PERSPECTIVE

Drug-Drug-Gene Interactions: A Call for Clinical Consideration

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It is widely accepted that both comedications and genetic factors may contribute to variation of drug response. Clinical decision support systems increasingly consider recommendations on drug–drug interactions (DDIs) during electronic prescribing, and some guidelines on drug–gene-interactions (DGI) have been implemented in drug labels. Potentially synergistically or antagonistically acting drug-drug-gene interactions (DDGIs) have hardly been considered. This Perspective article highlights examples and the complexity of DDGI, aiming to strengthen consideration into clinical decision support.

BACKGROUND

The incidence of complex diseases and multimorbidity is increasing with the growing age of the population. As a consequence, the rate of polypharmacy is increasing, bearing an elevated risk for potential drug–drug interactions particularly prevalent in elderly patients. DDIs are a challenge for all prescribers since they are major causes of adverse drug events which can be harmful, sometimes causing treatment failure or even being life-threatening. Routine clinical decision support systems have been developed and introduced into clinical practice aiming to help prescribers to avoid or mitigate the risk of potentially harmful drug combinations.

Moreover, pharmacogenetic information is increasingly considered in medicinal product information and introduced—at least in some cases—into hospital information systems and electronic health records. Recommendations on how to deal with pharmacogenetic information with respect to interindividual differences of drug response have been developed, e.g., by the Clinical Pharmacogenetics Implementation Consortium (CPIC) in more than 25 guidelines,[1] covering hereditary variants in drug metabolizing enzymes and some drug transporters contributing to varying drug distribution. Furthermore, selected genetic markers of the human leukocyte antigen (HLA) system have been included that are strongly associated with hypersensitivity to specific drugs. At least some DGIs have been implemented in electronic prescribing systems with obligation for testing before prescription, e.g., HLA-B*5701 for abacavir or HLA-B*1502 for carbamazepine, preferentially in Asian populations. More recently, several countries implemented mandatory testing of the dihydropyrimidine dehydrogenase (*DPYD*) gene before treatment with 5-fluoruracil or its prodrugs.

DDGIS

So far it is still a challenge to deal with the combination of both putative harmful problems, DDI and DGI. In general, three scenarios should be distinguished: In category 1, DDGIs boost clinically relevant interactions on the same pathway, while in category 2, DDGIs cause clinically relevant interactions on different pathways. In category 3, DDIs and DGIs lead to contrary effects so that clinically relevant interactions are diminished.

The individual effects of DDIs and DGIs on drug pharmacokinetics as well as the three complex DDGI scenarios are illustrated in **Figure 1**. A DDI may occur, e.g., when the metabolism of a victim drug V (mediated normally by an active "wild-type" enzyme) is inhibited or induced by a perpetrator drug P, leading to reduced or increased metabolism of drug V, respectively (**Figure 1a**). A typical example is the inhibition or induction of the cytochrome P450 (CYP) 2C9–mediated metabolism of warfarin by fluconazole or rifampicin, respectively. A DGI can affect the same pathway in the case of variant *CYP2C9*3* genotype, conferring reduced metabolism of drug V (**Figure 1b**).

For DDGIs, the various combinations of DDI and DGI need to be considered.[2]

CATEGORY 1

An inhibitory DDGI takes place when a perpetrator drug P inhibits the metabolism of drug V and the same respective drug metabolizing enzyme has low activity due to loss-of-function variants. The combined effect could lead to a strongly

