REVIEW

Mechanisms and the clinical relevance of complex drug–drug interactions

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Abstract: As a result of an increasing aging population, the number of individuals taking multiple medications simultaneously has grown considerably. For these individuals, taking multiple medications has increased the risk of undesirable drug–drug interactions (DDIs), which can cause serious and debilitating adverse drug reactions (ADRs). A comprehensive understanding of DDIs is needed to combat these deleterious outcomes. This review provides a synopsis of the pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms that underlie DDIs. PK-mediated DDIs affect all aspects of drug disposition: absorption, distribution, metabolism and excretion (ADME). In this review, the cells that play a major role in ADME and have been investigated for DDIs are discussed. Key examples of drug metabolizing enzymes and drug transporters that are involved in DDIs and found in these cells are described. The effect of inhibiting or inducing these proteins through DDIs on the PK parameters is also reviewed. Despite most DDI studies being focused on the PK effects, DDIs through PD can also lead to significant and harmful effects. Therefore, this review outlines specific examples and describes the additive, synergistic and antagonistic mechanisms of PD-mediated DDIs. The effects DDIs on the maximum PD response (E_{max}) and the drug dose or concentration ($EDEC_{50}$) that lead to 50% of E_{max} are also examined. Significant gaps in our understanding of DDIs remain, so innovative and emerging approaches are critical for overcoming them.

Keywords: inhibition, induction, synergism, additive, antagonism, adverse drug reactions, ADRs

Introduction

The aging population in the USA is expected to rise in the foreseeable future and this group often deals with multiple health conditions.[1,2] To treat these multiple health conditions, individuals within this group have been required to take two or more prescription drugs simultaneously. This has led to a significant increase in the number of Americans that need to take multiple medications.[3] For those over 65 years old, nearly half take more than five drugs simultaneously.[4] In many cases, these individuals take drugs that they do not need.[4] Ultimately, taking multiple medications simultaneously increases an individual's risk for undesirable drug–drug interactions (DDIs) that lead to serious and debilitating adverse drug reactions (ADRs).[5–7]

A comprehensive understanding of DDIs is critical for safer coadministration of drugs and reduced risk of ADRs. In this review, a synopsis of the pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms that underlie DDIs is provided. In this work, the drug that causes the DDI will be called the "perpetrator" drug, while the drug of interest will be called the "victim" drug.[8–10] In PK, DDIs touch all aspects of

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drug disposition: absorption, distribution, metabolism and excretion (ADME). This review will discuss the cells that play a role in each aspect of ADME and have been the focus of DDI investigations. DDIs through PK occur through drug metabolizing enzymes and drug transporters that are found within these cells. This work provides representative DDI examples with a few key proteins and examines their effect on PK parameters. Although most current investigations have focused on how PK is affected by DDIs, significant DDIs have also been noted with PD. DDIs through PD can occur through additive, synergistic and antagonistic mechanisms. Several illustrative examples of DDIs from each of these mechanisms is provided in this work. Their effect on the maximum PD response (E_{max}) and the drug dose or concentration at 50% of E_{max} (EDEC$_{50}$) is discussed.

Pharmacokinetics (PK)

PK is what the body does to a drug and it includes ADME.[11] Depending on the process of ADME that is affected, PK-mediated DDIs can lead to elevated free plasma concentrations of the "victim" drug that can cause undesirable ADRs and toxicity. They can also lead to depressed free plasma concentrations of the "victim" drug and reduced therapeutic efficacy. The major cells, drug-metabolizing enzymes and drug transporters that have been implicated in DDIs and are discussed in this work are shown in Figure 1. The effect of DDIs on the PK is described below and summarized with additional detail in Table 1.

Absorption

Drug absorption can occur through both oral and extraoral routes such as through the skin.[11] Because oral drug administration is the preferred route for administration,[11] this review is focused on drug absorption through the gastrointestinal (GI) tract. The GI tract is composed of the mouth, esophagus, stomach, small intestines and the colon.[11] Of these anatomical structures, most of the drug absorption occurs in the small intestines as a result of its relatively large surface area.[11,12] The large surface area is due in large part to cells that contain microvilli called enterocytes that line the small intestine.[11,12] Drug absorption in these cells is controlled by passive diffusion across the plasma membrane and the presence of drug metabolizing enzymes and drug transporters (Figure 1).[11]

