

# Core Entrustable Professional Activities in Clinical Pharmacology: Pearls for Clinical Practice

The Journal of Clinical Pharmacology  
2018, 00(0) 1–13  
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Clinical Pharmacology  
DOI: 10.1002/jcph.1088

## Drug-Drug and Food-Drug Interactions

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### Introduction

Drug-drug interactions (DDIs) are defined as interactions of drug combinations resulting in a pharmacological or clinical response that differs from responses to the agents when either is given alone. Pharmacokinetic drug interactions are associated with decreased or increased drug exposure and hence with abolition or attenuation of pharmacological response or increased likelihood of side effects. The interactions associated with pharmacological drug response can be additive or synergistic (when the drug's effect is increased), be antagonistic (when the drug's effect is decreased or completely abolished), or even lead to a completely different effect(s) that neither drug confers on its own. DDIs can be used to enhance effectiveness, but they are also significant contributors to adverse drug reactions, causing a large number of hospital admissions as a result of medically important, sometimes serious or even fatal adverse events. Although the common approach and attitude to deal with DDIs are to avoid the interacting combinations by choosing alternative drugs, these choices may not always be an option. Therefore, alterations in dose, treatment (sequence and scheduling), or additional monitoring to maintain therapeutic effect or to prevent adverse outcomes may be required. There are certain characteristics that make drugs susceptible to clinically significant DDIs including a narrow therapeutic index, nonlinear pharmacokinetics, steep dose-response curves, and enzyme- or transporter-inhibiting or -inducing properties. Although there are numerous mechanisms of DDIs, from a clinical practice point of view there are basically 2 major categories to distinguish, namely pharmacodynamic and pharmacokinetic DDIs.

### Pharmacodynamic Interactions

The category of pharmacodynamic (PD) interactions consists of interactions that are not associated with significant changes in drug exposure; ie, they are linked with shifts in the concentration-response relationship. PD interactions occur either directly at the drug target level (eg, opioid receptors; antagonism of naloxone to treat opioid overdose) or at the level of downstream signaling pathways or by cross-talking pathways.<sup>1</sup> This implies that PD interactions occur if 1 drug has an antagonistic, additive, synergistic, or indirect pharmacologic effect on another. Additive or synergistic PD interactions are often used in established drug-combination treatments to take advantage of mutually potentiating drug effects via different mechanisms, eg, in the combined use of different classes of anti-infective, anticancer, antiviral, antihypertensive, or analgesic drugs.

It is important to note that PD interactions—unlike pharmacokinetic (PK) interactions—are often likely

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Submitted for publication 11 December 2017; accepted 9 January 2018.

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to represent class effects, ie, that interactions that are based on a specific mode of action of a certain drug class, eg, specific serotonin reuptake inhibitors (SSRIs), apply more or less to all representatives of this drug class sharing the specific mode of action, albeit with different potency (see below the example of SSRI/nonsteroidal antiinflammatory drug [NSAID] interaction).

The clinically most frequent and significant PD interactions are often based on mechanistically diverse effects on complex physiological systems involved in the homeostasis of critically important endogenous substrates (eg, blood glucose), electrolytes (eg, potassium), cellular functions (eg, QTc interval prolongation, inhibition of platelet aggregation), or complex biological cascades (eg, blood coagulation).

The renin-angiotensin-aldosterone system is an example of such a complex physiological system, in this case involved in potassium homeostasis. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers exert their serum potassium-increasing potential predominantly by inhibition of aldosterone release, whereas potassium-sparing diuretics either directly block the action of aldosterone at the aldosterone receptor (eg, spironolactone, eplerenone) or block renal sodium reabsorption (amiloride, triamterene), thereby reducing tubular secretion of potassium.<sup>2</sup> The resulting hyperkalemia of these PD interactions is of critical clinical importance as evidenced by Juurlink and co-workers.<sup>3</sup> The authors reported that elderly patients on ACE inhibitors with hospital admissions due to hyperkalemia were about 20 times more likely to have been treated with a potassium-sparing diuretic.

Another frequent and medically important PD interaction is based on dual-pathway impairment of platelet function that has been observed to occur with concomitant use of SSRIs and NSAIDs. Both drug classes are known to increase the risk of upper gastrointestinal bleeding (UGIB) by inhibition of platelet aggregation. A meta-analysis of several studies of patients on SSRIs and NSAIDs showed that patients taking SSRIs are twice as likely to have UGIB, and concomitant NSAID use increases the UGIB risk by more than 5-fold.<sup>4</sup> The risk of UGIB appears higher with antidepressants that elicit a more potent inhibition of serotonin uptake, thereby further supporting the validity of the mechanism.<sup>4</sup> The mechanistic background behind this interaction is that both serotonin and thromboxane A<sub>2</sub> are critical factors for platelet hemostasis and their primary biological function, platelet aggregation. SSRI-induced inhibition of serotonin reuptake by platelets goes along with serotonin depletion, and NSAIDs inhibit platelet cyclooxygenase, thereby blocking the formation of thromboxane A<sub>2</sub>.<sup>5</sup> Both mechanisms result in a dual-pathway inhibition of platelet aggregation

and consequently a mutually enhanced prolongation of the bleeding time.

The same holds for oral anticoagulants, including vitamin K antagonists such as warfarin and phenprocoumon and platelet inhibitors such as SSRIs and NSAIDs.<sup>6</sup> This serves as example that functional alteration of different body systems (eg, blood coagulation and platelet function) in the same direction (eg, functional impairment) may result in exaggerated pharmacological responses and serious clinical outcomes.

Another example of a distant PD interaction predominantly affects the intestinal microflora through the interaction between warfarin and various antibiotics including trimethoprim/sulfamethoxazole, ciprofloxacin, levofloxacin, azithromycin, and clarithromycin.<sup>7</sup> Warfarin produces its anticoagulant effect by inhibiting the vitamin K-dependent activation of clotting factors II, VII, IX, and X, and the antibiotics listed above are likely to eliminate vitamin K-producing bacteria in the intestines to further reduce vitamin K availability. Another possible interaction by inhibition of cytochrome P450-2C9 might be a probable secondary mechanism. The interactions between warfarin and antibiotics are referred to as “complex interactions” with both PD and PK elements. Warfarin users who are prescribed the antibiotics as listed above are at higher risk for serious bleeding events.