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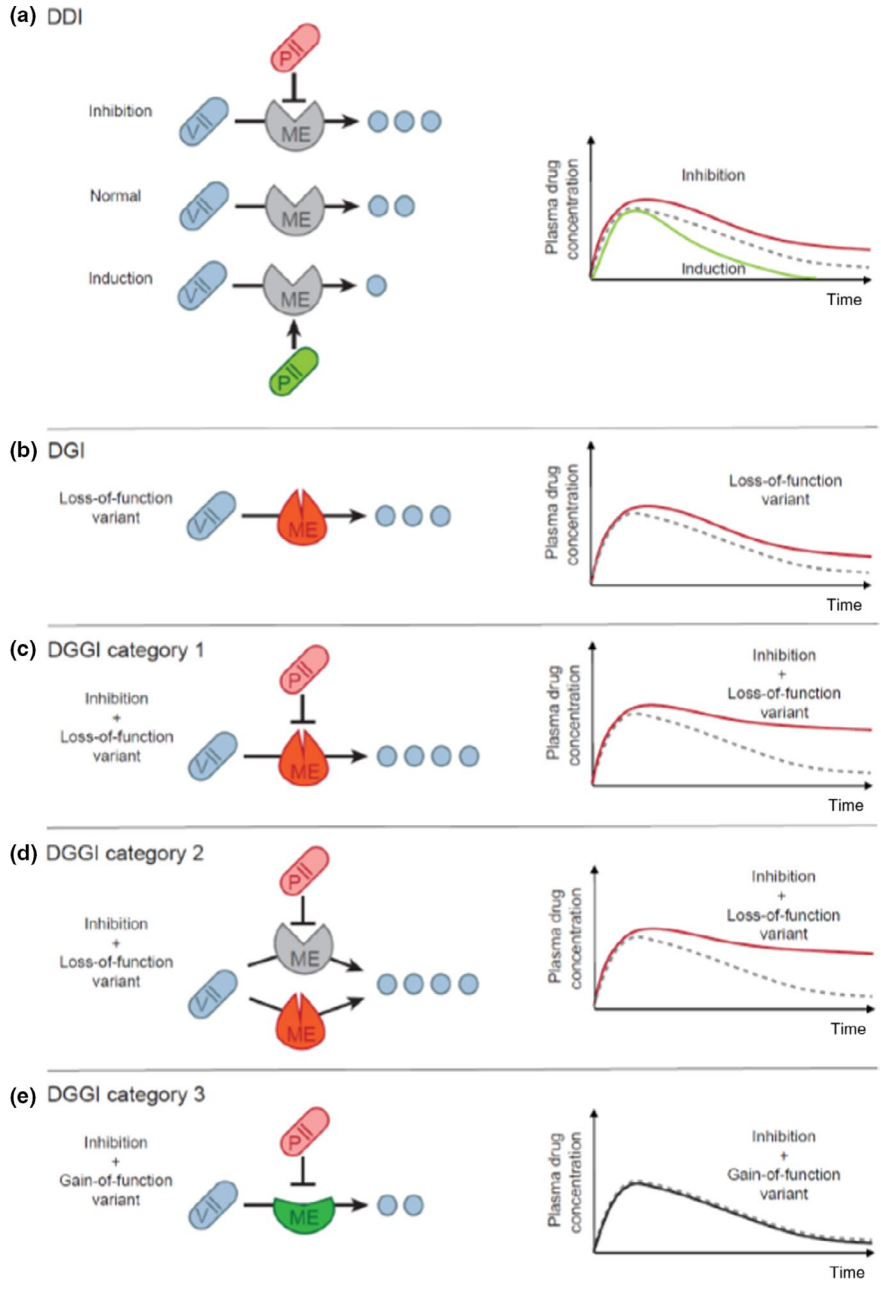

Figure 1 Scenarios of DDIs (drug–drug interactions), DGIs (drug–gene interactions), and DDGI (drug-drug-gene interactions). (**a**) DDI: Effects of inhibition or induction of the metabolism of a victim drug (V) by a perpetrator drug (P) leading to reduced (three blue dots, red concentration-time curve) or increased (one blue dot, green curve) metabolism compared with normal metabolism (two blue dots, gray dashed curve). The blue dots indicate proportions of the victim drug. (**b**) DGI: Drug V is metabolized by an enzyme with loss-of-function variant leading to increased plasma levels (three blue dots, red concentration-time curve). (**c**) DDGI category 1: Boost existing clinically relevant interactions due to combined reduction of metabolism of drug V due to coadministration of an inhibitory perpetrator drug P and the presence of loss-of-function variant in the drug-metabolizing enzyme (four blue dots, red concentration-time curve). (**d**) DDGI category 2: Drug V is metabolized by two enzymes, one is inhibited by perpetrator drug P while the other has low activity due to loss-of-function variant. The additive effect leads to strongly reduced metabolism of drug P (four blue dots, red concentration-time curve) and thereby introduces clinically relevant interactions. (**e**) DDGI category 3: Phenoconversion, the consequences of a gain-of-function variant (e.g., gene duplication), is attenuated by an inhibitory perpetrator drug P, thereby temporary shifting the ultrarapid phenotype to a normal metabolizer phenotype (two blue dots, black concentration-time curve) and leading to no clinically relevant interactions. ME, metabolizing enzyme (gray, normal activity; red, reduced activity; green, increased activity).

attenuated metabolism of drug V and thereby boost a clinically relevant interaction (**Figure 1c**). However, the inhibitory effect is not always additive, as the maximum reduction of enzyme activity might be already reached by the genetic variant, e.g., in homozygous *CYP2D6* poor metabolizers. In this case a perpetrating inhibitor P cannot lead to further activity reduction. As a consequence, DDI on the CYP2D6 enzyme level will not take place; hence if the pharmacogenetic information is already considered in dosing of drug V, any comediation with a CYP2D6 inhibitor can be made without affecting the pharmacokinetics of drug V.