Drug transporters

There are many drug transporters on the apical (lumen-side) and basal (blood-side) membrane surfaces of the enterocytes (Figure 1).[13] Two highly expressed drug efflux transporters on the apical side of the enterocytes are Pgp and the BCRP.[14]
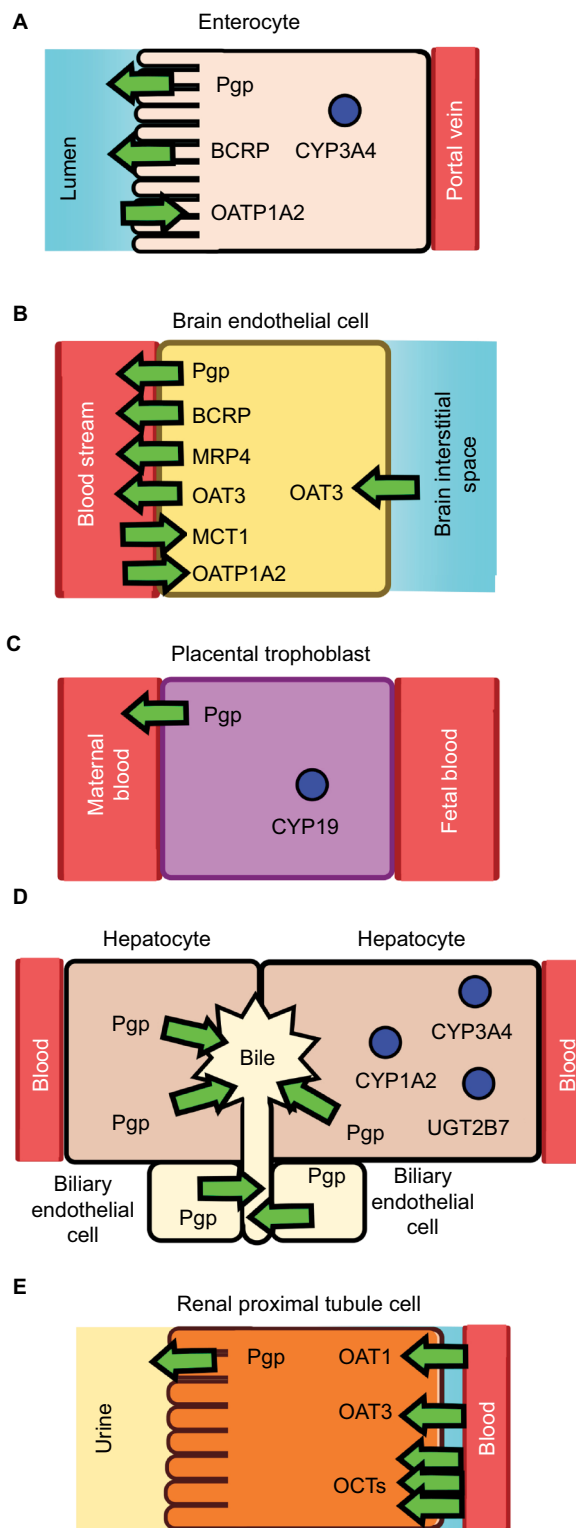

Figure 1 Drug-metabolizing enzymes and drug transporters in (**A**) an enterocyte, (**B**) a brain endothelial cell, (**C**) a placental trophoblast, (**D**) hepatocyte and biliary endothelial cells, and (**E**) a renal proximal tubule cell.
Notes: The drug metabolizing enzymes are shown as blue circles and the transporters are shown as arrows. The direction of the arrow reflects the direction of transport.
Abbreviations: BCRP, breast cancer resistance protein; CYP1A2, CYP/CYP450 1A2; CYP3A4, CYP/CYP450 3A4; MCT1, monocarboxylate transporter 1; OAT1, organic anionic transporter 1; OAT3, organic anionic transporter 3; OATP1A2, organic anionic transporting polypeptide 1A2; OCTs, organic cationic transporters; MRP4, multidrug resistance protein 4; Pgp, P-glycoprotein.