The most common examples of additive/synergistic and antagonistic PD interactions are summarized in Tables 1 (additive and synergistic effects) and 2 (antagonistic effects), respectively.

## PK Interactions

PK drug-drug interactions (DDIs) lead to changes in drug exposure (observed changes in the systemic drug concentration or postulated local drug concentration at the site of effect) of affected drugs. Blood concentrations of given drugs may be raised or lowered, thereby resulting in either toxicity/adverse events or in attenuation or abolition of efficacy. PK DDIs can occur at all levels of PK processes, that is, release/liberation from the dosage form, absorption, tissue uptake, metabolism, and excretion. Complex PK DDIs may affect more than just 1 of these processes, and some changes (involving drug transporters) may create a mismatch in direction of changes that occur in the systemic circulation vs those at the site of effect, for example, statins that need to be actively taken up by organic anion-transporting polypeptide (OATP) transporters into liver to access and inhibit their target enzyme HMG-CoA reductase.<sup>8</sup> When OATP-mediated uptake transport is inhibited, systemic (that is, extrahepatic) statin exposure is increased, which may go along with systemic off-target adverse effects (eg, rhabdomyolysis).

**Table 1.** Examples of Common Additive/Synergistic Pharmacodynamic Drug-Drug Interactions

Substance/Class A	Substance/Class B	Possible PD Effect/Outcome	Mechanism(s)
ACEi/ARBs	Potassium-sparing diuretics: spironolactone, eplerenone, amiloride, triamterene	Hyperkalemia	Inhibition of aldosterone release plus aldosterone receptor antagonism or reduction of renal tubular potassium secretion
NSAIDs	Warfarin, phenprocoumon	Increased bleeding risk	Inhibition of vitamin K–dependent clotting factors plus inhibition of platelet aggregation
SSRIs	NSAIDs	Increased bleeding risk	Dual-pathway inhibition (serotonin and thromboxane A <sub>2</sub> ) of platelet function
SSRIs	Triptans; opioids; MAOIs	Serotonin syndrome	Additive serotonin reuptake inhibition
Nitrates	PDE <sub>5</sub> Inhibitors	Acute drop in blood pressure, collapse	Additive cGMP elevation by increased formation (nitrates) and reduced clearance (PDE <sub>5</sub> i)
Tricyclic antidepressants	Antipsychotics/neuroleptics	Anticholinergic syndrome	Additive anticholinergic effects

ACEi indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MAOIs, monoamine oxidase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; PD, pharmacodynamics; PDE, phosphodiesterase; SSRIs, selective serotonin reuptake inhibitors.

**Table 2.** Examples of Common Antagonistic Pharmacodynamic Drug-Drug Interactions

Substance/Class A	Substance/Class B	Possible PD Effect/Outcome	Mechanism(s)
Opioids (eg, morphine)	Naloxone	Reversal of $\mu$ -receptor–mediated opioid effects, eg, respiratory depression	$\mu$ -receptor antagonism
Benzodiazepines	Flumazenil	Reversal of exaggerated benzodiazepine effects, eg, sedation	Benzodiazepine receptor antagonism
Heparin	Protamine sulfate	Reversal of heparin-mediated anticoagulatory effects	Interlinkage between the 2 substances to form inactive molecules
Warfarin	Vitamin K	Reduced anticoagulatory warfarin effect	Functional antagonism of warfarin-mediated vitamin K epoxide reductase inhibition by vitamin K supplementation
ACEi/ARBs	NSAIDs	Reduced antihypertensive ACEi/ARB effects	Reduction in glomerular perfusion by reduced local prostaglandin E <sub>2</sub> synthesis with corresponding reactive renin secretion. NSAID-mediated sodium and water retention. Elevated intrarenal aldosterone concentrations by inhibition of UGT2B7-mediated aldosterone glucuronidation (PK DDI with an endogenous substrate!) <sup>47</sup>
Antidiabetic drugs	Glucocorticosteroids	Attenuation of antidiabetic effects	Glucocorticoid-mediated inhibition of a number of steps in the insulin signaling network through several different mechanisms, resulting in direct actions of glucocorticoids on muscle, liver, and other tissues <sup>48</sup>
Levodopa	Antipsychotics/neuroleptics, eg, haloperidol	Attenuation/abolition of L-dopa effect	Dopa-receptor antagonism
Macrolide antibiotics	Drugs with capability for QTc-interval prolongation	Exaggerated QTc-prolongation, life-threatening ventricular arrhythmia (Torsade de Pointes, TdP)	Cardiac ion channel inhibition

ACEi indicates angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; NSAID, nonsteroidal anti-inflammatory drug; PD, pharmacodynamics; PK, pharmacokinetic.

PK DDIs are distinguished between drugs causing exposure alterations of other drugs (sometimes referred to as “perpetrators”) and drugs being the objects of exposure alterations (referred to as “victims” or “objects”).

For PK interactions the chemical structures determining the binding characteristics of a compound are important features. In contrast to PD interactions,

this implies that a PK-based DDI susceptibility does not uniformly apply to all representatives of a pharmacological class. Accordingly, there may be class representatives not showing a specific DDI that is present for other class members. Such compounds may be selected as therapeutic alternatives to prevent or manage DDIs. This can be exemplified by the class of proton-pump inhibitors (PPIs). Whereas omeprazole

acts a moderate inhibitor of cytochrome CYP2C19, an effect that results in exposure increases of CYP2C19 substrates (eg, R-warfarin and other vitamin K antagonists, cilostazol, diazepam, and phenytoin), pantoprazole does not significantly inhibit CYP2C19 and does not produce these interactions.

It is important to note that PK interactions are not confined to coadministered drugs (as in DDIs) but may also exist between drugs and constituents of foods or beverages. For instance, grapefruit,<sup>9</sup> Seville orange, and other fruit juices or products<sup>10</sup> and alcohol-containing drinks<sup>11</sup> are also known for their capacity to substantially alter drug absorption and bioavailability by a variety of mechanisms, thereby affecting clinical efficacy and safety of medicines (for details see Absorption Interactions below and the Grapefruit Juice Interaction Vignette).

