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**DETECTING ADVERSE EVENTS IN DIETARY SUPPLEMENT RESEARCH:  
LESSONS FROM EPHEDRA ALKALOIDS**

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**ABSTRACT**

DETECTING ADVERSE EVENTS IN DIETARY SUPPLEMENT RESEARCH: LESSONS FROM EPHEDRA ALKALOIDS. **Persky AM, Rawson ES. JEPonline.** 2004;7(4):84-99. In some countries, dietary supplements can be marketed with claims of efficacy or safety without any clinical trial support. As such, there is public concern whether these products are safe for use by the general population. Guidelines established by the United States Food and Drug Administration and the international pharmaceutical industry can be used to provide safety information within the umbrella term of dietary supplements. A dietary supplement would be clinically useful if the therapeutic benefits outweighed the side effects. Unfortunately, the side effects or adverse events associated with dietary supplement use are not well documented. Lack of statistical power and proper study design are the main reasons studies are unable to detect and determine the frequency of the adverse events associated with supplements. However, when adverse events are detected, the causality between the adverse events and the supplement can be diluted by factors such as underlying disease, the irregularity of product purity and uncertainty of how the subjects' exposure to the supplement is related to potential adverse events. As such, studies intending to detect adverse events need to carefully select the study population, document concomitant disease and medications, test product purity and determine the subjects' exposure to the supplement via blood sampling.

Key Words: ephedrine, ma huang, side effects, safety, clinical trials.

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**INTRODUCTION**

The definitions and legal status of "dietary supplements" (e.g., herbal products, isolated single nutrients) vary depending on the particular country. Some countries have rigorous standards regarding regulation and quality control of these types of products. For instance, Germany has well-established guidelines through their Commission E, an independent division of the German Federal Health Agency. In the United Kingdom, the proposed 'Directive on Traditional Herbal Medicinal Products' will require companies to

demonstrate that the sponsor's herbal product is not harmful in the specified condition intended to treat ([www.mca.gov.uk](http://www.mca.gov.uk)). Conversely, the United States considers dietary supplements in an independent classification to that of foods and drugs and therefore dietary supplements are not evaluated by the Food and Drug Administration (FDA) except for labeling claims. With the exception of new dietary ingredients, the sponsor does not need to provide the FDA with evidence to support safety or effectiveness before or after marketing (42). In the U.S., these types of products are not intended to diagnose, treat, cure or prevent disease unlike in other countries. There is considerable global variability in dietary supplement regulation, and the reader is directed to other publications on the matter (7, 18, 53, 72). In the U.S. there is considerable political debate regarding the regulation of dietary supplements stemming from the Dietary Supplement Health Education Act (DSHEA) of 1994. This debate ranges from quality control issues to safety/toxicology and whether dietary supplements should be held to stricter regulations. Supplement manufacturers and their advocacy groups push for the looser terms of regulation as currently stated by DSHEA but some medical and pharmaceutical organizations, as well as some public advocacy groups, are calling for stricter regulations and major modifications to DSHEA.

The worldwide market for dietary supplements has grown, in part, because of the belief that herbal products are free from side effects (18). However this seems an unfounded assumption given that many modern drug products were/are derived from plant sources (e.g., digitalis/digoxin, chemotherapeutic taxanes). Furthermore, countries with well-established regulatory guidelines have removed many herbal products from the market because of safety concerns (47). Even though regulatory agencies are in place, safety is still an ongoing issue (47). In the United States there are concerns over reports of safety issues related to the ingestion of several dietary supplements (e.g. ephedra and cardiovascular events; Kava and liver damage; St. John's Wort and drug interactions) (31, 39, 55). Unfortunately, the frequency and severity of adverse events associated with dietary supplements is largely unknown (68).

Even though dietary supplements may not possess an immediate or strong pharmacological action compared to modern drugs, they retain the ability to modulate physiology, thus possessing pharmacological properties. It therefore seems appropriate to discuss dietary supplement safety in context of modern drug safety and to use guidelines established by the pharmaceutical industry, governing bodies such as the U.S. FDA and the "International Conference on Harmonization" (ICH) (The International Conference on Harmonization is a project that brings together the regulatory authorities of Japan, Europe and the United States, and experts from the pharmaceutical industry, to discuss scientific and technical aspects of pharmaceutical product registration for human use) to apply to dietary supplement research. Previous reviews have focused on the global regulation of dietary supplements, the current state and definitions, and the pros and cons of each governing body (9, 18, 72). It is the purpose of this review to discuss general study-related principles to address the issues of dietary supplement safety using the pharmaceutical industry as a guide. We use the herbal supplement ephedra (Ma Huang) as a model to illustrate current research limitations and offer suggestions for developing studies that can more rigorously examine safety issues regarding nutritional supplements.

