM laboratories, integrate CYP3A4/5, CYP2C19, and CYP1A2 interaction data to translate mechanistic knowledge into safe and effective prescribing decisions.[5,22] The accompanying table summarizes the major PK and PD mechanisms of DDIs affecting OAAs, highlighting their clinical impact, common victim drugs, frequent perpetrators, and key references. The overall key points of the mechanisms are presented in Table 1 below.

1.1. Transporter-mediated Interactions [P-gp, Breast Cancer Resistant Protein (BCRP), Organic Anion-transporting Polypeptide (OATP)]

Transporter proteins, particularly the efflux pumps P-gp/ATP-binding cassette subfamily B member 1 and BCRP/ATP-binding cassette subfamily G member 2 and uptake carriers of the OATP/solute carrier organic anion transporter family, especially OATP1B1 and OATP1B3, play a fundamental role in the absorption, distribution, and the hepatic and intestinal clearance of most orally administered anticancer small-molecule drugs. In targeted oral therapies, transporter activity at the intestinal epithelial membrane and the hepatocyte sinusoidal membrane critically determine bioavailability and hepatic exposure. Consequently, alterations in transporter function can significantly modify systemic drug exposure independently of CYP-mediated metabolism.[23] Transporter-mediated DDIs generally arise through two principal mechanisms: inhibition, which results in an acute reduction of transporter activity, and induction or downregulation, which occurs over days to weeks and alters transporter expression. Concomitant administration of P-gp or BCRP inhibitors with a transporter substrate enhances intestinal absorption and reduces biliary or intestinal efflux, leading to marked increases in plasma area under the concentration-time curve and peak concentration. These changes are clinically relevant for drugs with narrow therapeutic indices.[24] In contrast, transporter induction, or increased efflux activity, reduces systemic exposure and increases the risk of subtherapeutic dosing. Importantly, several TKIs and other targeted agents inhibit hepatic OATP1B transporters, reducing hepatic uptake of co-administered drugs such as statins. This mechanism can elevate plasma concentrations of these co-medications and increase the risk of toxicity.[25] Clinical studies in cancer patients illustrate these effects. Many TKIs are substrates of P-gp and BCRP, and co-administration with strong transporter inhibitors, including azole antifungals, certain antivirals, and calcium-channel blockers, has been associated with clinically significant increases in the toxicity of anticancer drugs. Similarly, anticancer agents that inhibit OATP1B1 or OATP1B3 can raise plasma levels of OATP substrates such as rosuvastatin or methotrexate, leading to adverse effects. Because many perpetrator drugs affect both transporters and CYP enzymes, such as ketoconazole through simultaneous inhibition of intestinal P-gp and CYP3A, comprehensive clinical pharmacology studies are often required to determine the relative contribution of transporter-mediated versus metabolic interactions.[26] Management strategies for transporter-mediated DDIs parallel those used for metabolic interactions but require transporter-specific expertise. These strategies include avoidance or substitution of potent transporter inhibitors or inducers when feasible, empirical dose adjustment when the interaction magnitude is known, and TDM or MIPD for drugs with established exposure-response relationships.[27] Clinical decision-making is further supported by *in vitro*-to-*in vivo* prediction tools, including static models and mechanistic physiologically based PK (PBPK) models that incorporate transporter kinetics to estimate changes in drug exposure and guide clinical DDI study design and labeling recommendations. Multidisciplinary oncology teams, particularly pharmacists with expertise in transporter-mediated DDIs and access to current regulatory labeling and interaction tables, play a key role in translating mechanistic insights into safe and effective prescribing of oral anticancer therapies.[28]

1.2. Absorption-related Interactions (pH-dependent Solubility; ARAs)

Oral small-molecule anticancer drugs are typically weak bases whose solubility decreases as gastric pH increases, making them vulnerable to absorption-related DDIs when co-administered with ARAs, including PPIs, H_2 receptor antagonists, and antacids.[29] Even modest increases in intragastric pH can reduce gastric dissolution and intestinal absorption, leading to clinically relevant reductions in systemic exposure for drugs with pH-dependent solubility.[30] These interactions occur because many TKIs and targeted agents are highly soluble in acidic conditions but shift to a less soluble, non-ionized form as pH increases. The magnitude of exposure loss varies according to drug-specific factors such as pKa, intrinsic solubility, formulation, dose, and the duration and extent of ARA-induced pH elevation.[9] PPIs produce more sustained increases in gastric pH than H_2 receptor antagonists and are therefore most strongly associated with clinically significant reductions in exposure. Clinical studies have demonstrated lower plasma concentrations and, in some cases, reduced efficacy when PPIs are co-administered with pH-sensitive OAAs. Affected drugs include several TKIs, such as erlotinib, gefitinib, dasatinib, pazopanib, and crizotinib. Real-world and retrospective cohort studies have further linked concomitant PPI use with reduced progression-free survival for selected agents, including palbociclib and some epidermal growth factor receptor TKIs, although results vary by drug and study design.[31] Management of pH-dependent interactions should be drug-specific and evidence-based. PPIs should be avoided whenever a known pH-sensitive OAA is prescribed.[32] If acid suppression cannot be discontinued, substitution with an H_2 receptor antagonist or antacid, along with appropriate dose separation, may be considered when supported by data. Alternative anticancer therapies or non-pharmacologic gastroprotective strategies should be used when feasible. Regulatory labeling and clinical pharmacology data should guide dose adjustment decisions; TDM or MIPD may be applied to maintain therapeutic exposure when available. PBPK modeling and in vitro to in vivo prediction tools can further inform interaction magnitude and regulatory recommendations.[33] Routine medication reconciliation and multidisciplinary collaboration between pharmacists and oncology prescribers are essential to identify unnecessary acid suppression and reduce avoidable interactions. Regulatory guidance emphasizes individualized assessment, as pH sensitivity varies across OAAs, reinforcing the need for tailored risk evaluation and precision dosing when appropriate.[34]

1.3. PD Interactions (Overlapping Toxicities)

PD DDIs occur when two or more concurrently administered drugs exert additive, synergistic, or antagonistic effects at the site of action or through downstream physiological processes without altering systemic drug exposure.[35] In oncology, PD interactions most commonly arise from overlapping toxicities, in which an OAA and a concomitant medication affect the same organ system, thereby increasing the frequency and severity of adverse events. Common manifestations include myelosuppression, hepatotoxicity, QT interval prolongation, bleeding risk, and immune-related toxicity.[17] Because most OAAs have narrow therapeutic indices and are administered chronically, even modest increases in PD toxicity can prompt clinically significant decisions such as dose reduction, temporary treatment interruption, or permanent discontinuation.[36] These interactions may result from shared on-target effects, such as compounded myelosuppression from agents that inhibit rapidly dividing cells, or from off-target organ-specific vulnerability, including additive hepatotoxicity. PD interactions may also arise through physiological mechanisms, such as increased bleeding risk when an OAA that impairs platelet function is combined with an oral anticoagulant[37], or through immune modulation, where immune checkpoint inhibitors amplify toxicity from other immunomodulatory therapies. Importantly, PD interactions occur independently of plasma drug concentrations, meaning that routine PK monitoring may fail to detect clinically relevant risk.[38] Clinical evidence supports the high prevalence and impact of PD interactions in patients receiving oral anticancer therapy. Pharmacovigilance data and retrospective cohort studies report frequent exposure to potentially toxic co-medications, including non-steroidal anti-inflammatory drugs, anticoagulants, and cardiotoxic agents, with associated increases in bleeding, cardiotoxicity, and severe myelosuppression.[39] Real-world analyses further demonstrate that concomitant PPI use with selected TKIs can contribute to adverse outcomes through combined PK and PD mechanisms, underscoring the multifactorial nature of DDI-related harm.[9]

