



# Dietary Supplements and Drug Interactions: Should Flawed Study Designs and Biased Adverse Event Reporting Affect Regulation and Medical Causation?

by Christopher J. Borgert, Ph.D.; Kathleen Cullen Findley, MST, Pharm.D.; Susana Ulloa, M.D.; and George Casella, Ph.D.

See Author Bios on Page 5

The U.S. government's 2005 Annual Report on Americans' Health cites that 45 percent of Americans are taking at least one prescription medication, more than 17 percent are taking at least three and the percentage of Americans taking multiple medications has increased consistently over the past 10 years.<sup>1</sup> According to the National Association of Chain Drug Stores, this represents over 3.27 billion prescriptions filled in outpatient pharmacies in 2004<sup>2</sup> or more than 10 prescriptions for every person in the United States. In addition to multiple prescription medications, more than 60 percent of Americans take some form of dietary supplement every day.<sup>3</sup> As Americans consume increasingly complex combinations of prescription medications and dietary supplements, the concern for adverse events attributable to interactions between these agents increases accordingly.

## Drug-Dietary Supplement Interactions

When a person suffers an adverse health event while taking a drug, the medication is often considered to have contributed to the event and the issue of product liability litigation becomes significant. While FDA has strict criteria for defining prescription drug safety and new over-the-counter medications, the 1994 Dietary Supplement Health and Education Act (DSHEA) presumed the safety of substances with a history of use as herbal remedies and grand-fathered their regulatory status as dietary supplements.<sup>4</sup> Nonetheless, these products have come under particular government scrutiny and gained national attention when herbal ephedra supplements were blamed for the February 2003 death of Baltimore Orioles pitcher Stever Bechler.<sup>5</sup> Although the FDA

received less than 10 reports of adverse events from dietary supplement manufacturers in the five-year period preceding these events, thousands of lawsuits alleging adverse effects of ephedra products have been filed, millions of dollars in damages have been paid and manufacturers' insurance rates have skyrocketed.<sup>6</sup> To facilitate greater detection of adverse events, the Department of Health and Human Services has recommended that dietary supplement manufacturers be required to report any serious events to the FDA.<sup>3</sup>

Establishing that a single drug or dietary supplement caused an adverse outcome in a particular individual is a complex process and is often impossible due to technical limitations and confounding factors. However, if that patient is taking more than one drug and/or supplement at a time, it becomes even more difficult to attribute an outcome to a specific treatment. Not only is there more than a single potential treatment outcome, there is also the possibility that the outcome is the result of an interaction between the treatments. Interest in these potential interactions is increasing; for example, the National Library of Medicine and Institute of Health's (NIH) online database lists more than 250 "scholarly" articles on drug interactions involving St. John's wort, a dietary supplement commonly used to treat depression. Analysis of potential drug-dietary supplement interactions will be increasingly important for claims that supplements and drugs cause adverse health outcomes. The importance of these questions prompted the NIH's Office of Dietary Supplements to investigate the evidence for potentially life-threatening adverse drug interactions between dietary supplements and prescrip-

tion medications used to thin the blood of patients with severe coronary artery disease and disorders of the blood clotting system.<sup>7</sup>

Two emerging issues in medical causation are likely to affect litigation and regulatory activities involving dietary supplements. The first involves the scientific validity of methods used to confirm an adverse drug interaction, and the second involves the potential impact of reporting bias on data collected by the FDA. Each of these concerns has implications for *Daubert* challenges.

## Literature

Drug-dietary supplement interactions reported in the medical literature are often accompanied by warnings of potential adverse health outcomes. However, the methods used to identify and study such interactions are often flawed. In a paper by McInnes and Brodie<sup>8</sup> entitled, "Drug Interactions that Matter," the authors criticized the published literature on drug-drug interactions for methodological problems, as well as for failing to focus on interactions that have real clinical significance. Although published a decade prior to the emergence of concerns over interactions between drugs and dietary supplements, their criticisms of the literature on drug-drug interactions in 1988 apply quite well to the literature on drug-dietary supplement interactions today. To paraphrase two of the concerns expressed by McInnes and Brodie, the literature is over-populated with discussions of interactions and potential interactions based on anecdotal case reports and the terminology used to describe interactions is at best unclear and often misleading.