## **EPHEDRA (MA HUANG)**

Ephedra is a herb (e.g., *ephedra sinica*) that contains complex mixtures of alkaloids including ephedrine, pseudoephedrine, norephedrine (phenylpropanolamine), and methylephedrine (35,37). Ephedrine is a sympathomimetic drug and central nervous system stimulant (41), which is used in weight loss because of its thermogenic and anorectic properties (5,22). As such, ephedrine, ephedra, and ephedra/caffeine supplements are marketed for weight loss and stimulants to sports performance. Nevertheless, reports of adverse events have called into question the safety of these products (38,61).

The exact prevalence of ephedra use is unknown, especially worldwide. However, survey data in the U.S. indicate that ephedra use is 1% in the general population (11), 3.5% for collegiate athletes (33), and 13 to 25% in health club members (46). It should be noted that the United Kingdom and some European countries already restrict ephedra in herbal remedies ([www.mca.gov.uk](http://www.mca.gov.uk)). We use ephedra as an example throughout

this paper because of alkaloid standardization issues (34,37), known time course of drug disposition (43), reports of common adverse events (3,13,14), reports of serious but more rare adverse events (38,64), and because ephedrine is an FDA approved drug with known side effects and drug interactions (43).

### **Defining Safety**

The average development time for a drug (from discovery to approval) is approximately 10-15 years (approximately ½ in clinical testing), involving safety and efficacy research on thousands of subjects, with associated costs approximating \$800 million (60). However, the greatest portion of the \$800 million is spent in Phase III, large-scale efficacy studies, whereas the initial safety/tolerability studies are much smaller and less expensive in comparison. Studies designed to investigate the safety of dietary supplements often pale in comparison to the initial drug tolerability studies and are not designed adequately to detect even the more frequent safety concerns. For example, a recent study of the cardiovascular effects of an ephedra/caffeine supplement showed no effect on heart rate or blood pressure (45). However, increases in blood pressure and heart rate following ephedra/caffeine ingestion have been observed with both higher (13,14) and lower doses (39). These discrepancies demonstrate the need for more rigorous standards in dietary supplement research studies designed to assess safety, as is typical of early-phase drug studies.

Using the pharmaceutical industry as a guide, drugs in development are considered safe until proven otherwise through industry-sponsored pre-clinical (cell-culture, animal) and clinical (human) testing. The burden to demonstrate safety (and efficacy) is placed upon the sponsoring industry and not the government. Conversely, in the U.S., there is very little obligation placed on the sponsoring supplement industry to indicate product safety at the dose strengths marketed to the public. This lack of safety evaluation transfers the burden upon the government and on university-sponsored research. In Germany under the German Medicines Act, bibliographic data (i.e., well-documented review articles, clinical trials and experimental studies) are needed to assess efficacy and safety (47). Additionally, pharmaco-vigilance of their herbal products is a staple of the marketplace and a systematic risk evaluation must include the plausible proof of efficacy (47).

When discussing safety (whether it is a drug or supplement) it is important to understand that 'safe' does not mean harmless but means that the therapeutic benefits outweigh the risks for the intended population. As an example, chemotherapeutic agents (e.g., etoposide, taxol, vincristine, etc.) can have common side effects (e.g., nausea/vomiting, alopecia, myelosuppression, gastrointestinal distress) that are unacceptable for drug classes for non-life threatening diseases. The tolerance for risks (side effects) is higher for products for life-threatening conditions than non-life threatening illness.

A dietary supplement would be clinically useful if the desired therapeutic effects (e.g., increased vigor, increased sense of well-being, increased muscle strength, decreased feelings of depression) outweighed the undesired pharmacological/toxicological effects. For example, ephedrine/caffeine and ephedra/herbal caffeine, in conjunction with behavioral modification (diet, diet and exercise) causes a slightly greater increase in weight loss (< 3.5 kg over 6 months) when compared to behavioral modification alone in obese subjects (3,13,14,17). However, it is debatable whether the therapeutic benefit (modest weight loss) is greater than the risk of occurrence of commonly reported (increased blood pressure and heart rate) or more rarely reported (myocardial infarction, stroke) side effects of ephedra and ephedra mixtures. This risk to benefit ratio is true for approved weight loss drugs, too and has limited the therapeutic utility of similarly acting weight loss medications. In the past, safety concerns have driven the removal of effective weight loss products such as fenfluramine and phentermine from the market. Even though phentermine is still available as a prescription drug in some countries, it is not endorsed by the Royal College of Physicians because of inadequate long-term safety data (20).