2. High-risk OAAs

TKIs are particularly susceptible to CYP3A-mediated DDIs. Imatinib exposure increased by approximately 40% in a randomized crossover study when co-administered with the strong CYP3A inhibitor ketoconazole, with a concurrent reduction in its active metabolite CGP74588, indicating a clinically relevant perpetrator effect and the need for avoidance or dose adjustment.[40] Absorption-related interactions further affect epidermal growth factor receptor TKIs that exhibit pH-dependent solubility. In a prospective patient study,

concomitant PPI therapy reduced erlotinib exposure, while administration with an acidic beverage partially restored bioavailability, supporting mitigation strategies for PPI-related underexposure.[41] Similar CYP3A liability has been demonstrated for other TKIs, including crizotinib, whose exposure increased with ketoconazole and decreased with rifampin, consistent with regulatory labelling.[42] CDK4/6 inhibitors also show marked sensitivity to CYP3A modulation. Abemaciclib undergoes extensive CYP3A4 metabolism, and clinical DDI studies, combined with PBPK modeling, demonstrated an approximately 95% reduction in exposure with rifampin and an approximately 3.4-fold increase in area under the curve (AUC) with clarithromycin. The model accurately predicted interactions with other CYP3A inhibitors and moderate perpetrators, supporting dose modification or avoidance strategies.[43] These findings are consistent across the CDK4/6 inhibitor class, including palbociclib and ribociclib, reinforcing the need for careful medication reconciliation and consideration of TDM in patients with complex polypharmacy. Among poly (ADP-ribose) polymerase inhibitors, olaparib clearance is primarily mediated by CYP3A4 and CYP3A5. In Phase I studies, itraconazole increased olaparib C_{max} and AUC by approximately 1.42-fold and 2.70-fold, respectively, while rifampin reduced olaparib C_{max} and AUC to approximately 0.29 and 0.13 of control values, respectively. These findings support avoidance of strong CYP3A modulators or dose adjustment to maintain target exposure and safety.[44] Severe CYP3A liability has also been demonstrated for non-TKI targeted therapies. For the BTK inhibitor ibrutinib, healthy-volunteer studies showed that rifampin reduced AUC by approximately 10- to 13-fold, while ketoconazole increased AUC by approximately 24-fold, and additional increases were observed with grapefruit juice. Given the narrow therapeutic window and exposure-toxicity relationships, strong inhibitors and inducers should be avoided or managed with substantial dose modification and close monitoring.[45] Venetoclax, a BCL-2 inhibitor, exhibits pronounced interactions with azole antifungals. Posaconazole markedly increases venetoclax exposure, necessitating dose reductions, typically to 70 to 100 mg daily, to limit cytopenias and tumour lysis syndrome risk.[46,47] Collectively, these studies demonstrate that CYP3A inhibition can increase exposure to OAAs, modestly or by orders of magnitude, thereby increasing toxicity risk, whereas CYP3A induction can profoundly reduce exposure and compromise efficacy. ARAs further decrease the absorption of weakly basic TKIs with pH-dependent solubility. Quantitative effect sizes from these studies support label-concordant dose-adjustment or avoidance strategies and enable precision dosing for high-risk combinations that cannot be avoided, such as venetoclax during antifungal prophylaxis. When interacting medications are unavoidable or patient-specific variability is high, measurement-informed care using TDM or population PKs should be considered whenever feasible.[48] The image illustrates the interaction between OAA and co-administered drugs in Figure 1.

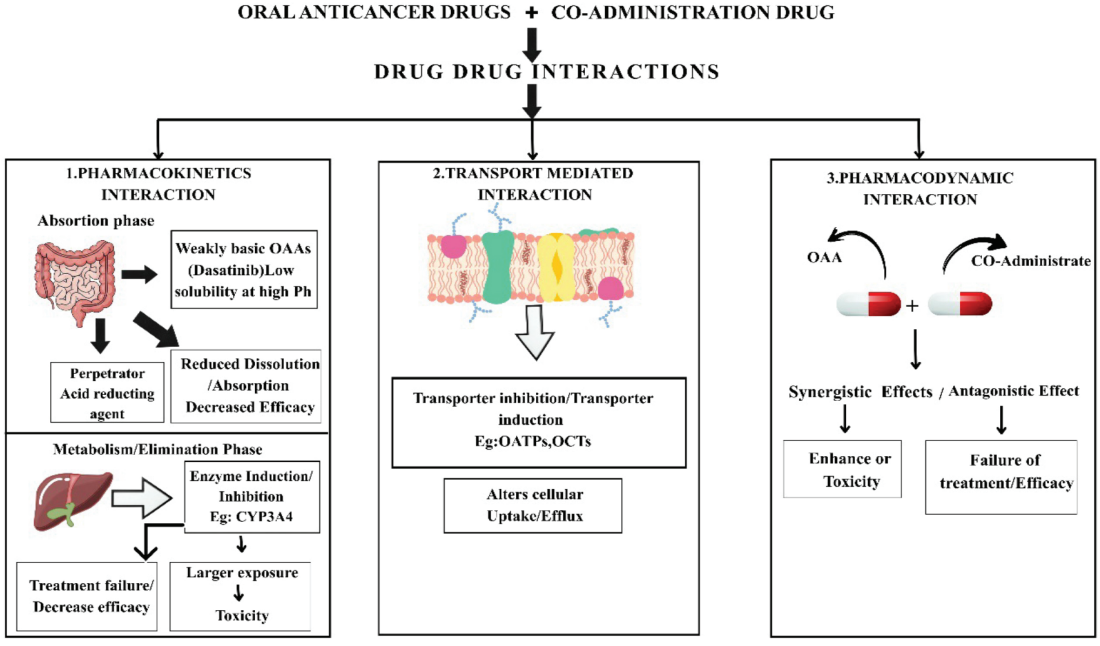


FIGURE 1: The pharmacokinetic, transporter-mediated, and pharmacodynamic drug-drug interactions with oral anticancer agents are summarized in the figure. Reduced efficacy, treatment failure, or increased toxicity can result from these interactions, which alter, metabolism, or drug action.

OAA: Oral anticancer agent; OATP: Organic anion-transporting polypeptide; OCT: Organic cation transporter

3. Common Perpetrator Drug Classes

Azole antifungals: OAAs that are CYP3A substrates show marked increases in exposure when co-administered with triazole antifungals due to strong inhibition of CYP3A and P-gp. In a randomized crossover study, itraconazole increased erlotinib AUC and Cmax, with consistent effects on its active metabolite OSI-420, supporting avoidance or dose adjustment when co-prescribed.[49] In patients with acute myeloid leukemia, posaconazole markedly increased venetoclax exposure, necessitating a predefined dose reduction of approximately 75% to maintain safety without loss of efficacy.[47,48] Itraconazole similarly increased exposure to the third-generation epidermal growth factor receptor-TKI alflutinib in a first-in-human DDI study, reinforcing the generalizability of strong CYP3A inhibition across TKIs and the need for model-informed dosing when azoles are required.[50]

Macrolide antibiotics: TKI exposure may increase when co-administered with clarithromycin, a potent CYP3A and P-gp inhibitor. In a controlled DDI study, clarithromycin significantly altered sunitinib PKs, whereas azithromycin had minimal effect, indicating that antibiotic selection can mitigate interaction risk.[51]

Anticonvulsant enzyme inducers: CYP3A-inducing antiepileptics such as phenytoin and carbamazepine substantially reduce TKI exposure and increase the risk of treatment failure. Clinical cases and pediatric studies have demonstrated markedly reduced imatinib trough concentrations during co-therapy with phenytoin or carbamazepine, with restoration of response following dose escalation or use of alternative anticonvulsants. These findings support proactive TDM and exposure-guided adjustment when inducers cannot be avoided.[52-54]