There is a tendency for the literature to discuss a few case reports or small clinical studies repeatedly until phrases such as “well accepted” and “clear potential for interaction” begin to be associated with a particular combination of drugs and herbal products. Case reports can provide valuable information about the possibility that an interaction may exist, but rather than establishing the basis of causation, they are more properly used to generate hypotheses for scientific testing. Repeated reporting of a possible drug-supplement interaction should not serve as evidence that an interaction exists, but should instead emphasize the need for appropriate laboratory and clinical studies to test the hypothesis that an interaction occurs between the products. In this fashion, a database of the literature on drug-supplement interactions can evolve, providing a scientific basis for evaluating health outcomes and their relationship to drug-supplement interactions. Much of the current interaction literature lacks a scientific basis, is confusing and does not provide useful information on which to judge causality for adverse health effects.

The ambiguous use of terminology regarding interactions is a primary source of confusion. From a pharmacological perspective, the term “drug interaction” has a very precise meaning, but the term is often used in a general sense. Similarly, the terms synergism, antagonism and potentiation also have very specific meanings, but these terms are often used ambiguously, and even incorrectly, in the literature. The terms “no interaction” or “zero interaction” are absent from the majority of the literature despite the integral importance of this concept for evaluating interactions. Ambiguous use of terminology can lead to rather imprecise interpretations and conclusions about interactions.

One of the most serious deficiencies in the published literature stems from the lack of critical evaluation of data quality on interactions. For example, knowing that a patient was stabilized on warfarin, that a change in the patient’s INR occurred concomitant with introduction of an herbal supplement, and that the patient was again stabilized on war-

*“As Americans consume increasingly complex combinations of prescription medications and dietary supplements, the concern for adverse events attributable to interactions between these agents increases accordingly.”*

farin after discontinuation of the herbal supplement, does not provide the information necessary to determine that an interaction has occurred between warfarin and the supplement. Although this scenario might serve to generate hypotheses about a potential interaction, it does not supply the data required to support a conclusion that an interaction actually occurred. A clinician may accept this low level of evidence that an interaction exists to advise patients receiving these therapies, but the reliability of the data must be much higher to confirm an interaction. Presumably, regulatory or legal decision-making is concerned with confirmed facts rather than presumptions.

We have previously published a critical evaluation of the literature on drug and chemical interactions wherein we proposed five criteria for evaluating interaction studies<sup>9</sup>. In that paper, we concluded that much of the published literature appears to ignore the foundations of interaction study design and interpretation. These criteria incorporate previously cited requirements of interaction analysis<sup>10</sup> and address the most common mistakes that appear in the literature. Any study can be reviewed using our criteria, and we recently developed a simple algorithm to allow the reviewer to compare studies or to assess a broader body of literature.<sup>11</sup> Future studies designed to investigate interactions between medications and herbal supplements could use these criteria as a standard.

Establishing a body of literature based on accepted scientific principles of investigation and using the clear language of interaction analysis is necessary for future evaluations of causation regarding dietary supplements and health outcomes.

#### Reporting Adverse Events

Finally, an emerging problem that will likely affect clinicians’ perceptions and, thus, expert judgments about interactions, stems from the use of anecdotal adverse event reports to evaluate drug and dietary supplement safety. Unfortunately, the only broad-based collection of information concerning adverse events from drugs and supplements is the FDA-sponsored voluntary reporting system. Because this database does not provide a representative sample of adverse events in the population, the statistical tests and the inferences from them, must be made with great care. There are at least two underlying sources of bias inherent in the statistical tests when using non-randomly sampled data.