### **Defining Adverse Events**

Side effects of drug therapies are described using the terms adverse drug reactions (ADR) and/ or adverse events (AE). Although the definitions of these concepts are different, we will use AE as an umbrella term and define AE using the World Health Organizations (WHO) definition of "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." (24). Therefore, an AE is any

unfavorable or unintended sign or symptom temporally associated with the use of a product (drug or supplement) but the AE may or may not be related to the product itself. These temporal relationships can include 1) AE that occur shortly after the initiation of the product's use, 2) AE that occur with long-term use of the product, and 3) AE that occur after the product therapy has been terminated (16). For example, Haller et al. (39) reported AE (i.e., shakiness, palpitation, restlessness) at one hour and five hours after ephedra administration while case studies report severe AE (e.g., myocardial infarction, stroke, psychosis, death) after days to years of ephedra use (38,61,64).

There are two distinct categories of AE. The first category, or 'type A' events, are events that are predictable in nature because they are dose-related as a function of the pharmacological actions of the active ingredients (50). Susceptibility of individuals to these types of events can be dependent on differences in an individual's drug disposition (pharmacokinetics) and/or the tissue response to the drug/supplement (pharmacodynamics). For example, ephedra is a  $\alpha$ - and  $\beta$ -adrenergic agonist and can increase heart rate. Therefore, a direct relationship between plasma concentrations and changes in heart rate can be established and titrating the dose down can reduce the magnitude of the increase in heart rate. The effects of dose amount of ephedrine/caffeine on exercise performance (8) and weight loss (6,56) has been studied, however, true tolerability studies to find an "optimal" dose of ephedra/herbal caffeine as it relates to decreasing AE while enhancing weight loss are not available.

The second category of AE, or 'type B' events, is idiosyncratic, unpredictable in nature and often appear unrelated to the dosage or pharmacological activity of the drug. These latter events are relatively rare (> 1 in 10,000), do not usually improve with dose reduction, and are more difficult to separate from underlying disease states. In pharmaceutical research, type B events are only detected after the drug has been available for several years and used in a large number of patients. For example, heart valve abnormalities associated with the weight loss combination, Fen-Phen (fenfluramine and phentermine) that appeared years after the drugs were approved for market, would be considered a type B event. For ephedra, an example of an idiosyncratic event would be a case report of 32 year old female who had a premature delivery and subsequent neonatal death after approximately 4 years of 20 mg ephedra/day and a history of smoking (38). A direct cause-effect related to ephedra was not and cannot be established. Again, because of the rarity and difficulty in determining causality in type B events, we will focus the majority of the discussion on type A events.

### **Proving Safety**

The FDA (U.S.) and other global health agencies such as the Canadian Health Protection Branch (HPB, Canada), Medicines and Healthcare Products Regulatory Agency (MHRA, United Kingdom), and the European Agency for the Evaluation of Medicinal Products (EMA, Europe) have become more involved in the potential regulation of dietary supplements given the fact that a sufficient system is not already in place. Three examples of the FDA involvement are: 1) establishing a draft guidance (i.e., a non-implemented document with possible future implementation) for botanical drug products (23); and 2) in 1997, the FDA proposed (and later withdrew) that the maximal daily dose of ephedrine in a supplement not be greater than 24 mg and a single dose not exceed 8 mg (26) and 3) most recently removal of herbal ephedrine products from the market in December 2003. As such, it is important to understand the goals of regulating bodies with respect to safety. The general goals of a 'safety review' are (1) to identify important AE that are causally related to the use of the drug, (2) to estimate incidence for those events, and (3) to identify factors that predict the occurrence of those events (25); these goals can be obtained through proper experimental design.

In a recent review, it was summarized that three issues need to be addressed when determining the efficacy of performance enhancing supplements (62). These three issues can also be applied to the goals of a "safety review" (and supplement safety) and include: 1) study design, 2) factors associated with the substance and 3) subject factors. The differences between efficacy assessment and a safety assessment during typical drug clinical trials are 1) safety hypotheses for typical AE are generally not specified *a priori* and 2) clinical trials are usually not prepared to test hypotheses regarding rare safety events (19). Nonetheless, although statistical differences between groups may not be achieved, no safety finding should be ignored.