### Absorption Interactions

With concomitant administration of oral dosage forms, 1 drug may reduce or abolish the absorption of another drug by various mechanisms.

Complex formation is 1 mechanism that may substantially alter the oral bioavailability of certain drugs and can happen with the concurrent presence of 2 potentially interacting drugs in the stomach or gastrointestinal tract. One example is bisphosphonates (eg, alendronate) used in the treatment of osteoporosis, which have a very poor bioavailability (BA) of only 0.5% to 2%. Calcium ions in mineral water or milk, calcium supplements, and antacids reduce this low BA further. Similarly, the absorption of fluoroquinolones (eg, moxifloxacin, levofloxacin, ofloxacin) and tetracycline antibiotics (eg, doxycycline) may be impaired by formation of insoluble complexes with concurrently administered antacids or other drugs containing polyvalent cations such as aluminum, calcium, or magnesium and by oral zinc, iron salts, or bismuth. The same interaction mechanism applies to levodopa, carbidopa, or catechol-O-methyltransferase inhibitors (eg, entacapone). A time-separated intake of perpetrators (including respective foods and beverages) and susceptible victim drugs is usually recommended to manage such interactions.

Another mechanism for absorption DDIs may result from changes in the gastric pH, as absorption of orally administered weak base drugs with pH-dependent solubility (eg, dipyridamole) may be altered when one is coadministered with a gastric acid-reducing agent such as an antacid, H<sub>2</sub>-receptor antagonists, or PPIs.<sup>12,13</sup> Coadministration of the human immunodeficiency virus (HIV) protease inhibitor atazanavir with the H<sub>2</sub>-receptor antagonist famotidine, for instance, substantially decreases atazanavir plasma concentrations,

which may result in loss of therapeutic effect and development of resistance.<sup>14</sup>

Another example is the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib, which is characterized by a decrease in solubility at pH above 5. Coadministration of erlotinib with the PPI omeprazole decreased the erlotinib exposure (measured as the area under the concentration-time curve [AUC]) and maximum concentration (C<sub>max</sub>) by 46% and 61%, respectively. Concomitant administration of erlotinib with 300 mg of the H<sub>2</sub>-receptor antagonist ranitidine decreased erlotinib AUC and C<sub>max</sub> by 33% and 54%, respectively. Erlotinib must be taken 10 hours after the H<sub>2</sub>-receptor antagonist dosing and at least 2 hours before the next dose of H<sub>2</sub>-receptor antagonist. Furthermore, the concomitant use of erlotinib with PPIs should be avoided, as PPIs inactivate the proton pump by irreversible binding, resulting in suppression of gastric acid production for more than 24 hours after dosing. Therefore time-separated intake of PPIs is not a viable strategy to avoid absorption DDIs of drugs with pH-dependent solubility.

Alteration of intestinal drug absorption and oral bioavailability may also be based on inhibition or induction of intestinal efflux transporters of the ABC family (ABCB1 [P-gp], ABCG2 [BCRP]), or inhibition of uptake transporters such as organic anion-transporting polypeptides (OATP1A2, OATP2B1) or organic cation transporters (OCT1-3), which are solute carriers of the SLC22 family. Such transporter-based interactions can be conferred by a variety of drugs, foods, and beverages (in particular fruit juices). As a general rule, inhibition of efflux transporters will result in enhanced oral BA and systemic exposure of P-glycoprotein (P-gp) and BCRP substrates, whereas induction of these transporters will enhance the efflux capacity resulting in reduced BA. In turn, inhibition of OATP uptake transporters by various fruit juices has been shown to reduce the oral BA of OATP1A2 and OATP2B1 substrate drugs such as certain  $\beta$ -blockers (atenolol, celiprolol, talinolol), ciprofloxacin, and fexofenadine<sup>10</sup> (see Grapefruit Juice Interaction Vignette). Inhibition of intestinal OCT transporters is a further important absorption interaction mechanism, as OCT-mediated uptake governs the oral BA of cationic drugs such as metformin.<sup>15</sup>

Inhibition or induction of presystemic CYP3A-mediated metabolism in the gut wall by potent CYP3A inhibitors, a major contributor to the first pass effect, is another important mechanism determining the oral bioavailability of sensitive CYP3A substrates.

Examples of relevant P-gp (ABCB1), BCRP (ABCG2) substrates, inhibitors and inducers, and OATP1A2, OATP2B1, and OCT1-3 inhibitors and substrates are given in Table 3.

**Table 3.** Examples of Intestinal Efflux and Uptake Transporter Substrates and Inhibitors

P-gp (ABCB1)	BCRP (ABCG2)	OTPIA2	OATP2B1	OCT2
<i>Substrates</i>				
Amiodarone	Cladribine	Atenolol	Aliskiren	Amantadine
Cyclosporine	Dipyridamole	Celiprolol	Atorvastatin	Amiloride
Digoxin	Glyburide	Ciprofloxacin	Benzylpenicillin	Cimetidine
Diltiazem	Gefitinib	Darunavir	Bosentan	Dopamine
Doxorubicin	Imatinib	Enoxacin	Eltrombopag	Famotidine
Etoposide	Irinotecan, SN-38	Erythromycin	Fexofenadine	Memantine
Indinavir	Methotrexate	Fexofenadine	Fluvastatin	Metformin
Itraconazole	Mitoxantrone	Imatinib	Glibenclamide /Glyburide	Pindolol
Nelfinavir	Nitrofurantoin	Labetalol	Montelukast	Procainamide
Paclitaxel	pitavastatin	Levofloxacin	Pravastatin	Ranitidine
Ritonavir	Prazosin	Lopinavir	Pitavastatin	Varenicline
Saquinavir	Rosuvastatin	Nadolol	Rosuvastatin	Oxaliplatin
Sirolimus	Topotecan	Norfloxacin	Thyroxine (T <sub>4</sub> )	
Tacrolimus		Pitavastatin		
Verapamil		Rocuronium		
Vinblastine		Rosuvastatin		
Vincristine		Saquinavir		
		Sotalol		
		Thyroxine (T <sub>4</sub> )		
		Triiodothyronine (T <sub>3</sub> )		
<i>Inhibitors</i>				
Amiodarone	Cyclosporine	Apple juice	Cyclosporine	Cimetidine
Chinidin	Flavonoids (chrysin and biochanin A)	Grapefruit juice	Gemfibrozil	Cetirizine
Cyclosporine	Gefitinib	Hesperidin		Desipramine
Clarithromycin	Imatinib	Naringin		Quinidine
Erythromycin	Nelfinavir	Orange juice		
Itraconazole	Ritonavir	Rifampicin		
Ketoconazole		Verapamil		
Nelfinavir				
Ritonavir				
Saquinavir				
Spiroonolactone				
Tacrolimus				
Verapamil				

P-gp indicates P-glycoprotein; SN-38 is a much more active metabolite of irinotecan.