First, adverse event reports for specific outcomes are often recruited through advertising. When this is done, the adverse event reports are biased and may result in erroneous associations between products and specific adverse outcomes. Thus, advertising can produce a database that reflects trends in reported associations due to fluctuations in public awareness and worse, is vulnerable to reporting of associations influenced by special interests. A valid statistical analysis of such data would require an adaptation of specialized techniques for bias correction, such as those that were originally developed for meta-analysis studies.<sup>12, 13</sup>

A second type of bias results from over-reporting of disease or adverse events. It may seem that a well-studied population is very ill, but in reality, that perception can be created simply from an increased amount of information. A recent *New York Times* article<sup>14</sup> that reported on work of Dr. Lisa Schwartz of the Dartmouth Medical School, noted that “if everyone had the recommended tests for blood cholesterol, blood sugar,

continued on page 4



### Dietary Supplements and Drug Interactions

continued from page 3

body mass index and diabetes, 75% of adults in the United States would be labeled as diseased.” This underscores the importance of carefully choosing the control population if valid inferences are to be made about drug interactions. If the control population is not as well documented as the study population, the control population will appear to be healthier simply because of underreporting of disease. The FDA is considering changes to the voluntary reporting system to minimize sampling bias. Until improvements are made, particularly regarding the use of the database in product liability litigation, reporting bias must be recognized and accounted for.

#### Conclusion

High standards of evidence that medications and supplements are the cause of adverse health outcomes are imperative for any regulatory action that may limit the public’s access to these products. Effective product liability litigation involving dietary supplements depends on the availability of valid scientific information concerning causation rather than case reports and anecdotal information. Flawed methods of collecting data about the incidence of adverse events, the dearth of scientific studies on medication and supplement interactions, and inappropriate analyses of the literature provide for neither.

#### References

- <sup>1</sup> United States Center for Disease Control and Prevention, National Center for Health Statistics. 2005. Health, United States, 2005. Available at: [www.cdc.gov/nchs/data/abus/abus05.pdf](http://www.cdc.gov/nchs/data/abus/abus05.pdf)
- <sup>2</sup> National Association of Chain Drug Stores. 2004 Community Pharmacy Results. Available at: [www.nacds.org/user-assets/PDF\\_files/2004results.pdf](http://www.nacds.org/user-assets/PDF_files/2004results.pdf)
- <sup>3</sup> United States Department of Health and Human Services, Office of Inspector General. 2001. Adverse event reporting for

dietary supplements: An inadequate safety valve. Available at: <http://oig.hhs.gov/oei/reports/oei-01-00-00180.pdf>

<sup>4</sup> United States Food and Drug Administration, Center for Food Safety and Applied Nutrition. 1995. Dietary supplement health and education act of 1994. Available at: [www.cfsan.fda.gov/~dms/diet-suppl.html](http://www.cfsan.fda.gov/~dms/diet-suppl.html)

<sup>5</sup> CBS Evening News. 2003. Ephedra tied to pitcher’s death. Available at: [www.cbsnews.com/stories/2003/02/17/eveningnews/main540848.shtml](http://www.cbsnews.com/stories/2003/02/17/eveningnews/main540848.shtml)

<sup>6</sup> Gugliotta G. 2000. Ephedra lawsuits show big increase: Stimulant’s critics try a new forum. Washington Post, Sunday, July 23, 2000, Page A01. Available at: [www.washingtonpost.com/ac2/wp-dyn/A25415-2000Jul21](http://www.washingtonpost.com/ac2/wp-dyn/A25415-2000Jul21)

<sup>7</sup> Marder VJ, Ortel TL, Grollman A, & Hasan AK. 2005. Preface to Papers from the NIH Conference on Dietary Supplements, Coagulation, and Antithrombotic Therapies. *Thrombosis Research* 117: 1-3.

<sup>8</sup> McInnes GT, & Brodie MJ, 1988. Drug interactions that matter. A critical reappraisal. *Drugs* 36: 83-110.

<sup>9</sup> Borgert CJ, Price B, Wells C, & Simon GS. 2001. Evaluating chemical interaction studies for mixture risk assessment. *Human and Ecological Risk Assessment* 7(2): 259-306.