Table 1 Pharmacokinetically mediated DDIs

ADME	Protein	"Victim" drug	"Perpetrator" drug	DDI	PK effect	Ref
Intestinal absorption	Pgp	Talinolol	Erythromycin	Inhibition	AUC: increased C_{max}: increased F: increased	20
Intestinal absorption	Pgp	Talinolol	Rifampicin	Induction	AUC: decreased 35% C_{max}: decreased 38% F: decreased 35%	21
Intestinal absorption	BCRP	Rosuvastatin	Fostamatinib	Inhibition	AUC: increased 196% C_{max}: increased 188% F: increased	22,23
Intestinal absorption	OATP1A2	Fexofenadine	Naringin	Inhibition	AUC: decreased 22% C_{max}: decreased 18% F: decreased	24
Intestinal absorption	CYP3A4	Midazolam	Itraconazole	Inhibition	AUC: increased F_g: increased	33
Intestinal absorption	CYP3A4	Alfentanil	Troleandomycin	Inhibition	AUC: increased C_{max}: increased F_g: increased	34
Intestinal absorption	CYP3A4	Alfentanil	Rifampicin	Induction	AUC: decreased C_{max}: decreased F_g: decreased	34
BBB distribution	Pgp	Verapamil	Tariquidar	Inhibition	$V_{T,brain}$: increased	53
Placental distribution	Pgp	Verapamil	Cyclosporine A	Inhibition	$V_{T,fetus}$: increased	64
Liver metabolism	CYP3A4	Felodipine	Intraconazole	Inhibition	AUC: increased 634% C_{max}: increased 775% F: increased ~400% $t_{1/2}$: increased 171%	79,80
Liver metabolism	CYP3A4	Nifedipine	Rifampicin	Induction	AUC: decreased 30% F: decreased ~800% $t_{1/2}$: decreased 26%	81
Liver metabolism	CYP1A2	Caffeine	Fluvoxamine	Inhibition	AUC: increased 27% C_{max}: increased 26% $t_{1/2}$: increased >11-fold	83
Liver metabolism	UGT2B7	AZT	Valproate	Inhibition	AUC: increased 44% C_{max}: increased 29%	91
Liver metabolism	UGT2B7	AZT	Rifampicin	Induction	AUC: decreased 47% C_{max}: decreased 43% F: decreased	93,94
Renal excretion	Pgp	Digoxin	Various	Inhibition	AUC: increased C_{max}: increased	97
Renal excretion	OAT1, OAT3	Furosemide	Probenecid	Inhibition	AUC: increased 2.7-fold CL_R: decreased 66%	96,101
Renal excretion	OCTs	Metformin	Lansoprazole	Inhibition	AUC: increased C_{max}: increased CL_R: decreased $t_{1/2}$: increased	102
Biliary excretion[a]	Pgp	Thienorphine	Tarquidar	Inhibition	AUC: increased ~3-fold C_{max}: increased ~3-fold $t_{1/2}$: decreased 56%	106

Notes: [a]Data from Kong et al.[106] The $t_{1/2}$ of thienorphine is "paradoxically" increased due to interrupted enterohepatic circulation.
Abbreviations: AUC, area under the curve; C_{max}, maximum drug plasma concentration; CL_R, renal clearance; DDI, drug–drug interactions; F, oral bioavailability; F_g, gut oral bioavailability; PK, pharmacokinetic; Ref, reference; $t_{1/2}$, elimination half time; $V_{T,brain}$, apparent brain volume distribution; $V_{T,fetus}$, apparent fetal volume distribution.

Pgp and BCRP are part of the ATP-Binding Cassette (ABC) transporter superfamily and function by effluxing drugs out from the cytosol to the intestinal lumen.[15,16] Each of these transporters has distinct specificities with Pgp and BCRP being functional monomers and dimers, respectively.[15,16] Also found on the apical side of enterocytes is the organic anionic transporting polypeptide 1A2 (OATP1A2), which is a drug influx transporter.[17–19] In contrast to Pgp and BCRP,

this transporter influxes a diverse range of ligands including fexofenadine and imatinib from the intestinal lumen to the cytosol of the enterocyte.[17–19]

Inhibition and induction of the transporters from DDIs within the enterocyte can lead to significant effects on drug absorption. In a randomized crossover clinical study, the Pgp inhibitor and antibiotic erythromycin was coadministered with the cardiovascular drug and Pgp substrate talinolol.[20] Erythromycin inhibition of Pgp reduced the secretion of talinolol into the intestinal lumen and increased its oral bio-availability.[20] In contrast, induction of Pgp by the antibiotic rifampicin in another clinic study with talinolol found that it decreased the oral bioavailability.[21] Because BCRP is an efflux transporter like Pgp, one might expect the oral bio-availability of drugs to increase for substrates, when BCRP is inhibited. Indeed, inhibition of the BCRP by the tyrosine kinase inhibitor fostamatinib did increase the oral bioavail-ability of rosuvastatin in addition to doubling the peak serum concentration (C_{max}) and area under the curve (AUC).[22,23] In contrast to Pgp and BCRP, the influx transporter OATP1A2 moves drugs in the opposite direction in the enterocyte.[17–19] Selective inhibition of the OATP1A2 by naringin from grape-fruit juice leads to significant decreases in the AUC, C_{max} and the oral bioavailability of the antihistamine fexofenadine.[24]

Intestinal cytochromes P450 (CYPs)