Gastric acid-suppressing agents: PPIs and H_2-receptor antagonists reduce the absorption of TKIs with pH-dependent solubility. In randomized crossover studies, both ranitidine and omeprazole significantly decreased erlotinib AUC and C_{max}, while staggered ranitidine dosing partially mitigated the effect.[55] Similar reductions were observed for dasatinib under elevated gastric pH, supporting avoidance of PPIs or careful timing of acid suppression when required.[56] Population and translational studies further link PPI co-prescription with adverse outcomes for selected pH-sensitive TKIs.[41]

Anticoagulants and antiplatelets: Ibrutinib increases bleeding risk through on-target platelet effects, which are amplified by concomitant anticoagulant or antiplatelet therapy. Clinical trials and real-world analyses demonstrate significantly higher rates of major bleeding with dual exposure, guiding cautious co-prescription and consideration of alternative Bruton TKIs when feasible.[12,57] In contrast, not all TKI-anticoagulant combinations behave similarly. Nilotinib did not alter warfarin PKs or PDs in a dedicated crossover study, whereas increased international normalized ratio and bleeding were reported with regorafenib, indicating the need for drug-specific assessment and close monitoring.[58,59]

Herbal medicine: St. John's wort, a potent CYP3A and P-gp inducer, significantly reduces TKI exposure. Controlled crossover studies demonstrated reductions of approximately 30 to 32% in imatinib AUC, supporting a clear contraindication during oral anticancer therapy.[60,61]

Precision-dosing implications: Effective management requires anticipation of the magnitude of interactions, avoidance or substitution of potent perpetrators when possible, and use of dose reduction, exposure-guided escalation, or TDM when interactions are unavoidable. PPIs should be avoided in patients receiving pH-sensitive TKIs, and timed H_2 receptor antagonists or antacids should be used only when supported by evidence. Ibrutinib, when combined with anticoagulation, warrants heightened bleeding surveillance and careful selection of agents. Together, these strategies translate mechanistic understanding into safe, precision-based management of oral anticancer therapy.[48]

4. Clinical Consequences of DDIs

4.1. Toxicity with TKI + Azole Antifungals

Potent azole CYP3A inhibitors markedly increase exposure to many TKIs, often resulting in clinically significant toxicity. In patients with *FLT3*-mutated acute myeloid leukemia, coadministration of posaconazole with the CYP3A substrate midostaurin produced substantial PK interactions and was associated with more frequent dose interruptions and modifications due to adverse events, reflecting the narrow therapeutic window during induction therapy.[62] TDM data from a prospective cohort further demonstrated increases of at least eightfold in midostaurin trough concentrations during posaconazole co-therapy, necessitating careful dose management to limit toxicity.[63]

Similar findings have been reported for ibrutinib. Dose-optimization analyses indicated that, when posaconazole cannot be avoided, daily ibrutinib doses should be reduced to approximately 70 mg to maintain safety. Mechanistic PK studies confirmed that posaconazole markedly increases ibrutinib exposure, reinforcing the need for proactive dose adjustment when strong CYP3A inhibition is present.[64]

4.2. Reduced Efficacy with TKI + PPIs (Acid Suppression)

PPIs raise gastric pH and can reduce bioavailability, potentially causing clinical repercussions. Many TKIs (weak bases) depend on gastric acidity for dissolution. Concurrent PPI use

was prevalent and independently associated with higher all-cause mortality and earlier discontinuation of therapy in a sizable real-world cohort of older adults receiving TKIs. This finding is consistent with decreased antitumor efficacy resulting from impaired TKI exposure.[9] Methodologically, pH-sensitive TKIs like dasatinib provide a good example of the mechanism: biopharmaceutical studies and controlled studies demonstrate 40-80% reductions in exposure under PPIs or H2 blockers, and timing in relation to omeprazole can significantly exacerbate the interaction.[65] The fifth Dasatinib's dramatic pH-dependent solubility loss is also documented in regulatory clinical pharmacology reviews, supporting the biological plausibility of efficacy attenuation with acid suppression.[63]

4.3. Real-world Evidence on DDI Burden and Outcomes

High DDI loads that cause therapy modifications and affect care are routinely observed in prospective and observational studies conducted in oncology clinics and go beyond single pairs. DDIs requiring interventions during active anticancer treatment were systematically identified in a prospective study of ambulatory cancer patients, demonstrating how frequently regimens need to be modified to prevent harm.[17] A multicenter, real-world analysis of oral antineoplastics revealed a high prevalence of potentially serious DDIs and emphasized the necessity of structured screening to maintain safety and efficacy.[21]

5. Patient- and Population-specific Considerations

5.1. Elderly with Comorbidities

In geriatric oncology, polypharmacy and multimorbidity substantially increase the risk of DDIs. In a multicentre Dutch cohort, 46% of ambulatory patients receiving OAAs had at least one potential interaction, many of which were classified as major, underscoring the need for proactive screening in patients with multiple comorbid medications.[1] Prospective studies focused on older adults undergoing systemic therapy have similarly reported high rates of polypharmacy and severe interactions. Cardiac comorbidities and the use of high-risk concomitant medications further increased interaction burden, supporting pharmacist-led medication review at treatment initiation.[66] In metastatic settings, where supportive therapies such as anticoagulants and QT-prolonging agents are common, population data show that the likelihood of major potential DDIs rises significantly with increasing medication count, particularly in patients receiving more than seven total drugs or three or more anticancer agents.[1]

5.2. Hepatic/Renal Impairment

The Child-Pugh class modifies exposure differently for each agent because many TKIs are hepatically cleared. The AUC of nilotinib increased by approximately 19-35% in subjects with mild to severe hepatic impairment compared with controls in an open-label, parallel-group study. This suggests caution but does not automatically reduce dosage after a single dose, underscoring the need for agent-specific guidance rather than general guidelines.[67] On the other hand, exposure variations in capmatinib's single-dose PK across graded hepatic impairment influenced label recommendations, reaffirming that impairment effects are drug-specific and should be confirmed prior to co-prescribing inhibitors/inducers in patients with liver disease.[68]

5.3. Renal Impairment

As with nephrotoxic or renally cleared drugs, kidney dysfunction can both alter drug disposition and amplify the effects of DDI. In patients with mild-to-moderate renal dysfunction, a phase I Journal of Clinical Oncology trial found that imatinib up to 600-800 mg/day was tolerated despite higher exposure. This finding guides dose ceilings and monitoring rather than categorical avoidance. These patients are particularly susceptible to CYP3A modulators that affect imatinib levels.[69] Prior PK studies in dialysis demonstrated imatinib exposure equivalent to normal renal function, indicating that standard dosing might be possible on hemodialysis; however, cautious monitoring is necessary when other interacting medications are present.[70]

5.4. Polypharmacy in Metastatic Disease

Antiemetics, acid suppressants, anticoagulants, and antimicrobials are frequently coadministered with OAAs in metastatic care, creating intricate interaction networks. Outpatients on OAAs frequently had pDDIs, many of which were clinically significant (e.g., QT-prolonging pairs, CYP3A substrates with strong inhibitors/inducers), according to the original Br J Cancer prevalence study.[1] In a sizable BMC Cancer cohort, higher drug counts independently predicted major pDDIs. This finding supports routine DDI screening and, when practical, deprescribing in late-line therapy.[1]

5.5. Pediatric Oncology

The impact of DDI and dosage modifications in children may differ from that in adults due to differences in supportive care patterns and enzyme ontogeny. In a prospective npj Precision Oncology study, VEN doses were adjusted during venetoclax-based induction in newly diagnosed pediatric AML when azole antifungals were co-administered (CYP3A inhibition).