## Metabolism-Based Interactions

The metabolism of the majority of drugs is mediated by the cytochrome P450 enzyme family. Cytochromes of the CYP1-, CYP2-, and CYP3-family are major contributors to drug metabolism. Together, CYP3A, CYP2D6, and CYP2C family members account for about 55% to 60% of the overall hepatic CYP-enzyme content and contribute to about 70% of the overall metabolism of marketed drugs. Due to its broad substrate specificity, CYP3A alone is the primary clearance mechanism for more than 30% of all marketed drugs.<sup>16</sup> Besides the liver, CYP3A is also abundantly expressed in the small intestinal wall, where it acts as major contributor to presystemic gut wall metabolism (also referred to as presystemic first-pass effect). Some of the CYP3A substrates, inhibitors, and inducers share affinity to P-gp, revealing an evolutionary cooperative synergism (ie, shared responsibility) between a key metabolic enzyme and a key efflux transporter in gov-

erning the oral bioavailability of harmful/toxic food constituents and xenobiotics in the gut.<sup>17,18</sup>

The activity and capacity of CYP enzymes can be inhibited or induced. Table 4 summarizes prominent examples of potent inhibitors and inducers of the clinically most important cytochrome P450 enzymes, ie, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. In this context it is worth noting that inducibility and susceptibility to inhibition are not of similar magnitude and clinical relevance for the major CYP enzymes in drug metabolism. CYP2D6, for instance, is hardly inducible at all (ie, no inducers of CYP2D6 are known), and only few inhibitors of CYP2B6 (eg, ticlopidine, clopidogrel)<sup>19</sup> and CYP2C19 have been identified.

### Inhibition

There are 2 distinct forms of enzyme inhibition. (1) Competitive inhibition exists when substrates share the same CYP enzyme as a metabolic pathway,

**Table 4.** Interactions With the Key Cytochrome P450 Enzymes: Inhibitors and Inducers

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
<i>Inhibitors</i>				
<b>Fluoroquinolones</b>	Amiodarone +	<b>SSRIs</b>	<b>SSRIs</b>	<b>HIV protease inhibitors</b>
Ciprofloxacin ++	Fluconazole ++	Fluoxetine	Duloxetine +	Indinavir ++
Ofloxacin	Isoniazide	Fluvoxamine	Fluoxetine ++	Nelfinavir ++
Levofloxacin			Paroxetine ++	Ritonavir ++
<b>Miscellaneous</b>		<b>PPIs</b>	<b>Miscellaneous</b>	<b>Macrolides</b>
Amiodarone		Lansoprazole +	Amiodarone	Clarithromycin ++
Cimetidine +		Omeprazole +	Bupropion	Erythromycin +
Fluvoxamine ++			Cimetidine	
Ticlopidine			Quinidine ++	
			Chlorphenamine	
			Clomipramine	
			Ritonavir	
		<b>Miscellaneous</b>		<b>Azole antimycotics</b>
		Ketoconazole		Fluconazole +
		Ticlopidine		Itraconazole +
				Ketoconazole ++
				Voriconazole
				<b>Miscellaneous</b>
				Aprepitant +, Amiodarone
				Cimetidine +
				Diltiazem
				Naringin + (in citrus fruits)
				Verapamil +
<i>Inducers</i>				
Tobacco smoke	Rifampicin			Carbamazepine
Omeprazole				Efavirenz
				Hyperforin (in St. John's wort)
				Phenobarbital
				Phenytoin
				Rifampicin

++ = strong inhibition; + = intermediate inhibition; no + = weak or undefined inhibition. PPI indicates proton pump inhibitor; SSRI, specific serotonin reuptake inhibitor. Adapted from ref. 49.

competing for the same binding sites. Competitive inhibition requires high perpetrator affinity for the target enzyme and reasonable physical presence at the binding site. Competitive inhibition disappears without a time delay as soon as the perpetrator drug molecules vanish from the binding site. Therefore, competitive inhibition is rapid in onset but transient in duration, depending on the residence time of substrates. Competitive inhibition may be clinically managed by staggering administration.<sup>20</sup> (2) Irreversible inhibition, also denoted “time-dependent” or “mechanism-based” or “suicidal inhibition,” occurs due to covalent or tight binding of formed inhibitor metabolites at the binding site of the CYP enzyme during the normal catalysis reaction. This leads to a time-dependent increase of enzyme inhibition, resulting in potent inhibition with repeated use and persistence of altered/abolished enzyme activity long after termination of inhibitor drug administration.<sup>21</sup> Irreversible inhibition only disappears as a function of de novo enzyme synthesis and is usually of major clinical relevance. Irreversible

enzyme inhibition cannot be managed by timely separation of inhibitor and substrate intake.