## Study Design

### Identification and Monitoring AE

The first goal of a safety review is to identify important AE that are related to the use of the product. Studies attempting to evaluate dietary supplement safety must first identify the relevant AE or appropriate biomarkers (i.e., surrogate markers) that may predict AE. This can be a variety of physiologic, pathologic, or anatomic measurements thought to relate to some aspect of normal or pathological biological or psychological processes (51). For example, ephedra alkaloids are sympathomimetic compounds (41). As such they can have effects on the cardiovascular (CV) system and central nervous system (CNS) and hence, CV (e.g., blood pressure and heart rate) and CNS (e.g., psychometric and performance tests) parameters are appropriate measures of AE.

The results of many laboratory tests are influenced by diet, physical surroundings, physical activity, mental state, circadian/ biological rhythm, and sub-clinical viral infection (32). Therefore, researchers must be cautious in their interpretations of biomarkers used as proxy measures of AE. Cardiovascular parameters such as heart rate and blood pressure can have large variability throughout a typical day, and it is plausible that the normal within subject variability in heart rate and blood pressure might make changes associated with a supplement like ephedra difficult to detect. In the numerous studies that have reported on the cardiovascular effects of ephedrine/ephedra supplements, the variability of the measure has not been provided (3,4,6,13-15). Therefore reliable baseline values need to be established, as well as a placebo control to help eliminate the variability in clinical assessment.

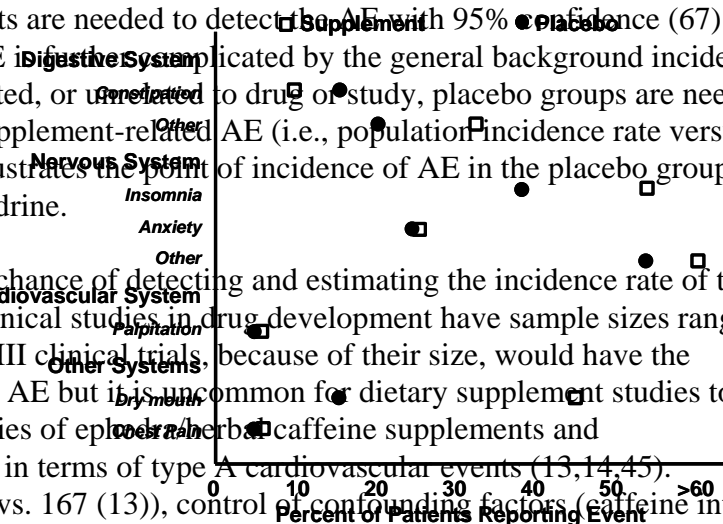
Adequate study duration is also crucial to detect AE. The length of supplement administration is critical because some AE are much more common early in therapy(48). It is not quite known how this relates to ephedra, but reportedly the frequency of AE with ephedrine use are more common in the first 4 weeks of use and decline with prolonged use (3,5,15). Even though some individuals use ephedra for short-term weight loss, others ingest it over longer periods of time for the treatment of obesity. The guidelines from the FDA for safety assessment during long-term therapy for non-life threatening illness states that most AE first occur within the first few months of drug treatment and the number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of AE over time (28). However, the cohort of exposed subjects should be large enough to observe whether AE increase or decrease over time and to observe delayed events of reasonable frequency (28). It is likely that studies lasting only a few weeks in duration, with small sample sizes and more importantly, infrequent assessment of AE biomarkers, do not have adequate power to detect or predict occurrence rates of AE.

### Sample Size

The second goal of the safety review was to estimate incidence rates of AE. A trial sized to address safety issues may need larger numbers of subjects than a trial sized to address efficacy (29). Common AE (e.g., restlessness, insomnia, increased heart rate, dry mouth) occur at a frequency of <1 in 100 individuals (67). If an AE occurs in 1 in 100 patients, 300 patients are needed to detect the AE with 95% confidence (67). The issue of number of subjects to detect an AE is complicated by the general background incidence rate. Since AE may be drug-related, study-related, or unrelated to drug or study, placebo groups are needed to distinguish between supplement- and non-supplement-related AE (i.e., population incidence rate versus incidence rate due to supplement). Figure 1 illustrates the point of incidence of AE in the placebo group compared to an experimental group given ephedrine.