This study documented remission rates alongside venetoclax PK and showed higher troughs with azoles-evidence for on-therapy TDM and prespecified VEN reductions under strong CYP3A inhibition.[71] The disposition of venetoclax in children with leukemia has been described by additional pediatric PK/PD research, which supports exposure-matched dosing strategies and increased attention to interactions during antifungal prophylaxis.[72]

6. Tools for Prediction and Management

Many oral targeted anticancer agents are substrates of CYP3A4 and CYP3A5 as well as drug transporters such as P-gp and breast cancer resistance protein, making them highly susceptible to PK variability and clinically significant DDIs. This vulnerability is particularly pronounced for TKIs. Strong CYP3A inhibitors can substantially increase systemic exposure and toxicity, whereas CYP3A inducers may reduce systemic exposure to subtherapeutic levels and cause treatment failure. These mechanisms explain common real-world interaction patterns and underpin current clinical DDI guidance.[73] Pharmacogenomics further contributes to interindividual variability by identifying germline variants in drug-metabolizing enzymes and transporters, including CYP3A4, CYP3A5, CYP2D6, UGT1A1, and DPYD that influence drug exposure and toxicity. Well-established examples include UGT1A1 polymorphisms associated with irinotecan toxicity and variable CYP3A expression affecting TKIs clearance. Incorporation of genotyping into clinical workflows can identify patients at higher interaction risk and guide proactive dose adjustment or monitoring strategies.[74]

TDM has emerged as a practical approach for long-term oral targeted therapies with defined exposure-response relationships, including imatinib, sunitinib, and pazopanib. Prospective and retrospective studies demonstrate that TDM can identify underexposure or overexposure due to DDIs, adherence issues, organ dysfunction, or pharmacogenomic variability, enabling individualized dose adjustment to improve efficacy and reduce toxicity. However, implementation remains limited by infrastructure requirements, lack of standardized target ranges for many agents, and sampling constraints.[75] MIPD extends TDM by integrating Bayesian forecasting; individual concentration data; patient-specific covariates (such as genotype, organ function, and concomitant medications); and population PK and PD models. This approach allows explicit simulation of DDI effects and the calculation of individualized dose modifications. Emerging clinical studies and systematic evaluations demonstrate improved dose selection compared with fixed dosing or simple TDM-based adjustments, although broader adoption requires validated models, dedicated software, and clinician training.[76]

In practice, an integrated precision-dosing strategy for OAAs includes pre-treatment pharmacogenomic screening for high-impact variants, systematic medication review to identify CYP- and transporter-mediated interactions, baseline and on-treatment TDM for agents with established exposure targets, and use of MIPD tools when available. This layered approach addresses multiple sources of variability and supports safer and more effective individualized therapy.[48]

7. Precision Oncology Approaches

Many OAAs are small-molecule substrates, inhibitors, or inducers of CYP enzymes, particularly CYP3A4, and drug transporters such as P-gp, making them highly susceptible to clinically significant DDIs. Polypharmacy in oncology, including supportive therapies, antifungals, anticoagulants, acid-suppressing agents, and herbal products, further increases DDI risk. These interactions may reduce efficacy through enzyme induction and decreased exposure or increase toxicity through enzyme inhibition and elevated exposure. Understanding interaction mechanisms involving absorption, metabolism, transport, and PD synergy is therefore the foundation of precision dosing.[77] Pharmacogenomics modifies the baseline PKs of many OAAs and can alter the magnitude of DDIs, particularly through polymorphisms in CYP enzymes (e.g., CYP3A4, CYP3A5, CYP2C9, and CYP2D6) and in transporter genes. For example, coadministration of a CYP3A inhibitor in patients who are poor or non-expressors of CYP3A5 may markedly increase drug exposure and the risk of toxicity, whereas CYP3A induction may lead to subtherapeutic drug levels in rapid metabolizers. Incorporation of germline pharmacogenetic data into prescribing can therefore prevent high-risk interactions and guide individualized starting doses or enhanced monitoring strategies.[78] For targeted therapies with established exposure-response or exposure-toxicity relationships, TDM provides an additional precision tool. Prospective, multicentre studies indicate that TDM-guided dosing can reduce toxicity while maintaining efficacy for selected oral targeted agents. TDM is particularly relevant for drugs with narrow therapeutic indices, high interpatient variability, and defined PK or PD targets. However, implementation remains limited by assay availability, sampling logistics, and lack of validated therapeutic ranges for many agents.[22]

MIPD builds on TDM by integrating population PK and PD models, Bayesian forecasting, and patient-specific covariates, including genotype, organ function, and concomitant

medications. This approach is especially useful when DDIs or genetic variants cause nonlinear or time-dependent changes in exposure, as it allows simulation of interaction scenarios and dose adjustments using sparse sampling. Although prospective outcome validation is ongoing, recent reviews and position papers identify MIPD as a scalable strategy to replace uniform dosing with model-based individualized regimens.[79] In practice, an integrated precision pathway for OAAs includes systematic DDI screening and medication reconciliation, selective pre-treatment pharmacogenetic testing, early TDM with model-based interpretation, and dynamic dose adjustment using MIPD when interacting drugs are introduced or withdrawn. This layered approach operationalizes precision dosing, addresses key DDI mechanisms, and reduces the clinical impact of variability in oral anticancer therapy.[78]

8. Regulatory and Clinical Guidance

OAAs are highly susceptible to clinically meaningful DDIs because they are administered chronically, have narrow therapeutic windows, and depend extensively on metabolic enzymes and transporters, particularly CYP3A and P-gp. PK mechanisms include enzyme inhibition or induction, transporter modulation affecting absorption and distribution, and pH-dependent reductions in oral bioavailability for weakly basic drugs. PD interactions, such as additive QT prolongation or myelosuppression, further increased risk, making DDIs a combined consequence of drug properties and oncology-related polypharmacy.[80] Epidemiologic studies show that DDIs are common in ambulatory oncology practice. Large multicenter analyses report that approximately 40 to 50 percent of patients receiving oral anticancer therapy have at least one potential DDI and that 15 to 20 percent have at least one interaction classified as major. Key risk factors include polypharmacy, advanced age, supportive-care medications such as opioids and anticoagulants, acid-suppressing agents, and comorbidities affecting drug handling. These data indicate that many electronically identified interactions are clinically actionable and support routine multidisciplinary medication review involving oncologists and pharmacists.[81]

Clinically, DDIs lead either to reduced efficacy, through enzyme induction resulting in lower exposure or to increased toxicity, through enzyme inhibition resulting in elevated plasma concentrations. Real-world reports describe outcomes ranging from loss of tumor control to severe toxicity and hospitalization, highlighting the need for anticipatory management when interacting drugs are initiated or discontinued. Practical strategies include avoiding high-risk combinations when alternatives exist, dose adjustment based on known interaction magnitude, enhanced clinical and laboratory monitoring, and timing strategies for pH-sensitive agents, such as dose spacing or use of acidic vehicles.[1] Precision-dosing approaches provide a framework to mitigate DDI-related harm. TDM, model-informed dosing, and individualized regimen adjustment are particularly relevant for oral targeted agents with substantial interpatient PK variability and plausible exposure-response relationships.[48] Recent expert reviews support precision dosing for selected agents, using TDM and population PK or PBPK models, to predict interaction magnitude and guide adaptive dosing. However, implementation remains limited by logistical and regulatory barriers, including standardized sampling, validated therapeutic ranges, and limited prospective outcome data for many agents.[80] From a regulatory perspective, when robust evidence supports a clinically relevant DDI and an exposure-response relationship, labeling may recommend dose modification, a contraindication, or enhanced monitoring. Effective implementation therefore requires coordinated pharmacovigilance, access to TDM infrastructure, and integrated multidisciplinary workflows to translate regulatory guidance into safer clinical practice.[75]