The smooth endoplasmic reticulum of enterocytes contains drug metabolizing monooxygenases, which are also found in high concentrations in the liver, called cytochromes P450 (CYPs).[25] These enzymes are highly promiscuous and have several distinct isoforms.[26] The enterocytes contain mostly the CYP3A (82%) subfamily enzymes with some the CYP2C9 (14%) isoform and minor concentrations of other CYPs.[27,28]

The expression level of CYP3A enzymes was found to vary across the small intestine with the highest levels in the duodenum.[29,30] These enzymes are responsible for metabolism of a significant portion of commercially avail-able drugs and have exhibited a significant amount of DDIs.[31] However, determining specific DDIs with CYP3A enzymes is complicated by the fact that they are also present in the liver.[27,28,32] However, a clinical study found that inhibition of intestinal CYP3A4 by the antifungal drug itraconazole and its metabolites increased the gut oral bioavailability (F_g) of the sedative midazolam.[33] In another clinical study, inhibi-tion of CYP3A4 by the macrolide antibiotic troleandomycin led to large increases in the AUC and increased gut oral bioavailability of the opioid drug alfentanil.[34] The opposite effect occurred with the inducer rifampicin, which reduced both the AUC and the gut oral bioavailability.[34]

Distribution

Drug distribution involves the transfer of drugs from the systemic circulation to the rest of the body. All tissues in the body facilitate the distribution of drugs to varying degrees.[35] Distribution can occur by passive diffusion and membrane protein-mediated transport.[35] The membrane barriers that provide the largest roles in drug distribution are the blood–brain barrier (BBB), blood–testis barrier (BTB), blood–cere-brospinal fluid barrier (BCSFB) and the placental barrier.[35] DDIs from drug distribution within these membrane barriers have been known to occur, when protein-mediated transport is inhibited or induced.[11] These DDIs will result in changes in the apparent volume distribution (V_d).[11] The most studied membrane barriers in terms of DDIs and distribution is the BBB followed by the placental barrier, so they both will be the focus of this review.

Blood–brain barrier

The BBB functions as a barrier for drugs into the brain and central nervous system (CNS) from the blood stream (Figure 1).[36,37] The BBB is a complex structure that is composed of endothelial cells and pericytes that are sur-rounded by the end-feet of astrocytes.[36,37] In addition, the endothelial cells that form the inner half of the BBB are held together by proteins that form tight junctions between the cells.[36,37] These tight junctions prevent molecules from going between the cells. However, drugs can cross into the brain through the BBB by passive diffusion or through pro-tein transporters located on the plasma membrane. The rate at which a drug passively diffuses across the BBB depends on its lipophilicity,[38–41] its hydrogen bond donors and accep-tor characteristics[40,42] and its size.[43] On the apical surface (lumenal or blood-side) are a variety of drug transporters that control the flow of drugs into the brain.[44] On the apical plasma membrane, transport from the cytosol to the blood stream is mediated by BCRP, Pgp, the multidrug resistance protein 4 (MRP4) and the organic anionic transporter 3 (OAT3).[44] Transport from the blood stream to the cytosol is controlled by the monocarboxylate transporter 1 (MCT1) and the organic anionic transporting peptide 1A2 (OATP1A2).[44] On the opposite (basal) side of the endothelial side is the OAT3 transporter.[44]

The most studied BBB transporter is Pgp. The strongest evidence that Pgp is involved in drug transport across the BBB is from studies with Pgp knockout mice.[45,46] Studies

with the mouse mdr1a variant of Pgp showed large differences in drug distribution were observed between the brain and other tissues.[45,46] On the other hand, there have been some question of the clinical relevance of Pgp-mediated DDIs at the BBB.[47,48] In two positron emission tomography (PET) studies, there were large increases in verapamil concentration in the brain of rats and only modest changes in the human brain in the presence of the Pgp inhibitor cyclosporine A.[49,50] These differences were attributed to differences in the transporter makeup between human and rodent BBB.[47] In humans, the most convincing evidence of Pgp-mediated drug transport comes from PET studies with potent Pgp inhibitor tariquidar.[48,51,52] This inhibitor was shown to increase brain penetration of verapamil, loperamide and a loperamide metabolite.[48,51,52] In a group of healthy individuals, tariquidar increased the apparent brain volume distribution of the cardiovascular drug verapamil.[53]

Placental barrier

The placenta is a layer of tissue that separates the mother from the unborn child.[54] Distribution of drugs across the placenta are regulated by phase I and phase II drug metabolizing enzymes and transporters within the syncytiotrophoblast.[55] Unfortunately, our current understanding of DDIs with the placenta remains limited.[140]