Logically, larger sample sizes provide the best chance of detecting and estimating the incidence rate of the less frequent AE. Typical Phase I, II and III clinical studies in drug development have sample sizes ranging from <100 to >1000 subjects (Table 1). Phase III clinical trials, because of their size, would have the greatest ability to estimate an incidence rate for AE but it is uncommon for dietary supplement studies to be as large as Phase III clinical trials. Recent studies of ephedra/herbal caffeine supplements and cardiovascular AE reported discrepant findings in terms of type A cardiovascular events (13,14,45). Differences in sample size (30 (45) vs. 67 (14) vs. 167 (13)), control of confounding factors (caffeine intake, co-medication), and a stable cardiovascular parameter (continuous vs. single time point assessments) may explain these discrepant findings.

**Figure 1: Percent of patients reporting adverse events following ephedra/herbal caffeine (63 mg/d ephedrine, 300 mg/d caffeine) or placebo ingestion for 8 weeks in overweight individuals. Data summarized from <sup>13</sup>.**



Boozer et al. (14) reported the percent of patient reporting AE grouped by body system following ephedra/herbal caffeine or placebo ingestion (Figure 1). Some AE were reported with similar frequency in the experimental group as in the control group (nervous system: anxiety; CV system: palpitation; other systems: chest pain), while others were quite divergent (digestive system: other; nervous system: insomnia; CV system: general; other systems: dry mouth). The frequency of reported AE of the nervous system by subjects ingesting placebo was 25% (anxiety), 40% (insomnia), and 55% (other). These data illustrate several other important points to consider when designing studies to detect AE: 1) the importance of a placebo group for comparison and 2) the need for AE to be classified based on body systems.

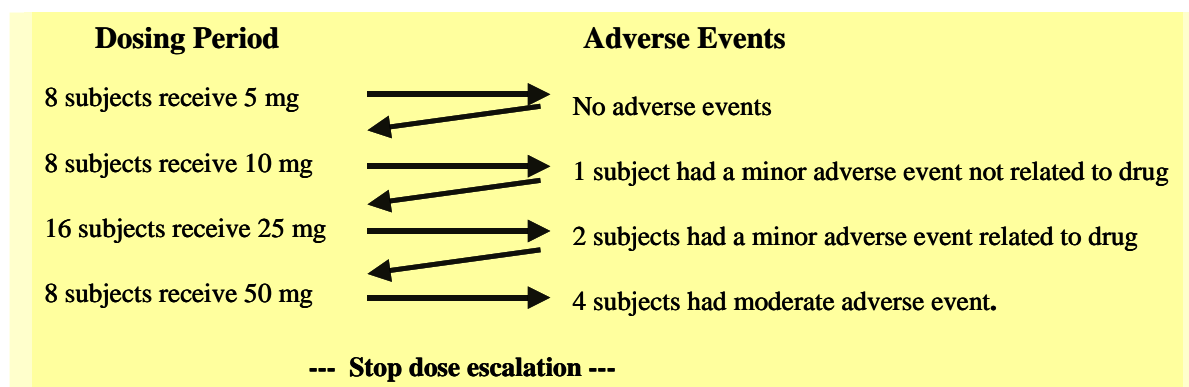
**Table 1: The overall objectives of pre-marketing (phase I to III) and post-marketing (phase IV) drug trials with emphasis on evaluating safety in healthy volunteers and in patient populations. Summarized from Gad (32).**

Phase	Primary Objective	Purpose in regards to Safety	Typical Sample Size
<b>I</b>	Tolerability	Safety in healthy volunteers following a single dose and short-term multiple doses	20-80
<b>II</b>	Efficacy	Safety in intended patient populations	100-300
<b>III</b>	Efficacy	Safety in intended patient populations Safety in patients with multiple diseases, organ impairment or on concomitant medications during long-term use	1000-5000
<b>IV- (Post-marketing)</b>	Safety	Safety surveillance	General population

An additional concern is a lack of assessment and tracking of dropouts of supplementation studies. Boozer et al. (13) reported that 8 subjects receiving placebo and 7 subjects receiving the ephedra/herbal caffeine supplement withdrew from the study as a result of AE. Similar findings can be seen with FDA approved weight loss agents such as sibutramine where in one study withdrawal due to AE were greater in placebo than treatment groups (66). Valuable information can be gained from subjects who do not complete the study, and so these individuals should be tracked, assessed when possible, and included in the results of the study. The largest and longest duration studies of ephedrine/caffeine and ephedra/herbal caffeine supplemented 141 subjects for 6 months (3) and 167 subjects for 6 months (13), respectively. The reasons for and number of subjects who drop out of dietary supplement studies are rarely published.

