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

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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.[1] According to the National Association of Chain Drug Stores, this represents over 3.27 billion prescriptions filled in outpatient pharmacies in 2004[2] 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.[3] 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.[4] 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.[5] 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.[6] 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.[3]

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 at 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 prescription medications used to thin the blood of patients with severe coronary artery disease and disorders of the blood clotting system.[7]

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[8] 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 warfarin 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.

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We have previously published a critical evaluation of the literature on drug and chemical interactions wherein we proposed five criteria for evaluating interaction studies[9] . 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[10] 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.[11] 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.[12, 13]

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[14] 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,

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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.

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