Clinical Studies of Drug–Drug Interactions: Design and Interpretation

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Abstract The potential importance of drug-drug interaction (DDIs) is increasing as polypharmacy becomes more and more prevalent. In vitro data cannot directly predict clinical DDIs, but may provide a rationale for initiation of human studies to confirm or exclude possible interactions. Clinical DDI studies are designed to determine whether there is a real drug interaction not due to chance, how big the interaction is, and whether the DDI is of clinical importance. Statistical significance is not equivalent to clinical significance, and supplemental pharmacodynamic or clinical outcome information is needed to address the importance of a pharmacokinetic DDI.

24.1 Introduction

Drug–drug interactions (DDIs) have become a topic of substantial scientific and public health concern over the last 20 years. While the clinical phenomenon of DDIs had been recognized for a number of decades, several events in and around the years 1988–1993 brought the topic of DDIs to a position of high attention and priority in the scientific community, as well as in the public arena. During this period, multiple human cytochrome P450 (CYP) isoforms became identified, along with increasing understanding of their substrate and inhibitor specificities, relative quantitative importance in human drug metabolism, and mechanisms of genetic regulation (Clarke, 1998; Smith et al., 1998; b; Venkatakrishnan et al., 2001; Venkatakrishnan et al., 2003). Of particular importance in this context was CYP3A, with its unique hepatic and enteric distribution, and its major contribution to clearance of many clinically relevant drugs as well as naturally occurring chemicals (Venkatakrishnan et al., 2001; Venkatakrishnan et al., 2003; Guengerich,

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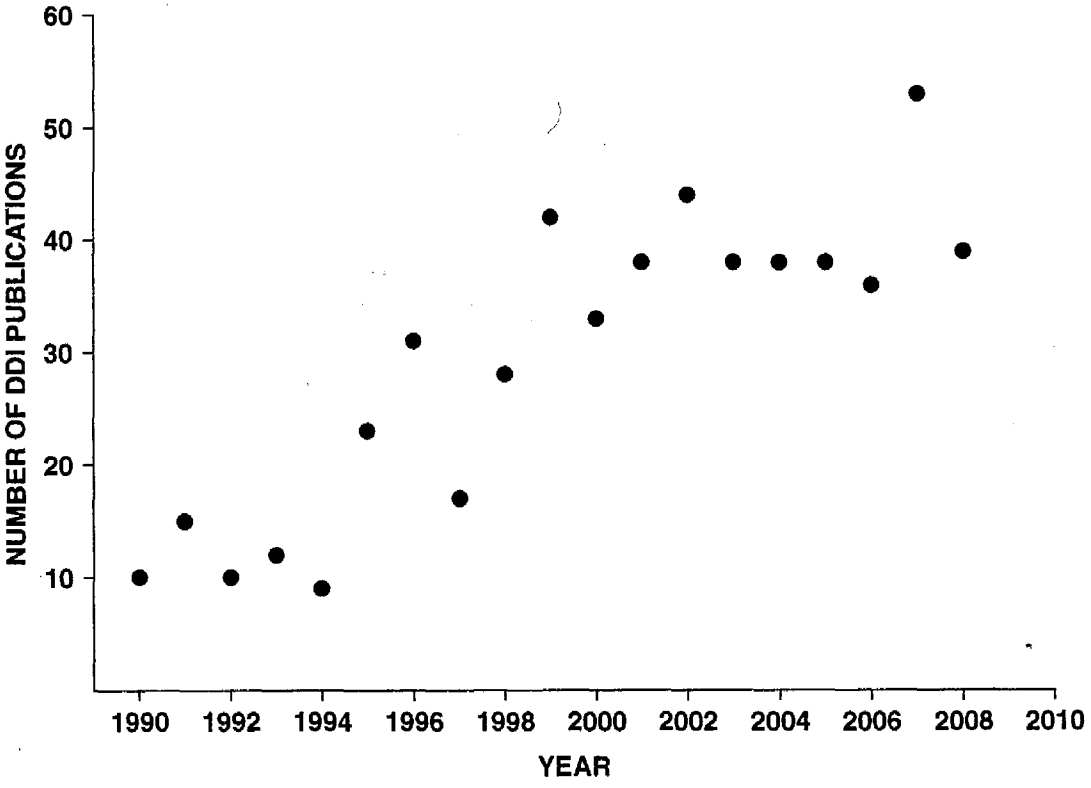
1999; Greenblatt et al., 2008). At the same time, in vitro techniques for studying human drug metabolism became increasingly developed and refined, including predictive models for in vitro–in vivo scaling, and the availability of heterologously expressed individual human CYPs. At a clinical level, polypharmacy was becoming increasingly prevalent, as the population aged, the number of patients with multiple illnesses increased, and our capacity to provide pharmacologic treatments for serious disorders became more and more effective. Some newly introduced classes of medications – such as the azole antifungal agents and the selective serotonin reuptake inhibitor (SSRI) antidepressants – offered unique therapeutic options, but also had the secondary property of inhibiting certain human CYPs, thereby elevating the risk of DDIs (Greenblatt et al., 1999; Hemeryck and Belpaire, 2002; Venkatakrishnan et al., 2000). A dramatic and widely publicized event was the interaction of the nonsedating antihistamine terfenadine with potent CYP3A inhibitors such as ketoconazole and erythromycin (Honig et al., 1993b; Honig et al., 1992; Honig et al., 1994; Honig et al., 1993a). Under usual circumstances, terfenadine itself served only as a prodrug, being essentially completely transformed via hepatic and enteric CYP3A into fexofenadine, which was the entity having antihistaminic properties. Although terfenadine had effects on the cardiac QT_c interval (Rampe et al., 1993; Crumb et al., 1995), this was of minimal concern since intact terfenadine does not ordinarily reach the systemic circulation. However, during co-treatment with CYP3A inhibitors, conversion of terfenadine to fexofenadine is blocked, and potentially hazardous levels of the parent drug reach the circulation (Honig et al.,