9. Future Directions

Cancer therapy is shifting from static, population-level DDI lists toward dynamic, data-driven risk management that integrates real-world data, mechanistic modeling, and prospective clinical evaluation. Analyses of electronic health records, pharmacy claims, and TDM datasets consistently demonstrate a high real-world prevalence of clinically relevant DDIs involving OAAs, underscoring the limitations of clinical trials in capturing the frequency and outcomes of such interactions. Integration of real-world data with curated clinical endpoints enables hypothesis generation, prioritization of high-risk interactions, and targeted prospective evaluation.[21] PBPK and combined PK-PD models are now established tools for predicting the magnitude and clinical relevance of CYP- and transporter-mediated DDIs and for simulating special populations such as older adults and patients with hepatic impairment. Methodological reviews emphasize the need for rigorous verification of model inputs and for a stronger linkage of model outputs to real-world exposure-response data to improve external validity. Iterative integration of modeling with real-world evidence allows *in silico* screening of multiple interaction scenarios and supports regulatory labeling or focused prospective studies when uncertainty remains high.[81]

Machine learning and artificial intelligence approaches offer complementary, high-throughput predictions of previously unrecognized DDIs using chemical structures, interaction networks, and large pharmacovigilance datasets. While recent reviews highlight the promise of graph-based and hybrid mechanistic-machine-learning models, they also stress the need for interpretability, bias control, and external validation prior to clinical use. A combined workflow in which machine learning prioritizes candidate interactions, PK modeling quantifies exposure changes, and real-world or prospective studies assess clinical outcomes is emerging as a practical strategy.[82] TDM and MIPD represent the clinical translation of these approaches. Reviews in clinical pharmacology support the integration of TDM with population PK models and Bayesian forecasting to individualize dosing of oral targeted agents that exhibit high variability and DDI risk. Embedding these tools into pragmatic prospective studies, including randomized or stepped-wedge designs, is critical to demonstrate benefits in efficacy, toxicity reduction, and cost-effectiveness in routine oncology care.[22]

Despite advances in modeling and data science, prospective clinical evaluation remains essential. DDI registries, adaptive trials incorporating model-derived dose adjustments, and implementation studies of decision-support systems informed by real-world data, modeling, and machine learning are needed to translate predictions into safer prescribing. Recent oncology pharmacology reviews call for multidisciplinary consortia to standardize data elements, share model outputs, and conduct targeted prospective validation to support guideline-level adoption of these approaches.[83]

TABLE 1: PK/PD drug-drug interactions in oral anticancer agents.

Mechanism type	Detailed PK/PD mechanism	Resulting clinical impact	Common OAA victims	Common perpetrators	Reference
PD-additive toxicities	Combined organ toxicity without PK change (e.g., QT prolongation, bleeding, myelosuppression)	Severe AEs, hospitalizations	TKIs, ibrutinib, PARP inhibitors	QT-prolonging agents, anticoagulants, NSAIDs	84
PD-antagonistic effects	Opposing physiological effects (e.g., immunosuppressants reducing efficacy of immunotherapy)	Reduced treatment effect	Immunotherapies, targeted therapies	Corticosteroids, immunosuppressants	84
OATP1B1/1B3 inhibition	Reduced hepatic uptake → increased systemic exposure of co-medications	↑ Statin toxicity, ↑ methotrexate toxicity	TKIs (as perpetrators), pazopanib	Statins, methotrexate (victims)	84
CYP3A4/3A5 inhibition	Competitive or irreversible inhibition of CYP3A4/5; intestinal CYP inhibition increases oral absorption	Increased AUC/C_{max} → toxicity risk	Imatinib, ibrutinib, midostaurin, venetoclax, abemaciclib, olaparib, crizotinib	Azole antifungals, macrolides, ritonavir/cobicistat, verapamil	85
CYP3A4/3A5 induction	PXR/CAR activation → increased CYP3A expression and metabolic clearance	Decreased exposure → loss of efficacy	Abemaciclib, olaparib, imatinib, crizotinib, ibrutinib	Rifampin, carbamazepine, phenytoin, St. John's wort	86
P-gp (ABCB1) inhibition	Inhibition of efflux transporter in gut/liver → increased absorption and decreased biliary/renal efflux	High exposure → toxicity	Imatinib, dasatinib, ibrutinib, venetoclax	Verapamil, azoles, macrolides, ritonavir	87
P-gp (ABCB1) induction	Upregulation of ABCB1 → increased drug efflux	Subtherapeutic exposure	Imatinib, several TKIs	Rifampin, St. John's wort	87
BCRP (ABCG2) inhibition	Inhibition of ABCG2 efflux → increased absorption and hepatic exposure	Hepatic/systemic toxicity	Gefitinib, pazopanib, imatinib	Azoles, protease inhibitors	88
pH-dependent absorption issues (ARAs)	PPIs/H2RAs increase gastric pH → reduced solubility and dissolution of weakly basic OAAs	40-80% ↓ exposure → reduced efficacy	Dasatinib, erlotinib, gefitinib, pazopanib, crizotinib	PPIs, H_2RAs, antacids	65

OAAs: Oral anticancer agents; PK: Pharmacokinetics; PD: Pharmacodynamics; P-gp: P-glycoprotein; ABCB1: ATP-binding cassette subfamily B member 1; ABCG2: ATP-binding cassette subfamily G member 2; AUC: Area under the curve; BCRP: Breast cancer resistance protein; CYP: Cytochrome P450; NSAIDs: Non-steroidal anti-inflammatory drugs; TKIs: Tyrosine kinase inhibitors; ARAs: Acid-reducing agents; AEs: Adverse events; PPIs: Proton pump inhibitors; PXR: Pregnane X receptor; H_2RAs: Histamine H_2 receptor antagonists.

CONCLUSION

It can be difficult to manage DDIs in patients using oral anticancer drugs. These therapies have narrow safety margins and complex PKs and are often prescribed in conjunction with numerous other medications. Because of this, interactions involving CYP enzymes, drug transporters, acid-reducing drugs, or overlapping side effects can result in serious clinical problems, such as decreased treatment efficacy, severe adverse reactions, or even preventable hospitalizations. A multidisciplinary team must be involved; careful interaction screening must be conducted; and evidence-based decisions must be made to guarantee that patients receive safe and efficient care. PBPK modeling, pharmacogenomics, TDM, and MIPD are examples of emerging precision tools that have the potential to revolutionize the management, prevention, and prediction of DDIs. These strategies allow customized dose optimization by combining patient-specific metabolic capacity, genetic variability, co-medication patterns, and dynamic clinical parameters. Therefore, to guarantee the safe and efficient use of oral anticancer medications, a forward-thinking oncology practice must adopt individualized and mechanism-driven approaches. To reduce DDI-related risks and maximize therapeutic results, interdisciplinary collaboration must be strengthened, patient education improved, and data-driven clinical decision support systems utilized.

Footnotes

Authorship Contributions

Concept: Y.M., R.S., R.A.P., A.R., Design: Y.M., R.S., R.A.P., A.R., Analysis or Interpretation: Y.M., R.S., R.A.P., A.R., Literature Search: Y.M., R.S., R.A.P., A.R., Writing: Y.M., R.S., R.A.P., A.R.