<sup>10</sup> Berenbaum MC. 1989. What is synergy? [published erratum appears in *Pharmacol Rev* 1990 Sep;41(3):422]. *Pharmacol Rev* 41: 93-141.

<sup>11</sup> Borgert CJ, Borgert SA, & Findley KC. 2005. Synergism, antagonism, or additivity of dietary supplements: application of theory to case studies. *Thrombosis Research* 117: 123-132.

<sup>12</sup> Cleary R & Casella G. 1997. An application of Gibbs sampling to estimation in meta analysis: accounting for publication bias. *Journal of Educational and Behavioral Statistics* 22: 141-154.

<sup>13</sup> Eberly LE, & Casella G. 1999. Bayesian estimation of the number of unseen studies in a meta-analysis. *Journal of Official Statistics* 15: 477-494.

<sup>14</sup> Kolata G. 2006. The Nation: Health of Nations: If you’ve got a pulse, you’re sick. *New York Times*, May 21, 2006.



**Christopher J. Borgert, Ph.D.**

Dr. Borgert received an artium baccalaurei from Kenyon College and a doctoral degree in Medical Sciences from the Department of Pharmacology and Experimental Therapeutics, University of Florida College of Medicine. Dr. Borgert is currently president of Applied Pharmacology and Toxicology, Inc., Gainesville, FL ([www.apt-pharmatox.com](http://www.apt-pharmatox.com)), and is a faculty member at the Center for Environmental and Human Toxicology in the Department of Physiological Sciences, University of Florida College of Veterinary Medicine, where he has an active research program in collaboration with other faculty and lectures on pharmacology, toxicology and environmental policy. He has been appointed to several federal and international committees and advisory panels, is active in professional societies, has published numerous peer-reviewed articles, book chapters and commissioned documents, and provides consultation to industrial, governmental, and legal clients on a variety of issues in pharmacology and toxicology.

**Kathleen Cullen Findley, MST, Pharm.D.**

Dr. Findley received a Bachelor of Science in Science Education, a Master of Science Teaching in Chemistry and a Doctor of Pharmacy from the University of Florida. She completed a pharmacy practice residency in Adult Internal Medicine at the Veterans Administration Medical Center in Gainesville, FL and is Board Certified in Pharmacotherapy. She has served as a Clinical Specialist to intensive care and cardiology patients for seven years and currently serves as a Clinical Cardiology Specialist at the VA Medical Center and is a Clinical Pharmacist consultant with Applied Pharmacology and Toxicology, Inc., Gainesville, FL. Her experience also includes 12 years as an educator in chemistry.

**Susana Ulloa, M.D.**

Dr. Ulloa received her medical degree in Colombia, South America, from the Colombian School of Medicine. She held staff positions in various hospitals, including the Colombian Diabetes Association, Cardioinfantil Foundation, and The Woman's Clinic, where she served as general physician in the fields of Internal Medicine, Emergency Care, and Obstetrics and Gynecology. She is a Certified Nursing Assistant and a Certified Medical Assistant from the National Registry of Medical Assistants, and she reads, writes, and speaks Spanish and English fluently. Dr. Ulloa is currently a Medical Specialist consultant at Applied Pharmacology and Toxicology, Inc., Gainesville, FL.

**George Casella, Ph.D.**

Dr. Casella is Distinguished Professor and Chair, Department of Statistics, University of Florida is active in many aspects of statistics, having contributed to theoretical statistics in the areas of decision theory and statistical confidence, environmental statistics, and recently in statistical genomics. He also maintains active research interests in the theory and application of Monte Carlo and other computationally-intensive methods. Dr. Casella has served as editor of several premier journals in statistics and is currently the Executive Editor of *Statistical Science*. He has also held numerous positions in professional societies in statistics. Dr. Casella has authored more than 120 peer-reviewed papers as well as numerous commentaries and reviews and four textbooks.