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Editors

Enzyme- and Transporter-Based Drug–Drug Interactions

Progress and Future Challenges

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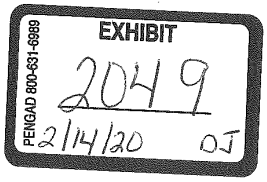

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Chapter 24
Clinical Studies of Drug–Drug Interactions: Design and Interpretation

David J. Greenblatt and Lisa L. von Moltke

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.,

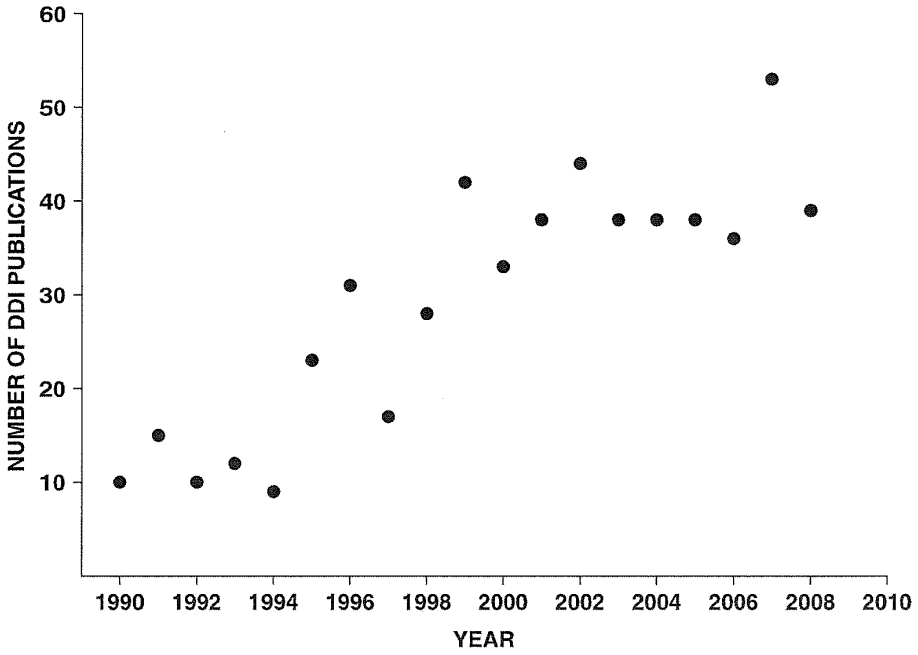

Fig. 24.1 Number of articles indexed as DDI studies published per year in the Journal of Clinical Pharmacology, 1990–2008

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 change

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