Irreversible inhibition of CYP enzymes could be beneficial and is sometimes used for intended therapeutic drug interactions to boost the effects of other drugs such as ritonavir, a potent mechanism-based inhibitor of CYP3A and other HIV protease inhibitors. The mechanistic background of this concept is based on the observation that many of the key HIV treatment entities are CYP3A and/or P-gp substrates and consequently have low oral systemic availability. Even with high doses, achievement of therapeutic plasma concentrations may be difficult or impossible without coadministration of a boosting agent.<sup>22</sup> The US Food and Drug Administration approved boosting HIV therapy in the year 2000 with the approval of a fixed combination product<sup>23</sup> containing lopinavir as the principal therapeutic agent together with low-dose ritonavir as the boosting agent.<sup>24</sup> Systemic AUC for lopinavir is increased by a factor of 70- to 80-fold with ritonavir coadministration.<sup>25</sup>

Potent inhibition of CYP3A is produced by azole antifungals (eg, ketoconazole, fluconazole, itraconazole, voriconazole; see Simvastatin-Itraconazole Interaction Vignette), HIV protease inhibitors (eg, ritonavir, nelfinavir), some calcium antagonists (eg, verapamil, diltiazem), macrolide antibiotics (eg, clarithromycin, erythromycin), and some SSRIs such as fluvoxamine and fluoxetine. Grapefruit juice (GFJ) is also a potent and irreversible inhibitor of CYP3A and can confer a complete inhibition of intestinal CYP3A that may last up to 3 days (see Grapefruit Juice Interaction Vignette). Effect sizes of CYP3A inhibitors (in terms of exposure increases of sensitive CYP3A substrates) depend on the oral BA of the affected substrate: effect sizes are larger for substrates with low BA. For example, the exposure of felodipine (15% oral BA) is about 2-fold increased when taken after a glass of GFJ.<sup>26</sup> Another factor determining the effect size of CYP3A inhibition is the individual abundance of intestinal CYP3A, which has been shown to be highly variable between subjects, with GFJ-associated felodipine  $C_{max}$  increases ranging from 64% to 597% and AUC from 4% to 368%.<sup>27</sup> A third factor for the overall effect size of enzyme inhibition is whether a substrate exclusively relies on a single metabolic enzyme or whether other CYPs contribute to its metabolism. The fraction that undergoes metabolism by a specific CYP enzymatic pathway is expressed as fraction metabolized. A high fraction metabolized by a certain pathway (eg, CYP3A) is associated with high exposure changes of the concerned substrate when this pathway becomes inhibited. Such substrates are therefore denoted “sensitive” substrates. Multiple metabolic pathways of a given substrate allow for alternative metabolic clearance, termed “metabolic switching,” when 1 pathway gets inhibited, and the resulting changes in drug exposure are expected to be modest.

A specific subcategory of metabolic DDIs by CYP inhibition represents the altered or blocked metabolic activation of prodrugs, which does not result in adverse drug reactions but loss of efficacy. This may not be readily clinically detectable, for example, in the case of the anti-breast cancer drug tamoxifen or the platelet inhibitor clopidogrel. These DDIs are therefore referred to as “silent interactions.” Tamoxifen can be considered a “prodrug” requiring metabolic activation to elicit pharmacological activity. CYP2D6 is the rate-limiting enzyme catalyzing the conversion of tamoxifen into its active metabolites (endoxifen, 4-OH-tamoxifen) with significantly greater affinity for the estrogen receptor and greater ability to inhibit cell proliferation.<sup>28</sup> Accordingly, long-term coadministration of potent CYP2D6 inhibitors (such as the SSRIs fluoxetine and paroxetine) is expected to result in worse clinical cancer outcomes. A similar mechanism

**Table 5.** Cytochrome P450–Based Multipathway Inhibition: Examples of Important Dual- or Multi-CYP Inhibitors

Substance	Therapeutic Class	Inhibited CYP Enzymes
Clarithromycin	Antibiotic (macrolide)	3A4, 1A2
Fluvoxamine	SSRI antidepressant	<b>1A2</b> , 2B6, <b>2C19</b> , 3A4, (2D6)
Fluconazole	Triazole antimycotic	<b>2C9</b> , 2C19, 3A4
Fluoxetine	SSRI antidepressant	2C19, <b>2D6</b>
Paroxetine	SSRI antidepressant	2C19, <b>2D6</b>
Ticlopidine	Platelet inhibitor	1A2, <b>2B6</b>

Note: In vivo inhibition of different enzymes may be conferred at different concentrations and with different potencies. Substances that are potent in vivo inhibitors of CYPs are depicted in bold font. CYP indicates cytochrome P450; SSRI, specific serotonin reuptake inhibitor.

applies to the platelet inhibitor prodrug clopidogrel, which relies on a 2-step metabolic activation by CYP enzymes, of which CYP2C19 is considered to be of major importance. This is exemplified by omeprazole, which acts as moderate CYP2C19 inhibitor, and when administered 80 mg once daily either at the same time as clopidogrel or with 12 hours between the administrations of the 2 drugs decreases the exposure of the active clopidogrel metabolite by 45% (loading dose) or 40% (maintenance dose). This decrease is associated with a clinically significant reduction in inhibition of platelet aggregation. Further, it was shown that GFJ, a strong irreversible inhibitor of intestinal CYP3A constituents, can also inhibit CYP2C19 and markedly decrease the exposure to the active metabolite of clopidogrel with a corresponding impairment of its antiplatelet effect.<sup>29</sup> The results of this study suggest that both intestinal (CYP3A) and hepatic (CYP2C19) first-pass metabolism are important for clopidogrel bioactivation and may reflect a CYP2C19-inhibiting effect of GFJ in addition to CYP3A inhibition.<sup>29</sup> These results highlight the susceptibility of clopidogrel to inhibition of its metabolic activation and the quantitative impact of a concomitant dual-pathway inhibition of CYP3A and CYP2C19 by GFJ as compared to CYP2C19 inhibition by omeprazole.

Another special aspect of CYP inhibition with particular clinical relevance is the coinhibition of multiple CYP pathways. Table 5 lists examples of multiple and dual CYP enzyme inhibitors. The most promiscuous CYP inhibitor in clinical use is fluvoxamine, a SSRI and sigma 1 receptor agonist that inhibits CYP1A2, CYP2C19, CYP3A, CYP2B6, and CYP2D6 in vivo, albeit with different potencies. Accordingly, the PK DDI with largest effect size ever reported involved fluvoxamine as perpetrator drug on ramelteon, a melatonin receptor agonist with a very low oral BA that is cleared by CYP1A2, CYP2C19, and CYP3A enzymes. This study actually reported a 190-fold increase in the plasma AUC of ramelteon when coadministered with fluvoxamine.<sup>30</sup>

## Induction

CYP induction is mediated via certain nuclear receptors. Often the pregnane X receptor is involved, but there are also other nuclear factors playing a role in enzyme induction, such as the constitutive androstane receptor, the family of peroxisome proliferator-activated receptors, and the aryl hydrocarbon receptor.