The phase I drug metabolizing enzyme CYP/CYP450 19 (CYP19) (a.k.a. aromatase) has the highest level of mRNA expression in the placenta.[55] The enzyme has substrates, inhibitors and CYP19 expression modulators that could potentially lead to DDIs.[56] For example, the opioid drug methadone was found to be a substrate and mechanism-based inhibitor of CYP19.[57] As a result, methadone has significant risk for DDIs with CYP19 substrates including the anti-diabetic drug glyburide.[58] In terms of CYP19 expression modulators, the drug betamethasone, which is commonly administered to pregnant women, was shown to down regulate mRNA expression of CYP19.[59] The corticosteroid dexamethasone, which is often administered to pregnant women, was found to have the opposite effect and induce CYP19 expression.[60]

The placenta is also known to have a variety of drug transporters.[140] Most DDI investigations with the placenta have been focused on Pgp.[140] Pgp has been shown to play a protective role against drugs in wild type and Pgp knockout mice.[61,62] A study done with pregnant nonhuman primates showed that Pgp activity increased with gestational age for the mother and within the placental barrier suggesting that it might be an important factor to consider during pregnancy.[63]

Most Pgp DDI investigations have focused on Pgp inhibition.[140] In a perfused human placenta model, Pgp inhibition has increased drug penetration in the placenta including the anti-HIV drug lopinavir.[140] In a PET study of a nonhuman primate, the Pgp inhibitor cyclosporine A and the cardiovascular drug [¹¹C]-verapamil showed increased tissue distribution in the maternal brain and the fetal liver.[64] There is some in vitro evidence that Pgp may behave differently in the placenta than other tissues. The Pgp inhibitors, quinidine and verapamil, had no effect on Pgp-mediated digoxin transport in an isolated perfused human placenta.[65] However, verapamil did inhibit Pgp-mediated talinolol transport in the same in vitro system.[66]

Metabolism

Drug metabolizing enzymes can be found throughout the body including the brain,[67] heart,[68] lungs,[69] intestines[70] and even the skin.[71] Metabolism in ADME typically refers to enzymatic biotransformations that occur in the liver.[11] In the liver, drug metabolizing enzymes are expressed in the hepatocytes and the biliary epithelium (Figure 1).[25,72] There are both phase I and phase II drug metabolizing enzymes in these cells.[73] CYPs dominate the phase I drug metabolizing enzymes, while UDP glucuronosyl transferases (UGTs) and sulfotransferases (SULTs) dominate the phase II drug metabolizing enzymes.[73] Unlike the intestines, the major CYP isoforms and subfamilies are evenly distributed throughout the liver and include CYP1A2, CYP2B6, CYP2C, CYP2D6, CYP2E1, CYP4F and CYP3A.[29,32,74] The major UGT subfamilies found in the liver are UGT1A and UGT2B.[75] The SULT1A1 is the major sulfotransferase isoform in the liver.[76]

Hepatic CYPs

While intestinal CYPs affect drug absorption, the hepatic CYPs affect drug elimination.[11] DDIs from CYPs in the liver occur as a result of inhibiting or inducing expression of the CYPs.[11] Inhibiting CYP will increase the C_{max}, AUC and the elimination half-time ($t_{1/2}$), while inducing it will have the opposite effect on those PK parameters.[11] Many CYP DDI studies have focused on the CYP3A4 isoform.[77,78] Deciphering specific DDIs from liver CYP3A4 is complicated by the fact that there is significant expression of CYP3A4 in the liver and intestines.[27,28,32] There have been attempts to separate their individual effects.[79] For example, in a PK study, the anti-fungal drug and CYP3A4 inhibitor itraconazole was coadministered with the cardiovascular drug felodipine.[80] Itraconazole was found to increase the C_{max} and the AUC of felodipine several fold.[80] A later analysis suggested that intestinal and hepatic CYP3A4 caused similar increases in felodipine

bioavailability.[79,80] In another clinical study, the effects from intestinal and liver nifedipine metabolism by CYP3A4 after induction by rifampicin was examined.[81] Rifampicin induction of CYP3A4 caused the AUC and the elimination $t_{1/2}$ to decrease about 30%.[81] Rifampicin primarily affected the intestinal extraction ratio revealing that most of the DDIs are due to intestinal CYP3A4 and not hepatic CYP3A4.[81]