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REFERENCES

1. van Leeuwen RW, Brundel DH, Neef C, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer. 2013;108(5):1071-1078. [Crossref] [PubMed] [PMC]
2. Riechelmann RP, Tannock IF, Wang L, Saad ED, Taback NA, Krzyzanowska MK. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst. 2007;99(8):592-600. [Crossref] [PubMed]
3. Prely H, Herledan C, Caffin AG, et al. Real-life drug-drug and herb-drug interactions in outpatients taking oral anticancer drugs: comparison with databases. J Cancer Res Clin Oncol. 2022;148(3):707-718. [Crossref] [PubMed] [PMC]
4. Giraud JS, Korb-Savoldelli V, Perrin G, et al. Clinical and economic impact of pharmacist interventions to identify drug-related problems in multidisciplinary cancer care: a prospective trial. Oncologist. 2025;30(8):oyae213. [Crossref] [PubMed] [PMC]
5. Nowinski K, Chaireti R. Discrepancies in recommendations on pharmacokinetic drug interactions for anticancer medications and direct oral anticoagulants (DOAC): a comparative analysis of different clinical decision support systems and sources. Pharmaceuticals (Basel). 2025;18(7):1044. [Crossref] [PubMed] [PMC]
6. Ussai S, Petelin R, Giordano A, Malinconico M, Cirillo D, Pentimalli F. A pilot study on the impact of known drug-drug interactions in cancer patients. J Exp Clin Cancer Res. 2015;34(1):89. [Crossref] [PubMed] [PMC]
7. Ko Y, Tan SL, Chan A, et al. Prevalence of the coprescription of clinically important interacting drug combinations involving oral anticancer agents in Singapore: a retrospective database study. Clin Ther. 2012;34(8):1696-1704. [Crossref] [PubMed]
8. Waghray D, Zhang Q. Inhibit or evade multidrug resistance P-glycoprotein in cancer treatment. J Med Chem. 2018;61(12):5108-5121. [Crossref] [PubMed] [PMC]
9. Sharma M, Holmes HM, Mehta HB, et al. The concomitant use of tyrosine kinase inhibitors and proton pump inhibitors: prevalence, predictors, and impact on survival and discontinuation of therapy in older adults with cancer. Cancer. 2019;125(7):1155-1162. [Crossref] [PubMed] [PMC]
10. Wang H, Shi H, Wang Y, et al. Potentially hazardous drug-drug interactions associated with oral antineoplastic agents prescribed in Chinese tertiary care teaching hospital settings: a multicenter cross-sectional study. Front Pharmacol. 2022;13:808848. [Crossref] [PubMed] [PMC]
11. Wang TF, Clarke AE, Awan AA, Tanuseputro P, Carrier M, Sood MM. Hemorrhage Risk among patients with breast cancer receiving concurrent direct oral anticoagulants with tamoxifen vs aromatase inhibitors. JAMA Netw Open. 2022;5(6):e2219128. [Crossref] [PubMed] [PMC]
12. Mohamed MR, Mohile SG, Juba KM, et al. Association of polypharmacy and potential drug-drug interactions with adverse treatment outcomes in older adults with advanced cancer. Cancer. 2023;129(7):1096-1104. [Crossref] [PubMed] [PMC]
13. Rodrigues J, Marques P, Gomes C, Portela C. Mitigating the risk of drug interactions in cancer patients taking oral anticancer agents: the role of a multidisciplinary team-based medication reconciliation. Cureus. 2023;15(2):e35324. [Crossref] [PubMed] [PMC]
14. Abraham J, Montero AJ, Jankowitz RC, et al. Safety and efficacy of T-DM1 plus neratinib in patients with metastatic HER2-positive breast cancer: NSABP Foundation trial FB-10. J Clin Oncol. 2019;37(29):2601-2609. [Crossref] [PubMed] [PMC]
15. Anwar K, Nguyen L, Nagasaka M, Ou SI, Chan A. Overview of drug-drug interactions between ritonavir-boosted nirmatrelvir (paxlovid) and targeted therapy and supportive care for lung cancer. JTO Clin Res Rep. 2023;4(2):100452. Erratum in: JTO Clin Res Rep. 2023:100535. [Crossref] [PubMed] [PMC]
16. Ismail M, Khan S, Khan F, et al. Prevalence and significance of potential drug-drug interactions among cancer patients receiving chemotherapy. BMC Cancer. 2020;20(1):335. [Crossref] [PubMed] [PMC]
17. van Leeuwen RWF, Jansman FGA, van den Bemt PMLA, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015;26(5):992-997. [Crossref] [PubMed]
18. Kinnaer LM, Nelis M, Van Hecke A, Foulon V. Patient-centered care coordination, education and counseling of patients treated with

oral anticancer drugs: an importance-performance analysis. Eur J Oncol Nurs. 2020;47:101765. [Crossref] [PubMed]