The primary function of the pregnane X receptor is to sense the presence of foreign toxic substances and in response upregulate the expression of proteins (ie, enzymes and transporters) involved in the detoxification and clearance of these substances from the body. Hence, induction is based on increased enzyme and transporter expression predominantly in liver and gut wall. Induction is hardly specific but rather is an integrated detoxification strategy including coinduction of cooperating enzymes and transporters (eg, CYP3A and P-gp). Induction and reversal of induction (deinduction) are time-dependent processes that need to be carefully considered in the timing of dose adjustments of concomitant treatments. First induction effects may be notable as soon as 1 day after onset of treatment, although maximum induction may require up to 1 to 2 weeks of treatment.<sup>31,32</sup> For the full reversal of induction (deinduction) after withdrawal of an inducer, about 6 to 7 days are required for the complete decline to the basal liver CYP content. During that period the doses of concomitant treatments need to be adjusted stepwise. In case of concomitant treatment with narrow-therapeutic-index drugs (eg, cyclosporine, digoxin), particular care should be taken, and therapeutic drug monitoring should be considered (see Digoxin-Rifampin Interaction Vignette).

## Transporter-Based Interactions

Beyond transporter-based DDIs at the level of the gastrointestinal tract (see Absorption Interaction), there are additional important systemic transporter-based DDIs at the level of hepatic uptake and renal excretion. Because of their large effect size and clinical importance, this section focuses on hepatic uptake DDIs involving OATPs (OATP1B1, OATP1B3, OATP2B1).

OATPs are membrane influx transporters that regulate cellular uptake of a number of endogenous compounds (eg, unconjugated and conjugated bilirubin, bile acids, conjugated steroids, and thyroid hormones) and clinically important drugs (Table 6).<sup>33</sup> OATP1B1, 1B3, and 2B1 are mainly located at the sinusoidal membranes of human hepatocytes and mediate the influx of their substrates from blood into the hepatocytes, thereby representing an important step in the facilitation of hepatic drug metabolism<sup>33</sup> by facilitating access to drug-metabolizing enzymes located within the hepatocyte. Examples of widely used OATP substrates

**Table 6.** Organic Anion-Transporting Polypeptide Substrates

OATP1B1	OATP1B3	OATP2B1
Atorvastatin	Atrasentan	Aliskiren
Atrasentan	Bosentan	Atorvastatin
Benzylpenicillin	Digoxin	Benzylpenicillin
Bosentan	Docetaxel	Bosentan
Caspofungin	Enalapril	Fexofenadine
Cerivastatin	Erythromycin	Fluvastatin
Enalapril	Fexofenadine	Glibenclamide /glyburide
Ezetimibe	Fluvastatin	Montelukast
Fexofenadine	Imatinib	Pravastatin
Fluvastatin	Methotrexate	Rosuvastatin
Lopinavir	Olmesartan	Unaprostone
Methotrexate	Quabain	
Olmesartan	Paclitaxel	
Pitavastatin	Pitavastatin	
Pravastatin	Pravastatin	
Rifampicin	Rifampicin	
Rosuvastatin	Rosuvastatin	
Simvastatin		
Saquinavir	Telmisartan	
SN-38*	SN-38*	
Temocapril	Thyroxine	
Troglitazone	Valsartan	
Valsartan		

Modified from Ref. 50. OATP indicates organic anion-transporting polypeptide. \*SN-38 is the active metabolite of irinotecan with about 1000 times more activity than irinotecan itself.

are given in Table 6. It has been shown that inhibition of OATPs (eg, by cyclosporine, gemfibrozil, rifampicin, lopinavir/ritonavir) may result in remarkable increases of the systemic exposure of OATP substrate drugs (see Table 6). HMG-CoA reductase inhibitors (statins), which are widely used lipid-lowering drugs, represent the most prominent class of drugs relying on OATP-mediated hepatic uptake and become subject to substantial exposure increases when hepatic uptake is inhibited. Examples of respective DDIs are summarized in Table 7. Although statins are generally well tolerated, they can cause muscle toxicity (myalgia, myopathy, creatine kinase increase) in an exposure-related fashion, which can lead to severe rhabdomyolysis with subsequent renal failure, which may be fatal.<sup>34</sup> It has been shown that increased systemic exposure of statins in subjects with a nonfunctional OATP1B1 transporter polymorphism (noncoding rs4363657 SNP; so called c.521C variant) is associated with increased risk for statin-induced myopathy. The odds ratio for myopathy was 4.5 (95% confidence interval 2.6 to 7.7) per copy of the C allele, and 16.9 (95% confidence interval 4.7 to 61.1) in homozygote carriers of the C allele (CC) as compared with wild-type homozygotes (c.521TT). More than 60% of myopathy cases could be attributed to the c.521C variant.<sup>35</sup> In 1 study, homozygote carriers of the OATP1B1 c.521CC variant had a 91% and 74%

**Table 7.** Transporter-Based DDIs Affecting Hepatic Uptake by Organic Anion-Transporting Polypeptides (OATP1B1, OATP1B3, OATP2B1)

Perpetrator Drug (OATP Inhibitors)	Object/Victim	Total and Maximum PK Exposure Outcomes
Cyclosporine	Pravastatin	AUC↑ 890% and C <sub>max</sub> ↑ 678%
Cyclosporine	Rosuvastatin	AUC↑ 610%
Cyclosporine	Pitavastatin	AUC↑ 360% and C <sub>max</sub> ↑ 560%
Rifampicin (single dose)	Glyburide	AUC↑ 125%
Rifampicin (single dose)	Bosentan	C <sub>trough</sub> ↑ 500%
Lopinavir/Ritonavir	Bosentan	Day 4: C <sub>max</sub> ↑ 4700%; day 10: C <sub>trough</sub> ↑ 400%
Lopinavir/Ritonavir	Rosuvastatin	AUC↑ 107% and C <sub>max</sub> ↑ 365%

Adapted from Ref. 51. AUC indicates area under the concentration-time curve; C<sub>max</sub>, peak concentration; C<sub>trough</sub>, lowest concentration; DDI, drug-drug interaction; OATP, organic anion-transporting polypeptide; PK, pharmacokinetics.

larger pravastatin AUC than those with the c.521TT or c.521TC genotype, respectively.<sup>36</sup>

Based on this pharmacogenetic evidence along with DDI studies using different OATP inhibitors, it is now well established that alteration of regular OATP1B1, 1B3, and 2B1 function by coadministered inhibitors is associated with an increased risk of exposure-related statin-induced myopathy. Regarding the DDI studies it is, however, important to note that some of the employed inhibitor drugs (cyclosporine, gemfibrozil) are not specific to OATPs and are also known to inhibit other transporters (eg, cyclosporine) or metabolic enzymes (eg, CYP2C8 inhibition by gemfibrozil). This implies that for these inhibitors the overall quantitative outcome of a DDI cannot be solely attributed to OATP inhibition but is rather to be considered the result of a complex dual- or multipathway interaction.

