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Counterpoint

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In reviewing Dr DeVane's paper, I am struck more by how much common ground the papers have than their differences. Those differences are generally explained by whether the authors consider the glass to be half full or half empty and by the question of how risk avoidant one wants to be. In this respect, most readers realize that we have entered a particularly risk avoidant time in drug development as witnessed by the black box warning of serotonin selective re-uptake inhibitors (SSRIs) for children and adolescents and the removal of Vioxx from the market.

For the above reason, it seems most appropriate to begin this commentary by summarizing the common ground shared by these two papers.

First, Dr DeVane states—and I agree—that there are 'indisputable' differences between SSRIs and their effects on specific cytochrome *P*450 (CYP) enzymes.

Second, Dr DeVane, at the beginning of his paper, states: 'Serious and life-threatening events, as well as fatalities, have been documented when some drug pairs have been used in therapy.' At the end, he states: '… several predictable and well documented interactions will occur with high frequency ….' I agree with both of these statements although I would prefer that he define what constitutes 'high frequency.'

The reason is that such a definition is critical to understanding the differences in the positions taken in Dr DeVane's paper and ours. Such a definition is necessary to decide whether to call the glass half full or half empty and to understand the level of risk that one is willing to take for the patient.

Unfortunately, terms such 'prevalence' and qualifiers such as 'clinically unimportant' and 'clinically significant' are also used repeatedly in Dr DeVane paper without a definition. For this reason, it is hard to know what to say when Dr DeVane in his paper concludes that 'highly prevalent and clinically significant drug interactions are unfounded.' What metric is being used in that statement? The critical point is that drug–drug interactions (DDIs) are not dichotomously black or white risk but rather a graded phenomenon.

That is the reason why Dr Werder and I began our paper by defining these terms. The reader then can agree or disagree with us but they will unequivocally know what we meant by the critical metrics of prevalence and clinical significance. As we pointed out in our paper, DDIs can cause problems ranging from nuisance tolerability problems to sudden death. For a given patient, either of these outcomes can be clinically significant; whereas, the prevalence of a serious adverse event such as sudden death from a population standpoint does not have to be as high as the prevalence of a nuisance adverse effect to be judged an unacceptable risk.

To further put this matter in perspective, consider that assessing the relative risk of DDIs is analogous to assessing the relative risk:benefit analysis carried out to determine whether a drug should be approved. That analysis must of necessity consider: (a) the risk of the drug, (b) the benefit of the drug, and (c) the risk of the illness being treated. For this reason, the acceptable adverse profile for a life saving anticancer drug is vastly different from the acceptable profile for a drug to treat seasonal allergies.

Dr DeVane in his paper suggests that the pivotal issue is '…not whether SSRI drug interactions have resulted in serious adverse event but the frequency of the unanticipated drug interactions resulting in severe adverse events.' As an aside, this statement taken literally would mean that we can discount every patient who died because of an adverse DDIs interaction involving fluoxetine and paroxetine and a drug with a narrow therapeutic index (eg a tricyclic antidepressant) because such a DDI is expected. With this caveat, we concur and spent time in our paper discussing the twin considerations of frequency and severity.

Dr DeVane in his paper points out—and we agree—that there is less data on the issue of how prevalent clinically significant DDIs are in clinical practice. However, we also agree with Dr DeVane's admonition that '… lack of evidence does not equate to evidence of absence…' In our paper, we point out the reason for this lack of data: Research studies are not carried out purposely to expose human subjects to the risk of a serious adverse event or even a moderate adverse event solely to determine whether a DDI poses an 'unacceptable' risk. As we point out in our paper, conservative extrapolations of the existing knowledge indicates that the coadministration of a usual antidepressant dose of fluvoxamine in combination with 300 mg/day of clozapine would be expected to cause a three- to five-fold increase in the risk of clozapine induced seizures. We do not expect any readers are going to require a prospective study to test this hypothesis because of the ethical issues such a requirement would pose. Nevertheless, some data on the population prevalence of adverse DDIs does exist and this data is cited in our paper (de Leon *et al*, 2005; Spigset *et al*, 1997; Ray *et al*, 2004). In addition, we pointed out that another problem with the clinical detection of adverse DDIs is that they can present as almost any outcome clinically imaginable from an increase in population frequency of tolerability problems (de Leon *et al*, 2005), to seizures (Spigset *et al*, 1997) to sudden death (Ray *et al*, 2004).

To illustrate this latter point, I will use one of Dr DeVane's principal arguments as follows: That is fluvoxamine. I agree with Dr DeVane's characterization of fluvoxamine as the SSRI with 'broadest CYP inhibitory profile' of any SSRI. I further agree with Dr DeVane that fluvoxamine would be an example of an SSRI, which for this reason would be expected to have post marketing surveillance data demonstrating clinically relevant DDIs. That is the reason why I used fluvoxamine and its postmarketing data to illustrate how difficult it is to detect even lethal DDIs in clinical practice (Preskorn, 2002a). Garnier and coworkers in 1993 examined the postmarketing safety data with fluvoxamine in terms of its safety in drug overdoses (Garnier *et al*, 1993). In their article, they cited 13 cases of

what they classified as fatal overdoses. However, closer analysis of these cases indicates that three of these fatalities were more likely due to adverse DDIs rather than an overdose (Preskorn, 2002a). The interested reader can find this article on the website, www.preskorn.com, under the section on case studies. I have also published several detailed case examples of how fatal or near fatal DDIs can be misinterpreted as suicides or suicide attempts (Preskorn, 2002b; Preskorn and Baker, 1997).

The point is that clinical detection of even the most serious DDIs is not fool-proof. Further support is found in the recent study showing that the mortality rate in patients on erythromycin is five times higher than matched controls on comparable antibiotics but not substantial CYP 3A inhibitors (Ray *et al*, 2004).

In the final analysis, the question is: Why would a clinician chose to underestimate the risks of adverse DDIs and their potential to cause a less than optimal outcome for his/her patient regardless of whether the consequence of the DDI is less tolerability, less efficacy, or serious toxicity? In point of fact, avoidance of DDIs is arguably the most germane issue to the question of what is the level of training needed to prescribe drugs most effectively.

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*This articles can be found in their entirety on the website, www.preskorn.com.

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