19. Hu X, Hsieh CY, Zhang Y, et al. Effect of a strong CYP3A4 inhibitor and inducer on the pharmacokinetics of senaparib (IMP4297) in healthy volunteers: A drug-drug interaction study. Br J Clin Pharmacol. 2023;89(6):1767-1779. [Crossref] [PubMed]
20. Molenaar-Kuijsten L, Van Balen DEM, Beijnen JH, Steeghs N, Huitema ADR. A review of CYP3A drug-drug interaction studies: practical guidelines for patients using targeted oral anticancer drugs. Front Pharmacol. 2021;12:670862. [Crossref] [PubMed] [PMC]
21. Kim SH, Suh Y, Ah YM, Jun K, Lee JY. Real-world prevalence of potential drug-drug interactions involving oral antineoplastic agents: a population-based study. Support Care Cancer. 2020;28(8):3617-3626. [Crossref] [PubMed]
22. Groenland SL, van Eerden RAG, Westerdijk K, et al.; Dutch Pharmacology Oncology Group (DPOG). Therapeutic drug monitoring-based precision dosing of oral targeted therapies in oncology: a prospective multicenter study. Ann Oncol. 2022;33(10):1071-1082. [Crossref] [PubMed]
23. Turner JG, Gump JL, Zhang C, et al. ABCG2 expression, function, and promoter methylation in human multiple myeloma. Blood. 2006;108(12):3881-3889. [Crossref] [PubMed] [PMC]
24. Nanayakkara AK, Follit CA, Chen G, Williams NS, Vogel PD, Wise JG. Targeted inhibitors of P-glycoprotein increase chemotherapeutic-induced mortality of multidrug resistant tumor cells. Sci Rep. 2018;8(1):967. [Crossref] [PubMed] [PMC]
25. Khurana V, Minocha M, Pal D, Mitra AK. Inhibition of OATP-1B1 and OATP-1B3 by tyrosine kinase inhibitors. Drug Metabol Drug Interact. 2014;29(4):249-259. [Crossref] [PubMed] [PMC]
26. Ellfolk M, Tornio A, Niemi M, Leinonen MK, Lahesmaa-Korpinen AM, Malm H. Placental transporter-mediated drug interactions and offspring congenital anomalies. Br J Clin Pharmacol. 2020 May;86(5):868-879. [Crossref] [PubMed] [PMC]
27. Gagno S, Posocco B, Orleni M, et al. Increased plasma imatinib exposure and toxicity in chronically treated GIST patients with SARS-CoV-2 infection: a case series. Front Immunol. 2024;15:1441620. [Crossref] [PubMed] [PMC]
28. Moltó J, Rajoli R, Back D, et al. Use of a physiologically based pharmacokinetic model to simulate drug-drug interactions between antineoplastic and antiretroviral drugs. J Antimicrob Chemother. 2017;72(3):805-811. [Crossref] [PubMed]
29. Patel D, Bertz R, Ren S, Boulton DW, Någård M. A systematic review of gastric acid-reducing agent-mediated drug-drug interactions with orally administered medications. Clin Pharmacokinet. 2020;59(4):447-462. [Crossref] [PubMed] [PMC]
30. Yang E, Yu KS, Lee S. Prediction of gastric pH-mediated drug exposure using physiologically-based pharmacokinetic modeling: a case study of itraconazole. CPT Pharmacometrics Syst Pharmacol. 2023;12(6):865-877. [Crossref] [PubMed] [PMC]
31. Kim B, Lee J, Jang H, Lee N, Mehta J, Jang SB. Effects of acid-reducing agents on the pharmacokinetics of lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer. Adv Ther. 2022;39(10):4757-4771. [Crossref] [PubMed] [PMC]
32. Lee CH, Shen MC, Tsai MJ, et al. PPIs reduce survival in EGFR-TKI-treated lung cancer. Sci Rep. 2022;12:7002. [Crossref] [PubMed] [PMC]
33. Liu H, Yu Y, Guo N, Wang X, Han B, Xiang X. Application of physiologically based pharmacokinetic modeling to evaluate the drug-drug and drug-disease interactions of apatinib. Front Pharmacol. 2021;12:780937. [Crossref] [PubMed] [PMC]
34. Chan A, Tan SH, Wong CM, Yap KY, Ko Y. Clinically significant drug-drug interactions between oral anticancer agents and nonanticancer agents: a Delphi survey of oncology pharmacists. Clin Ther. 2009;31 Pt 2:2379-2386. [Crossref] [PubMed]
35. Kim D, Choi M, Jin BH, et al. Pharmacokinetic and pharmacodynamic drug-drug interactions between evogliptin and empagliflozin or dapagliflozin in healthy male volunteers. Clin Transl Sci. 2023;16(8):1469-1478. [Crossref] [PubMed] [PMC]
36. Tamargo J, Le Heuzey JY, Mabo P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. Eur J Clin Pharmacol. 2015;71(5):549-567. [Crossref] [PubMed] [PMC]
37. Ye W, Ding Y, Li M, et al. Drug-induced autoimmune-like hepatitis. PLoS One. 2025;20(2):e0317680. [Crossref] [PubMed] [PMC]
38. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-3175. [Crossref] [PubMed] [PMC]
39. Grymonprez M, Capiau A, Steurbaut S, et al. Pharmacodynamic drug-drug interactions and bleeding outcomes in patients with atrial fibrillation using non-vitamin K antagonist oral anticoagulants: a Nationwide cohort study. Cardiovasc Drugs Ther. 2025;39(1):133-143. [Crossref] [PubMed]
40. Dutreix C, Peng B, Mehring G, et al. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. Cancer Chemother Pharmacol. 2004;54(4):290-294. [Crossref] [PubMed]
41. van Leeuwen RW, Peric R, Hussaarts KG, et al. Influence of the acidic beverage cola on the absorption of erlotinib in patients with non-small-cell lung cancer. J Clin Oncol. 2016;34(12):1309-1314. Erratum in: J Clin Oncol. 2016;34(23):2806. [Crossref] [PubMed]
42. Xu H, O'Gorman M, Tan W, Brega N, Bello A. The effects of ketoconazole and rifampin on the single-dose pharmacokinetics of crizotinib in healthy subjects. Eur J Clin Pharmacol. 2015;71(12):1441-1449. [Crossref] [PubMed]
43. Posada MM, Morse BL, Turner PK, Kulanthaivel P, Hall SD, Dickinson GL. Predicting clinical effects of CYP3A4 modulators on abemaciclib and active metabolites exposure using physiologically based pharmacokinetic modeling. J Clin Pharmacol. 2020;60(7):915-930. [Crossref] [PubMed] [PMC]
44. Dirix L, Swaisland H, Verheul HM, et al. Effect of Itraconazole and rifampin on the pharmacokinetics of olaparib in patients with advanced solid tumors: results of two phase I open-label studies. Clin Ther. 2016;38(10):2286-2299. [Crossref] [PubMed]
45. de Jong J, Skee D, Murphy J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. Pharmacol Res Perspect. 2015;3(4):e00156. [Crossref] [PubMed] [PMC]
46. Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. Clin Ther. 2017;39(2):359-367. [Crossref] [PubMed]
47. De Gregori S, Gelli E, Capone M, et al. Pharmacokinetics of venetoclax co-administered with posaconazole in patients with acute myeloid leukemia. Pharmaceutics. 2023;15(6):1680. [Crossref] [PubMed] [PMC]