1994; von Moltke et al., 1994b). A few cases of serious and even fatal cardiac arrhythmias were reported as a consequence (Monahan et al., 1990; Woosley et al., 1993). The "terfenadine affair" led to an acutely increased awareness of the potential importance of DDIs. Terfenadine was withdrawn from clinical practice, and a number of regulatory reforms increased the requirements for DDI assessments as a component of drug development. The overall shift in focus of the scientific and drug development community is clearly evident from the prevalence of DDI studies among scientific publications (Fig. 24.1).

24.2 Epidemiology of Drug–Drug Interactions

Given the prevalence of polypharmacy in contemporary clinical practice, the number of *possible* DDIs can become very large. If an individual patient is taking n drugs concurrently, the number of pairwise combinations of these two drugs can be calculated as follows:

$$\frac{n!}{(n-2)!2!} \tag{24.1}$$

The larger the value of n, the greater the number of different drug combination pairs, and potential pairwise DDIs (Table 24.1). A patient with diabetes, hypertension, ischemic heart disease, and depression might well be taking 10 drugs concurrently, in which case the number of possible drug interactions is 45. Considering this large "denominator" of possibilities, the number of clinically important DDIs encountered in contemporary therapeutics actually is relatively small.

Table 24.1 Relation of number of drugs concurrently administered to the number of possible pairwise drug–drug interactions

Number of drugs	Possible pairwise drug interactions
2	1
3	3
4	6
5	10
6	15
7	21
8	28
9	36
10	45
11	55
12	66

The outcome options following concurrent administration of two drugs can be constructed based on a probability hierarchy (Fig. 24.2). The most probable outcome is that the two drugs act independently, with no evidence of any interaction. Less probable is a DDI which can be demonstrated in a controlled laboratory setting, but is not detectable in clinical practice either because the magnitude of the observed