### Public Health Burden of DDIs and Patient Factors

The true incidence and overall health burden of DDIs is difficult to determine; documentation of adverse drug reactions in medical case notes is poor because specific diagnostic codes for DDIs are lacking.<sup>37</sup> However, various studies have consistently shown that DDIs are a significant cause of hospital admissions and hospital visits.<sup>3,37,38</sup> A recent systematic review and meta-analysis showed that among patients referred to hospitals for adverse drug reactions, the median DDI prevalence rate for hospital admissions and emergency room visits were 22.2% and 8.9%, respectively.<sup>39</sup> These numbers likely underestimate the true health burden of DDIs, as DDIs that do not result in hospital referrals, such as DDIs resulting in fatality before hospital admission, DDIs that are recognized and managed on an ambulatory basis, and DDIs that only confer the risk of decreased effectiveness without notable adverse events (“silent DDIs”) are not accounted for in these studies. The latter DDI category alone is estimated to sum up to about 25% of all DDIs.<sup>38</sup>

Many of the DDIs leading to hospitalization represent well-known and labeled interactions and are there-

fore likely to be preventable.<sup>3</sup> Prescription of drugs with a low risk for DDIs and careful monitoring for possible adverse drug reactions are measures to minimize harm associated with DDIs,<sup>40</sup> and almost half of DDIs could be managed by monitoring laboratory values.<sup>38</sup>

To manage risks associated with DDIs it is important to consider patient DDI susceptibility factors including multimorbidity, polypharmacotherapy, advanced age, impaired liver or kidney function, genetic polymorphisms of metabolic enzymes and transporters, and simultaneous use of prescription medications along with over-the-counter (OTC) drugs, herbal medicines, supplements, and alcohol. Several longitudinal studies of community-dwelling older adults (62 to 85 years, USA) revealed that the concurrent use of at least 5 prescription medications is 35.8%,<sup>41</sup> and approximately 15.1% of older adults are at risk for a potential major DDI. Most of these interacting regimens involved medications and dietary supplements.<sup>41</sup>

Based on this, health care professionals should be aware of DDI risks in special populations with concurrent use of multiple prescription drugs, OTC medications, herbal drugs and supplements, and alcohol. Efforts should be applied to inquire and document the totality of medications that are concurrently used by patients (ie, medication plan) and to carefully review the medication list for possibly dispensable treatments. Doctors should also counsel patients to increase awareness of the risks associated with the use of multiple OTC medications, herbal drugs and supplements, and alcohol without seeking prior medical advice.

The following clinical vignettes provide examples of typical, clinically relevant DDIs and the prescriber's critical role in preventing, recognizing, and managing DDI-related issues to achieve a safe and efficient pharmacotherapy.

### Conclusions

Drug-drug interactions are an important clinical and public health concern, and their avoidance represents a demanding and highly complex day-to-day challenge in medical practice. With the concepts and mechanisms

reviewed in this article and exemplified by the vignettes, the reader is prepared with mechanistic fundamentals about the topic and its clinical significance. The interaction mechanisms described apply to drugs in current use as well as to those in development or those that may be developed in future.

## Conflict of Interest

The authors have no conflict of interest to report relative to this article.

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## Appendix: Clinical Vignettes

### Grapefruit Juice Interaction Vignette

Ms Smith is taking simvastatin to lower her blood lipids and fexofenadine for her allergies. She drinks a glass of Grapefruit Juice (GFJ) every morning for breakfast.

Lately, she suffers from muscle pain and notices that her allergies are not getting better.

**Commentary.** These are both results of drug interactions with components present in the juice. Simvastatin is metabolized in the gut wall by CYP3A to a large extent, resulting in low oral bioavailability. GFJ components can block this inhibition and raise the blood concentrations of simvastatin and its metabolites dramatically, leading to the observed myopathy. Because this enzyme inhibition is not reversible, temporal separation of drug intake in the evening from drinking the juice in the morning does not eliminate the problem. Ms Smith would have to wait approximately 3 days after the last glass of GFJ to restore the enzyme activity in her intestine so that blood concentrations of simvastatin would be back to normal. However, Ms Smith can switch to another statin (atorvastatin, pravastatin) that does not interact with GFJ significantly.

The lack of activity of the antihistamine fexofenadine is also a result of an interaction with GFJ. This drug is absorbed in the intestine by an uptake transporter that is inhibited by components of the juice, resulting in subtherapeutic drug concentrations. Hence, this interaction goes in the opposite direction, lowering blood concentrations rather than increasing them as in the case of simvastatin above. Unlike the enzyme interaction, this interaction is competitive and reversible, so avoiding taking the drug with GFJ and separating the time of drug intake from consuming the juice will result in regular absorption. Alternatively, another antihistamine that does not interact with GFJ (cetirizine, loratadine) should be considered. Hence, there are simple ways to avoid these drug interactions with GFJ. It should be noted that only a relatively small number of drugs show clinically significant drug interactions with GFJ and that in all cases alternative therapies are available.