48. van der Kleij MBA, Groot Beumer KWM, Koolen SLW, Mathijssen RHJ, Steeghs N, Huitema ADR. Therapeutic drug monitoring of oral targeted anticancer drugs: achievements, experiences, challenges, and the path forward. Ther Drug Monit. 2025;47(6):713-720. [Crossref] [PubMed] [PMC]
49. Vishwanathan K, Dickinson PA, So K, et al. The effect of itraconazole and rifampicin on the pharmacokinetics of osimertinib. Br J Clin Pharmacol. 2018;84(6):1156-1169. [Crossref] [PubMed] [PMC]
50. Heng J, Tang Q, Chen X, et al. Evaluation of the pharmacokinetic effects of itraconazole on alflutinib (AST2818): an open-label, single-center, single-sequence, two-period randomized study in healthy volunteers. Eur J Pharm Sci. 2021;162:105815. Erratum in: Eur J Pharm Sci. 2022;171:106143. [Crossref] [PubMed]
51. Szałek E, Karbownik A, Grabowski T, Sobańska K, Wolc A, Grześkowiak E. Pharmacokinetics of sunitinib in combination with fluoroquinolones in rabbit model. Pharmacol Rep. 2013;65(5):1383-1390. [Crossref] [PubMed]
52. Kantarjian HM, Larson RA, Guilhot F, et al.; International Randomized Study of Interferon and STI571 (IRIS) Investigators. Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer. 2009;115(3):551-560. Erratum in: Cancer. 2010;116(15):3750. Santini, Valeria [added]. [Crossref] [PubMed] [PMC]
53. Taguchi K, Kouroki M, Ohmura T, Jono H, Endo F, Saito H. Carbamazepine-imatinib interaction in a child with chronic myeloid leukemia. Pediatr Int. 2014;56(4):e33-e36. [Crossref] [PubMed]
54. Pursche S, Schleyer E, von Bonin M, et al. Influence of enzyme-inducing antiepileptic drugs on trough level of imatinib in glioblastoma patients. Curr Clin Pharmacol. 2008;3(3):198-203. [Crossref] [PubMed] [PMC]
55. Kletzl H, Giraudon M, Ducray PS, Abt M, Hamilton M, Lum BL. Effect of gastric pH on erlotinib pharmacokinetics in healthy individuals: omeprazole and ranitidine. Anticancer Drugs. 2015;26(5):565-572. [Crossref] [PubMed]
56. Eley T, Luo FR, Agrawal S, et al. Phase I study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. J Clin Pharmacol. 2009;49(6):700-709. [Crossref] [PubMed]
57. Mock J, Kunk PR, Palkimas S, et al. Risk of major bleeding with ibrutinib. Clin Lymphoma Myeloma Leuk. 2018;18(11):755-761. [Crossref] [PubMed]
58. Yin OQ, Gallagher N, Fischer D, et al. Effects of nilotinib on single-dose warfarin pharmacokinetics and pharmacodynamics: a randomized, single-blind, two-period crossover study in healthy subjects. Clin Drug Investig. 2011;31(3):169-179. [Crossref] [PubMed]
59. Kitade H, Hiromasa-Yamasaki A, Hokkoku K, et al. Elevated prothrombin time/international normalized ratio associated with concurrent administration of regorafenib and warfarin in a patient with advanced colorectal cancer. J Pharm Health Care Sci. 2016;2:15. [Crossref] [PubMed] [PMC]
60. Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. Clin Pharmacol Ther. 2004;76(4):323-329. [Crossref] [PubMed]
61. Smith P, Bullock JM, Booker BM, Haas CE, Berenson CS, Jusko WJ. The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. Pharmacotherapy. 2004;24(11):1508-1514. Erratum in: Pharmacotherapy. 2004;24(12):1837. [Crossref] [PubMed]
62. Menna P, Marchesi F, Cattaneo C, et al. Posaconazole and midostaurin in patients with FLT3-mutated acute myeloid leukemia: Pharmacokinetic interactions and clinical facts in a real life study. Clin Transl Sci. 2023 Oct;16(10):1876-1885. [Crossref] [PubMed] [PMC]
63. Sechaud R, Sinclair K, Grosch K, Ouatas T, Pathak D. Evaluation of drug-drug interactions between midostaurin and strong CYP3A4 inhibitors in patients with FLT-3-mutated acute myeloid leukemia (AML). Cancer Chemother Pharmacol. 2022;90(1):19-27. [Crossref] [PubMed]
64. Mintzer MZ, Griffiths RR. A triazolam/amphetamine dose-effect interaction study: dissociation of effects on memory versus arousal. Psychopharmacology (Berl). 2007;192(3):425-440. [Crossref] [PubMed]
65. Andersson P, Brisander M, Liljebris C, Jesson G, Lennernäs H. Severe impact of omeprazole timing on pH-sensitive dasatinib absorption: unveiling substantial drug-drug interaction. J Clin Pharmacol. 2025;65(5):588-597. [Crossref] [PubMed] [PMC]
66. 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 Geriatr. 2024;24(1):557. [Crossref] [PubMed] [PMC]
67. Yin OQ, Gallagher N, Tanaka C, et al. Effects of hepatic impairment on the pharmacokinetics of nilotinib: an open-label, single-dose, parallel-group study. Clin Ther. 2009;31 Pt 2:2459-2469. [Crossref] [PubMed]
68. Chen X, Cui X, Pognan N, et al. Pharmacokinetics of capmatinib in participants with hepatic impairment: a phase 1, open-label, single-dose, parallel-group study. Br J Clin Pharmacol. 2022;88(1):91-102. [Crossref] [PubMed] [PMC]
69. Gibbons J, Egorin MJ, Ramanathan RK, et al.; National Cancer Institute Organ Dysfunction Working Group. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of renal dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol. 2008;26(4):570-576. [Crossref] [PubMed]
70. De Luca I, Miliziano D, Guerra G, et al. Hemodialysis and imatinib: plasma levels, efficacy and tolerability in a patient with metastatic GIST - case report. Heliyon. 2024;10(7):e28494. [Crossref] [PubMed] [PMC]
71. Wen X, Lu Y, Li Y, et al. Remission rate, toxicity and pharmacokinetics of venetoclax-based induction regimens in untreated pediatric acute myeloid leukemia. NPJ Precis Oncol. 2024;8(1):248. [Crossref] [PubMed] [PMC]
72. Yang J, Wang H, Liu D, Cao W, Xing H, Wang P. A Population pharmacokinetics study of venetoclax concomitant with voriconazole in patients with hematologic malignancies. Drug Des Devel Ther. 2025;19:3681-3690. [Crossref] [PubMed] [PMC]
73. Santamaria F, Roberto M, Maltese G, et al. Tyrosine-kinase inhibitors for lung or breast cancer and drug-drug interactions: a clinical guide. Oncol Rev. 2025;19:1612249. [Crossref] [PubMed] [PMC]
74. Cicali EJ, Eddy E, Gong Y, et al. Implementation of a pharmacogenetic panel-based test for pharmacotherapy-based supportive care in an adult oncology clinic. Clin Transl Sci. 2024;17(7):e13890. [Crossref] [PubMed] [PMC]
75. Westerdijk K, Steeghs N, Tacke CSJ, et al. Therapeutic drug monitoring to personalize dosing of imatinib, sunitinib, and pazopanib: a mixed methods study on barriers and facilitators.

Cancer Med. 2023;12(22):21041-21056. [Crossref] [PubMed] [PMC]

76. Agema BC, Koch BCP, Mathijssen RHJ, Koolen SLW. From Prospective evaluation to practice: model-informed dose optimization in oncology. Drugs. 2025;85(4):487-503. Erratum in: Drugs. 2025;85(5):721-723. [Crossref] [PubMed] [PMC]
77. Lohr LK, Blake KT, Chan CM, Sturm S, Walsh GT. Managing drug interactions with oral anticancer treatments. J Adv Pract Oncol. 2023;14(5):419-438. [Crossref] [PubMed] [PMC]
78. Saiz-Rodríguez M, Almenara S, Navares-Gómez M, et al. Effect of the most relevant CYP3A4 and CYP3A5 polymorphisms on the pharmacokinetic parameters of 10 CYP3A substrates. Biomedicines. 2020;8(4):94. [Crossref] [PubMed] [PMC]
79. Pérez-Blanco JS, Lanao JM. Model-informed precision dosing (MIPD). Pharmaceutics. 2022;14(12):2731. [Crossref] [PubMed] [PMC]
80. Gonnabathula P, Li M, Nagumalli SK, Mehta D, Fairman K. Applications of PBPK modeling to estimate drug metabolism and related ADME processes in specific populations. Pharmaceutics. 2025;17(9):1207. [Crossref] [PubMed] [PMC]
81. Yang CG, Chen T, Si WT, Wang AH, Ren HC, Wang L. High-performance PBPK model for predicting CYP3A4 induction-mediated drug interactions: a refined and validated approach. Front Pharmacol. 2025;16:1521068. [Crossref] [PubMed] [PMC]
82. Gheorghita FI, Bocanet VI, Iantovics LB. Machine learning-based drug-drug interaction prediction: a critical review of models, limitations, and data challenges. Front Pharmacol. 2025;16:1632775. [Crossref] [PubMed] [PMC]
83. Brüggemann RJ, Verheggen R, Boerrigter E, et al. Management of drug-drug interactions of targeted therapies for haematological malignancies and triazole antifungal drugs. Lancet Haematol. 2022;9(1):e58-e72. [Crossref] [PubMed]
84. Tornio A, Filppula AM, Niemi M, Backman JT. Clinical studies on drug-drug interactions involving metabolism and transport: methodology, pitfalls, and interpretation. Clin Pharmacol Ther. 2019;105(6):1345-1361. [Crossref] [PubMed] [PMC]
85. Filppula AM, Laitila J, Neuvonen PJ, Backman JT. Potent mechanism-based inhibition of CYP3A4 by imatinib explains its liability to interact with CYP3A4 substrates. Br J Pharmacol. 2012;165(8):2787-2798. [Crossref] [PubMed] [PMC]
86. Pilla Reddy V, Bui K, Scarfe G, Zhou D, Learoyd M. Physiologically based pharmacokinetic modeling for olaparib dosing recommendations: bridging formulations, drug interactions, and patient populations. Clin Pharmacol Ther. 2019;105(1):229-241. [Crossref] [PubMed] [PMC]
87. Eadie LN, Hughes TP, White DL. Interaction of the efflux transporters ABCB1 and ABCG2 with imatinib, nilotinib, and dasatinib. Clin Pharmacol Ther. 2014;95(3):294-306. [Crossref] [PubMed]
88. Nagashima S, Soda H, Oka M, et al. BCRP/ABCG2 levels account for the resistance to topoisomerase I inhibitors and reversal effects by gefitinib in non-small cell lung cancer. Cancer Chemother Pharmacol. 2006;58(5):594-600. [Crossref] [PubMed]