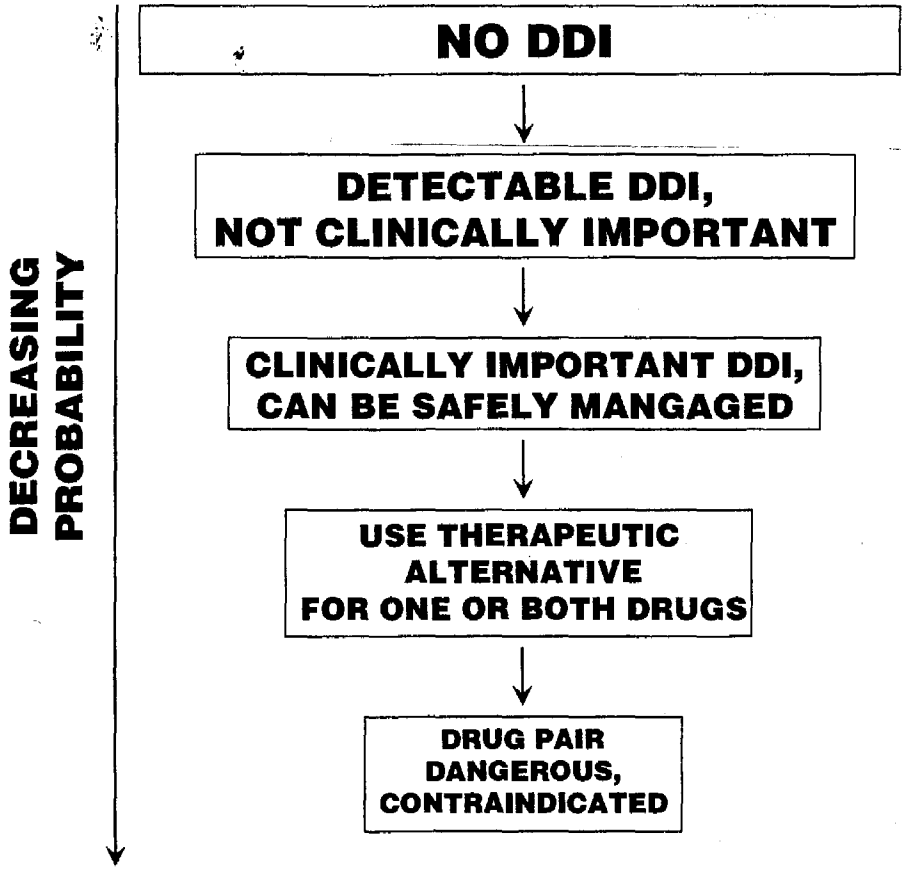


Fig. 24.2 Outcome possibilities in terms of DDIs when two drugs are coadministered, in order of decreasing probability from *top* to *bottom*

in plasma levels of the "victim" drug is so small as to be unimportant, or that the therapeutic index of the victim drug is very large. Still less probable is a DDI that is clinically important, but can be managed, for example, by reducing the dosage of the victim drug or by instituting closer monitoring of plasma levels and/or clinical outcome. Even lower in probability ranking is a DDI that is difficult to manage, such that co-treatment should be avoided if possible, and an alternative choice should be made for one or both drugs in the pair. The very least likely outcome – in fact, quite rare – is that the DDI potential carries an unacceptably serious risk, and the drug pair is contraindicated.

This probability hierarchy has been confirmed in studies of the epidemiology of DDIs. In a study of 9481 ambulatory patients in Germany, 13,672 actual drug combination pairs were identified (Bergk et al., 2004). Of these pairs, only 6.4% were known to cause DDIs with predicted outcome of moderate or major severity, and 0.5% were unmanageable DDIs such that the pair should be avoided. Findings were similar in a study of hospitalized patients in Denmark (Glintborg et al., 2005). The authors conclude that "although potential drug–drug interactions are highly prevalent, serious and clinically significant interactions are rare among recently hospitalized patients." In the specialty area of clinical psychopharmacology, there is extensive literature on the capacity of fluoxetine and paroxetine to inhibit the

with CYP2D6 substrate drugs such as desipramine (Hemeryck and Belpaire, 2002; von Moltke et al., 1994a; von Moltke et al., 1995; Preskorn et al., 1994; Alderman et al., 1997). Yet clinically important drug interactions are rarely reported in actual practice (Davies et al., 2004; deVane, 2006; Molden et al., 2005). One possible explanation is that the therapeutic index of the victim drug or drugs is large enough that even a substantial change in plasma levels is not clinically relevant. Another explanation is that clinicians recognize the potential DDI, and make a pre-emptive downward adjustment in the dose of the victim to prevent the DDI.

24.3 Drug Interaction Mechanisms and Terminology

We have used the term "perpetrator" to indicate the drug that is causing the DDI, while "victim" or "substrate" is the drug that is being interacted with (Greenblatt and von Moltke, 2008). In a pure pharmacodynamic DDI, the perpetrator does not alter the plasma concentrations or systemic pharmacokinetics of the victim. Instead, the two drugs produce either additive or antagonistic pharmacodynamic effects. The interaction may occur via additive or opposite actions on the same receptor systems that yield additive or opposite clinical actions. Ethyl alcohol and benzodiazepines produce additive sedation through their actions on the gamma-aminobutyric acid (GABA) receptor system (Chan, 1984; Greenblatt and von Moltke, 2008); the pharmacokinetic interaction between alcohol and benzodiazepines, if any, is small, and does not account for the additive sedative effects (Greenblatt et al., 1978; Greenblatt and von Moltke, 2008; Ochs et al., 1984;). Benzodiazepine agonists and caffeine have antagonistic pharmacodynamic actions. Benzodiazepines produce sedation via the GABA–benzodiazepine receptor system, whereas caffeine produces alertness due to its action as an adenosine receptor antagonist (Biaggioni et al., 1991; Kaplan et al., 1992a, b; Kaplan et al., 1993). When caffeine is given together with a benzodiazepine agonist such as zolpidem, the sedative effects of zolpidem are partially reversed (Cysneiros et al., 2007). However, there is minimal, if any, pharmacokinetic interaction between these two agents.

A pure pharmacokinetic interaction involves only the effect of the perpetrator on the systemic clearance of the victim drug, causing plasma levels of the victim to increase or decrease. The clinical actions of the victim may be correspondingly increased or decreased, but only because of the indirect effects of the perpetrator on systemic clearance, rather than a direct effect of the perpetrator on the target receptor mediating clinical action.

Pharmacokinetic DDIs involving drug-metabolizing enzyme systems (such as the CYPs) are generally classified as inhibition or induction. With metabolic inhibition, the perpetrator impairs the clearance of the victim drug, systemic exposure increases, and the clinical concern is toxicity. With induction, clearance of the victim increases, systemic exposure decreases, and the clinical concern is lack of efficacy (Table 24.2). However, inhibition and induction are not simply the same

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