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Counterpoint

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Drug interactions represent complex clinical and research issues. Problems include areas of inadequate data, acknowledged limitations of *in vitro* assessments, difficulties in extrapolation between species, and disagreement on interpretation of results. Dr Preskorn and Dr Werder's commentary is confusing because it frequently fails to distinguish between verifiable statements and personal opinion, includes dubious extrapolations of data (eg 'lowest effective dose of fluoxetine and paroxetine produces approximately a 500% increase in the plasma concentration of co-prescribed [CYP2D6] drugs'), appeals to fear (eg risk of sudden death from the non-antidepressant erythromycin), oversimplifies the issue (eg 'the detection of DDIs [is] difficult and that in turn [leads] to an underestimation of their apparent clinical relevance'), and contains other fallacies of logical reasoning. Nevertheless, it is such differences in our approach to drug interactions and points of argument for open discussion that allow the discipline to move forward.

My goals for this field are to provide guidance to clinicians for appropriate drug selection and dosage regimen design of antidepressants and to increase understanding and accurate prediction of drug interactions to aid in the drug discovery and development process. With advances in any field, areas for potential misinterpretation of historical data are revealed. As an example, cumulative research reveals that the blood concentration for a variety of psychoactive drugs can increase post mortem following re-distribution from tissues overestimating ante-mortem plasma concentration. This fact suggests that causality could have been inappropriately assigned in past cases of sudden unexpected death when the suicidal intent of the deceased may have been in question. I hope this suggestion is wrong. Dr Preskorn and Dr Werder state that the extent of clinically relevant drug interactions involving antidepressants may be substantially underestimated. I hope they are wrong in this assertion. Few drug classes have received more systematic study for this potential liability. Unfortunately, we may never have an accurate estimate of the extent and magnitude of significant interactions occurring with the currently available antidepressants. As drug development proceeds, newer antidepressants can be expected for routine use with less liability for participating in drug–drug interactions.

A concern expressed in both of our commentaries relates to defining and avoiding pharmacokinetic and pharmacodynamic drug interactions and their potential morbidity. Among the two major categories of drug–drug interactions, pharmacodynamic interactions are the most intellectually intriguing, potentially far more complex, and are significant for some (eg MAOI + SSRI), but likely not all, drug combinations. At present, defining and quantifying pharmacodynamic interactions between antidepressants and other therapeutic agents is a little like searching the universe for evidence of life away from earth. The field has a long way to travel. Our tools for discovery are limited as is our access to sites most likely to yield definitive answers. Even when we do discover that certain drugs interact, or if extra-terrestrial life exists, it may be inconsequential for the outcome of pharmacotherapy in specific patients or day-to-day living.