On the other side, if the perpetrator drug is a strong inhibitor, genetic variants may play only a negligible role. Such a scenario was demonstrated in a clinical study on warfarin, investigating the consequences of CYP2C9 inhibitors on warfarin anticoagulatory properties depending on *VKORC1*/*CYP2C9* genotypes.[3] One finding demonstrated that the impact of the genetic variant on outcome parameters like international normalized ratio or time to reach the therapeutic range was no longer detectable in the presence of an inhibitor. Second, it was observed that significant DDIs were only detectable in *CYP2C9* wild-type carriers, but not in carriers of *CYP2C9* variants, suggesting a lack of additive effects.

CATEGORY 2

If a drug V is metabolized by two or more enzymes, the inhibition of only one of these pathways by a perpetrator drug P may have only a minor effect. If, however, the activity of a second pathway is genetically reduced, the metabolism of drug V could be strongly negatively affected (**Figure 1d**). Such an example of combined effects leading in the same direction was demonstrated for voriconazole being a substrate of both CYP2C19 and CYP3A4. The bioavailability of this antimycotic was markedly increased in patients with reduced CYP2C19 activity being additionally treated with atazanavir or ritonavir, known to be strong inhibitors of CYP3A4.[4] However, if in the same scenario drug V is an inactive prodrug, the formation of active intermediates would be further reduced like for clopidogrel, being a high affinity substrate of polymorphic CYP2C19 and low affinity

substrate of CYP3A4. In another case, a life-threatening opioid intoxication occurred after administration of small doses of codeine in combination with CYP3A4 inhibitors, as the patient exhibited an ultrarapid CYP2D6 genotype which led to increased bioactivation of high codeine levels (due to CYP3A4 inhibition) to morphine.[5]

Examples of DDGI causing elevated activity through inducing compounds combined with the presence of gain-of-function variants are theoretically possible but not yet described.

CATEGORY 3

DDGIs may undergo phenoconversion interactions causing contrary effects of the perpetrator drug P and a genetically variant metabolizing enzyme that lead to a temporary phenotype shift. An example of such a phenomenon is the normalization of the nortriptyline metabolism phenotype in CYP2D6 ultrarapid metabolizers in the presence of the CYP2D6 inhibitor paroxetine as demonstrated by Laine *et al*.[6] (**Figure 1e**).

The complexity of DDGIs is further increased by the fact that genetic variants or haplotypes may have a different impact on the activity of a drug metabolizing enzyme or a drug transporter; likewise the inhibitory effect of a perpetrator drug is dependent on its inhibitory constant and the concentration at the site of action. Extremes are known, e.g., for CYP2D6 where the poor metabolizing genotype might lead to category 1 DDGIs, but ultrarapid metabolizers could result in a category 3 DDGI in the presence of a CYP2D6 inhibitor. Moreover, genotypes encoding intermediate phenotypes have to be considered. Consideration of pharmacodynamic effects, e.g., of receptor variants, will be an additional challenge.

In a retrospective study on potentially significant clinical interactions, Verbeurgt *et al*. identified a prevalence of 33.9% for DGIs and DDGIs among a total of 1,143 individuals.[7] This pinpoints the increasing need to merge DDI and DGI data to receive better information about DDGIs. However, the number of clinical studies analyzing DDGIs such as the above-mentioned warfarin study[3] is quite low. An attempt to overcome this gap of prospective studies focusing on DDGIs is the usage of modeling or text mining tools.[8] Recently, a physiologically-based pharmacokinetic model was applied to estimate the consequences of DDGI on simvastatin considering pharmacogenetic variants *SLCO1B1*, *ABCG2*, and *CYP3A5* as well as four perpetrator drugs.[9] Such simulations are an excellent tool to give some guidance to fill the knowledge gap on potential DDGIs. However, there is a strong need to gain existing clinical information from electronic health records, e.g., data from therapeutic drug monitoring, but also more clinical studies to identify and quantify the DDGIs that can be implemented in clinical decision support systems in the future. So far, parallel information on both DGI and DGI may cause confusion in some cases, regardless of harmful combinations or even unnecessary prevention of potential deleterious effects from putative perpetrator drugs to the disadvantage of the patient. However, as long there are no systematic and evidence-based data on DDGI available, it is difficult to develop solid recommendations that could be implemented in clinical decision support systems on top of the current interaction alerts. Therefore, it requires systematic recording of patients' pharmacogenetic information and full drug history in electronic health records combined with newly developed algorithms considering this complex information.

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CONFLICT OF INTEREST

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DISCLOSURE

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