Of the CYPs, the CYP1A2 isoform makes significant contributions to the liver, but only plays a minor role in the intestine.[28,32] Therefore, clinically observed DDIs with this CYP will reflect liver metabolism and not biotransformations within the intestines. The serotonin reuptake inhibitor (SSRI) fluvoxamine is a specific inhibitor of CYP1A2.[82] When fluvoxamine was coadministered with caffeine, there were significant increases to the C_{max} and AUC of caffeine, and there was more than an 11-fold increase in the elimination $t_{1/2}$ of the stimulant.[83]

UDP-glucuronosyltransferases (UGTs)

UGTs are a family of conjugating phase II enzymes that catalyzes the transfer of glucuronic acid to hydroxyl, carboxyl, or amine functional groups of drugs.[84] UGTs in the liver are membrane anchored proteins that reside within the smooth endoplasmic reticulum in hepatocytes and biliary endothelial cells.[85] Glucuronidation through the UGT2B7 isoform is the primary pathway for metabolism of antiretroviral drug azidothymidine (AZT) making it an ideal probe substrate for UGT DDIs.[86–89] Both in vitro and in vivo investigations with AZT have noted significant DDIs with the drug.[90] In an in vitro study, the anti-seizure drug valproate inhibited glucuronidation of AZT by Chinese hamster lung fibroblasts overexpressing UGT2B7.[88] This in vitro result correlates well with a clinical study performed on HIV-infected individuals.[91] They found a significant reduction in the AUC and C_{max} of the glucuronidated product and an increase in the AUC and C_{max} of the parent drug.[91] UGTs in the liver can also be induced by rifampicin.[92] In a couple of clinical studies with HIV-infected patients, rifampicin induction of the UGT1A1 isoform caused significant reduction in the AUC and C_{max} of the AZT.[93,94]

Excretion

In this review, drug excretion is defined as the removal of drugs from the body, so that it is not confused with elimination, which includes biotransformation in the liver. More than two thirds of drug excretion occurs through the kidneys with most of the remaining excretion occurring through the liver via the bile.[11] Only a minor amount of drugs are excreted through the sweat and the lungs, so it will not be discussed in this review.[11]

Renal excretion

Renal drug excretion is primarily mediated by drug transporters within renal tubular cells (RTCs) of the proximal convoluted tubule found in the nephron (Figure 1).[95,96] The RTCs have a wide range of cationic and anionic drug transporters.[95,96] In this section, a brief discussion of DDIs is provided of Pgp, organic anionic transporters (OATs) and organic cationic transporters (OCTs).

One of the most investigated drug transporters in the kidney is the Pgp transporter. It is found in the brush-border apical membrane of RTCs and effluxes drugs from the cytosol into the urine.[95] Many DDI investigations have been performed with the cardiovascular drug digoxin due to its low therapeutic index, its propensity for DDIs with Pgp, and the fact that it is primarily excreted through the kidneys by Pgp.[97] Drug transport is inhibited by a wide range of "perpetrator" drugs including the anti-cancer drug paclitaxel and cholesterol lowering statin drugs.[97] Inhibition of digoxin transport by Pgp leads to significant increases in the AUC and the elimination $t_{1/2}$ with corresponding decreases in the renal clearance (CL_R).[97] Unlike other Pgp substrates, administration of the Pgp inducer rifampicin did not affect the CL_R or $t_{1/2}$ of digoxin.[98]

The OAT transporter family of exchange transporters are responsible for transporting anionic drugs including diuretics, antivirals and antibiotics.[99,100] The OAT 1–3 isoforms are located on the S2 segment of the proximal tubule on the basolateral membrane, while OAT4 and the urate/anion exchanger (URAT1) isoforms are located on the apical membrane.[95,99] This transporter family is an exchange transporter that exchanges drugs for carboxylates.[99] The OAT1 and OAT3 transporters are responsible for the transport of the diuretic furosemide.[101] When furosemide transport by OAT1 and OAT3 are inhibited by probenecid, there is significant elevations in the AUC of furosemide and reduction in its CL_R.[96,101]

Members of the OCT transporter family can transport cationic drugs such as the antihypertensive drug atenolol and the antiviral drug lamivudine.[96] These transporters are located on the basolateral membranes of the RTCs.[95] One of the most studied drugs within this transporter family is the antidiabetic drug metformin, which is a substrate for several isoforms of OCT transporters.[102] The drug is advantageous for studying renal DDIs because it does not undergo significant hepatic metabolism.[103] The proton pump and OCT inhibitor lansoprazole increased the AUC, increased the elimination

$t_{1/2}$ and reduced the CL_R.[102] Metformin PK parameters were similarly affected by DDIs with the histamine H2 receptor antagonist cimetidine and the drug pyrimethamine.[96]