### Digoxin-Rifampin Interaction Vignette

A 53-year-old patient suffering from hypertension and ischemic heart disease associated with persistent atrial fibrillation was taking 0.125 mg once a day digoxin tablets. The patient had normal renal function (creatinine clearance of 95 mL/min), and digoxin serum concentrations were routinely assessed ranging between 1.4 and 2.0 ng/mL. Because of a tuberculosis infection the patient was started on 600 mg once a day rifampin. Serum digoxin concentrations in the first week following the start of rifampin treatment fell to 0.9 ng/mL and dropped below quantifiable concentrations in the second week. Renal function at week 2 following the start of rifampin treatment was still normal (creatinine clearance of 95 mL/min) and confirmed by a serum creatinine concentration of 1.0 mg/dL. Digoxin dose was

subsequently increased to 0.250 mg digoxin once a day with serum digoxin concentration rising to 1.2 ng/mL. Two weeks following cessation of rifampin treatment the patient reported typical symptoms of digoxin intoxication (nausea, yellowish color vision) confirmed by a digoxin plasma concentration of 3.2 ng/mL. The patient was treated with a digoxin antidote, and digoxin was reduced to 0.125 mg once a day digoxin with subsequent digoxin serum concentrations returning into the therapeutic range of 1.0-2.0 ng/mL.

**Commentary.** Digoxin is a drug with a narrow therapeutic index cleared by renal elimination. Because of this, treatment with digoxin is recommended to be controlled and adjusted by therapeutic drug monitoring (quantification of digoxin serum concentrations). The interaction presented here cannot be explained by changes in renal elimination of digoxin, which remained constant over the entire duration of the concomitant treatment with rifampicin. The inductive effect of rifampicin fully developed after 2 weeks and reversed within 6 to 7 days on cessation of the antibiotic therapy.

Digoxin absorption is incomplete and depends on the oral formulation used. The effect underlying this case example is based on an induction of the intestinal efflux pump P-gp (also known as ABCB1). The transporter is expressed on the apical membrane of enterocytes in the small intestine, the site of digoxin absorption. It functions as an additional mechanism to gut wall metabolism in the epithelium of the intestine reducing the absorption of orally absorbed xenobiotics including digoxin. P-gp has a broad substrate specificity and is subject to increased expression following exposure with drugs such as rifampicin, which is also known as a strong inducer of the major drug-metabolizing enzyme CYP3A. Following induction of intestinal P-gp, digoxin oral bioavailability is reduced, resulting in lower plasma concentrations. The interaction is limited to intestinal P-gp, as the disposition of intravenously administered digoxin is not affected by concomitant administration of rifampin.<sup>42</sup>

Although the use of rifampin is limited to infections with *Mycobacterium tuberculosis* and *Staphylococcus aureus*, St. John's Wort, a herbal drug that is frequently used for the treatment of mild depression, induces intestinal P-gp following the same mechanism as rifampin. Daily administration of 900 mg St. John's Wort extract over 10 days reduced digoxin  $C_{max}$  at steady state by 26% and digoxin  $AUC_{0-24h}$  by 25%.<sup>43</sup> The use of digoxin is increasingly limited, but other drugs such as dabigatran etexilate, an oral anticoagulant, share the described pharmacokinetic characteristics of digoxin, limited oral bioavailability influenced by intestinal P-gp, making it an object of interactions with drugs that

increase intestinal P-gp expression. Coadministration of rifampin 600 mg once a day for 7 days with 150 mg dabigatran etexilate increased the  $C_{max}$  of dabigatran by 65% and the dabigatran AUC by 67%.<sup>44</sup> The label of dabigatran etexilate therefore contains the following warning and precaution "Avoid coadministration of rifampin with dabigatran etexilate because of effects on dabigatran exposure."

#### Simvastatin-Itraconazole Interaction Vignette

A 52-year-old woman had been taking simvastatin 40 mg once a day for the treatment of hypercholesterolemia for several years; during this time the patient had tolerated the treatment well. Following the diagnosis of onychomycosis, she was prescribed itraconazole 200 mg once a day by her dermatologist for the treatment of the local fungal infection.

On the third day following the initiation of itraconazole treatment, the patient developed severe muscle pain and was admitted to hospital with the suspicion of rhabdomyolysis. The patient had normal body temperature and did not report trauma or fever before the onset of muscle pain. The patient's creatinine kinase values were highly elevated (10,437 U/L, ie, more than 40 times the upper limit of normal) along with myoglobin concentrations of 1825  $\mu\text{g/L}$ . The patient's serum creatinine was 1.2 mg/dL. Based on this information, all medication was discontinued, and the patient received intravenous fluid therapy. No blood sample to measure simvastatin plasma concentration was taken. Following normalization of symptoms as well as creatinine kinase, the patient was switched to pravastatin 40 mg once a day.

**Commentary.** Simvastatin is widely used in the treatment of hypercholesterolemia. Simvastatin is a pro-drug that is converted reversibly to simvastatin acid by esterases or nonenzymatic hydrolysis. Its active metabolite simvastatin acid carries the pharmacologic effect by inhibition of HMG-CoA reductase. Simvastatin undergoes a substantial first-pass effect, reducing its oral bioavailability to 10%. Simvastatin acid is metabolized mainly by CYP3A and therefore is susceptible to interactions with CYP3A inhibitors. In a randomized, double-blind, 2-phase, crossover study, 10 healthy volunteers received either 200 mg itraconazole or placebo orally once a day for 4 days.<sup>45</sup> On day 4, each subject ingested a single 40-mg dose of simvastatin. Itraconazole increased the peak serum concentrations ( $C_{max}$ ) and total exposure (AUC) of simvastatin acid 19-fold.

Elevated plasma concentrations of simvastatin acid have been associated with an increased risk of myopathy and rhabdomyolysis. Therefore, itraconazole is listed among a number of strong CYP3A inhibitors on

the simvastatin label as a drug interaction associated with an increased risk of myopathy/rhabdomyolysis, and the concomitant use of simvastatin with strong CYP3A inhibitors including itraconazole is therefore contraindicated (which was, however, neglected by the itraconazole-prescribing dermatologist).<sup>46</sup>

Pravastatin, another HMG-CoA reductase inhibitor, is eliminated largely unchanged via renal and hepatic pathways, with only limited contribution of

drug metabolism to overall pravastatin elimination. Therefore, the interaction between 40 mg pravastatin and 200 mg itraconazole resulted in a much smaller change in peak serum concentrations ( $C_{max}$ ) and total exposure (AUC) of pravastatin by 2.5- and 1.7-fold, respectively.<sup>40</sup> In accordance with this study, the pravastatin label does not contain a contraindication or warning related to coadministration of pravastatin with strong CYP3A inhibitors.