Biliary excretion

Less than a third of drugs are excreted through the bile.[11] Excretion in the liver occurs through transporters that are located within hepatocytes and biliary endothelial cells of the bile ducts.[104] There is a diverse range of transporters in these cells including OATs and OCTs.[104] The most studied transporter is Pgp, which is located on apical membrane of hepatocytes and endothelial cells of the bile duct.[104] The opioid agonist thienorphine undergoes significant biliary excretion in rats.[105] When Pgp inhibitor tarquidar was coadministered to rats, the C_{max} and AUC of thienorphine increased, while the mean residence time (MRT) and the elimination $t_{1/2}$ decreased.[106] The "paradoxically" reduced MRT and elimination $t_{1/2}$ of thienorphine was attributed to interrupted enterohepatic circulation through the bile ducts.[106]

Pharmacodynamics

PD defines what a drug does to the body that leads to a physiological response.[11] Drugs can induce a PD response by interacting with protein receptors such as the case of agonists with the $GABA_A$ receptor.[107] They may also interact with proteins in the second messenger system such as the case of tyrosine kinase inhibitors that target the protein kinase.[108] PD can also occur with enzymes such as the nonsteroidal anti-inflammatory drugs (NSAIDs) and the platelet cyclooxygenase to inhibit platelet activation.[109]

PD DDIs occur when a coadministered drug alters the PD effect of another drug outside of their PK effects.[110] Like PK DDIs, these DDIs occur when two or more drugs are coadministered to a patient.[110] The drugs can antagonize or synergistically interact.[110] DDIs can also occur with drugs that have similar modes of action such as lowering blood pressure.[111] PD DDIs can have additive, synergistic or antagonistic effects on PD responses.[110]

The E_{max} and the $EDEC_{50}$ can change in response to PD-mediated DDIs. A decrease in the $EDEC_{50}$ leads to a "leftward" shift of the dose response curve and indicates synergism.[110,112] No change in the $EDEC_{50}$ of the dose response curve and an E_{max} that reflects the sum of individual PD responses indicates additivity.[110,112] An increase in the $EDEC_{50}$, which will lead to a "rightward" shift in the dose response curve, reveals competitive antagonism.[110,112] Depending on the PD DDI mechanism, a decrease in

the E_{max} can be due to noncompetitive or uncompetitive antagonism.[110,112,113]

Beyond analyses of dose response curves, there are analytical methods that can be used to quantitatively determine PD DDIs.[110] DDIs can be graphically assessed using an isobologram with the drug doses at 50% of E_{max} plotted along the axes.[110] Additive PD DDIs will typically appear as a diagonal straight line on these graphs, but can be nonlinear in cases where one of the drugs is a partial agonist.[110,114] Synergistic and antagonistic DDIs from PD will have leftward and rightward curvature, respectively, with respect to a diagonal in these graphs.[110] Competitive antagonists can also be assessed using Schild plots, which exploit the observed "rightward" shift of the dose response curves.[110] They will lead to positive linear slopes in these graphs.[110] Table 2 summarizes the PD-mediated DDIs for representative drugs and their effect on PD Parameters. Clinical examples of additive, synergistic and antagonistic PD DDIs are described below.

Additive

An additive PD DDI is when the overall PD response is the sum of the individual PD responses from the individual drugs.[115] This DDI is in contrast with a synergistic DDI where the overall PD response is greater than the sum of the individual PD responses.[110] For example, liraglutide is a derivative metabolic hormone that acts as a long-acting glucagon-like peptide-1 receptor agonist that lowers glucose,[116] while insulin detemir is a long acting insulin derivative that also functions to reduce blood glucose.[117] When the drugs are coadministered, the glucose lowering effect of the two drugs is additive and equal to the sum of the individual PD responses.[118] The drug interactions of phenprocoumon and nonsteroidal anti-inflammatory drugs (NSAIDs) is another example of an additive DDI.[115] Phenprocoumon is a vitamin K antagonist that inhibits vitamin K oxide reductase and indirectly prevents the activation of several clotting factors.[119] NSAIDs inhibit platelet cyclooxygenase, which prevents platelet activation.[109] The net effect of taking these drugs together is that their anti-coagulant effects are additive leading to an increased risk of bleeding.[120]

Synergistic

When the two or more drugs are taken together and the resulting DDIs are synergistic, the resulting PD response can be greater than the sum of the individual PD responses.[121] For example, the combination of diphenhydramine and ethanol leads to synergism in the PD response.[122] Ethanol acts as a $GABA_A$ receptor agonist increasing chloride conductance on

Table 2 Pharmacodynamically mediated DDIs

PD DDI	Drug #1	Drug #2	PD effects	Ref.
Additive	Liraglutide	Insulin determir	$EDEC_{50s}$: unchanged E_{maxs} of drugs additive PD: glucose lowered	118
Additive	Phenprocoumon	NSAIDS	$EDEC_{50s}$: unchanged E_{maxs} of drugs additive PD: additive anticoagulant effect	120
Synergistic	Diphenhydramine	Ethanol	E_{max} of combination greater than sum of individual E_{maxs} PD: enhanced impairment	122
Synergistic	Tramadol	Acetaminophen	$EDEC_{50s}$: reduced E_{max} of combination greater than sum of individual E_{maxs} PD: enhanced pain reduction	125
Competitive antagonistic	Naloxone	Opioids	$EDEC_{50s}$: increased E_{maxs}: unchanged PD: dampening of opioid effects	129
Noncompetitive allosteric antagonistic	Ruthenium red	Capsaicin	$EDEC_{50s}$: unchanged E_{maxs}: E_{max} of capsaicin reduced PD: reduce irritant effect of capsaicin.	127

Abbreviations: DDI, drug -drug interactions; NSAIDs, nonsteroidal anti-inflammatory drugs; PD, pharmacodynamics; Ref, reference.

the post synaptic neuron.[123] Diphenhydramine is a muscuranic acetylcholine receptor antagonist causing a reduction in positive charge of the neuron.[124] This leads to a net increase in the negative charge across the neuron and increased mental impairment.[122] Another example of PD synergism is with the drugs tramadol and acetaminophen.[125] These drugs exhibited a greater reduction in pain and an enhanced antihyperalgesic effect than the drugs taken alone.[125]

Antagonistic

Drug antagonism occurs when a "perpetrator" drug dampens or inhibits the PD response of a "victim" drug. Antagonism can be competitive, noncompetitive and uncompetitive. As mentioned above, competitive antagonism occurs when a "perpetrator" drug increases the $EDEC_{50}$, but has no effect on the E_{max}.[126] In contrast, noncompetitive antagonism causes a reduction in the E_{max}, but has no significant effect on the $EDEC_{50}$ (eg,[127]). Uncompetitive antagonism can have similar effects on E_{max} and $EDEC_{50}$ as noncompetitive antagonism, but requires interaction by the "victim" drug first to the receptor.[113]

A good use of competitive antagonism is with the drug naloxone (Narcan®). Naloxone counteracts the effect of opioids, which are μ-opioid receptor agonists, by competing for the μ-opioid receptor.[128] In rats, naloxone was more effective at blocking the effects of the μ-opioid receptor agonists

methadone and fentanyl than the μ-opioid receptor agonists heroin and morphine.[129] In a clinical study with opioid-dependent individuals, naloxone was found to counteract the PD response of the μ-opioid agonist buprenorphine.[130] Noncompetitive PD antagonism can be allosteric in that it occurs at an alternate site than the "victim" drug or it can be irreversible. The interaction of ruthenium red with capsaicin is an example of noncompetitive allosteric antagonism.[127] Ruthenium red was found to reduce contractile response induced by capsaicin in rat tissues.[127] The antagonistic effect is likely due to competition between these molecules at different sites on the transient receptor potential (TRP) channels.[131] The drug omeprazole (Prilosec®) is a noncompetitive irreversible antagonist by covalently modifying the H+,K+-ATPase in the stomach.[132,133] The Alzheimer's drug memantine is an example of an uncompetitive antagonist, which interacts with the N-methyl-D-aspartate (NMDA) receptor and is used in the treatment of Alzheimer's disease.[134,135] The uncompetitive antagonism of memantine differs from noncompetitive antagonists in that it requires activation of the NMDA receptor before memantine binding can occur.[113]

Conclusion and outlook

Understanding DDIs remains an ongoing challenge and significant gaps in our understanding remain. This review

was focused on representative DDIs between two drugs. However, it is quite common for individuals, especially the elderly, to be taking considerably more drugs at a time.[5,7] In this case, the DDIs may be very complex and exceedingly difficult to deconvolute. Several novel analytical approaches are emerging that will allow deconvolution of complex drug interactions from multiple drug targets simultaneously. An ensemble approach for multiple drug target deconvolution was recently used to decipher the interactions of inhibitors to multiple kinases.[136] A random walk algorithm was developed to unravel the protein–protein interaction network that underlies PD-mediated DDIs.[137] In silico methods have been developed to predict both PK and PD DDIs of arbitrary molecules.[138,139] Ultimately, novel future approaches to investigate and deconvolute DDIs will lead to safer and more efficacious coadministration of drugs.

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Disclosure

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