Since studies of large duration and equally large sample sizes are both expensive and difficult to manage, drug safety starts with a first-time-in-human (FTIH) study. In these studies safety and tolerability are the main endpoints along with pharmacokinetics. FTIH studies are performed under the guise of previous animal toxicological data, require a series of single, ascending dose levels (and placebo) to try to determine the maximum tolerable dose (MTD). These types of studies lead to an “ideal” efficacy to safety ratio to be determined in Phase II and III clinical trials. These studies involve rigorous screening of subjects (i.e., blood/urine tests, Holter monitoring and physical exam) and subjects are continually monitored during the subsequent dosing schedule (i.e., 12 lead electrocardiogram, frequent vitals signs and blood/urine chemistry tests); again, safety is the primary concern. Although a variety of designs are used for a FTIH study, an example is shown in Figure 2.

<b>Cohort 1 (n=8)</b>				
Subject	Period 1	Period 2	Period 3	Period 4
<b>1 and 5</b>	Placebo	5 mg	10 mg	25 mg
<b>2 and 6</b>	5 mg	Placebo	10 mg	25 mg
<b>3 and 7</b>	5 mg	10 mg	Placebo	25 mg
<b>4 and 8</b>	5 mg	10 mg	25 mg	Placebo
<b>Cohort 2 (n=8)</b>				
Subject	Period 1	Period 2	Period 3	Period 4
<b>9 and 13</b>	25 mg	50 mg	100 mg	Placebo
<b>10 and 14</b>	25 mg	50 mg	Placebo	100 mg
<b>11 and 15</b>	25 mg	Placebo	50 mg	100 mg
<b>12 and 16</b>	Placebo	25 mg	50 mg	100 mg



**Figure 2: Example of a dose escalation procedure (FTIH study) to determine maximum tolerable dose.**

Other methodical issues include: exposure assessment; multiple dosing; and determination of causality. Clinical trials should also study short-term multiple doses of the supplement (length of the study is usually dependent on the half-life of the active ingredient) and repeatedly assess and document any possible common AE; like FTIH studies, subjects are typically kept ‘in house’ for the duration of the study. One method to determine causality, that is relating the AE to the product and not another underlying cause, is through a 4-phase approach. The 4 stages include 1) positive challenge, 2) positive de-challenge, 3) positive re-challenge and 4) positive de-challenge (62). Although this technique can help answer the question of causality, re-challenges are not typically done during drug trials. Another method used to determine the causality of the AE in a patient to a drug (or supplement) is the use of a simple questionnaire about the AE and its relation to drug exposure (57). It is typical that the onsite physician of a drug study determines the causality of the event.

#### ***Factors associated with substance***

The third goal of a safety review is to identify factors that predict the occurrence of AE. This can include: product purity, product exposure (pharmacokinetics), and subject factors.

#### **Product Purity**

For herbal products, this offers new challenges since active ingredients are often not known and the quality of herbal supplements can be widely variable. In our ephedra example, herbal ephedra is a complex mixture of alkaloids including ephedrine, pseudoephedrine, norephedrine, and methylephedrine. The ephedrine content of ephedra plants is dependent on species, where the plant is grown, the type of growing conditions, and the time of harvest (63). The absolute ephedrine alkaloid content and the ratio of ephedrine alkaloids varies markedly both within and between lots of the same products (35,37). Gurley et al. (37) reported as little as 0% and as much as 154% deviation in total ephedra alkaloid content from label claim. Identification and quantification of active moieties of complex mixtures is necessary to determine causality and relate the causality to drug exposure. Clearly, this high within lot and between lot variability confounds any studies attempting to study the association between ephedra ingestion and AE. Investigators should provide independent analyses of supplement content in their research publications, but this practice is currently not common. In lieu of this, researchers could obtain written verification from supplement manufacturers indicating the level of product purity and whether or not they follow good manufacturing procedures. It should be noted, Good Manufacturing Practices (GMP) guidance’s have been proposed for dietary supplements (2)

#### **Product Exposure**

“Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.” (28). Exposure refers to the drug input into the body (i.e., the dose) and various measures of acute or integrated concentrations in plasma and other biological fluids can be used to characterize exposure (e.g., maximal concentrations or  $C_{MAX}$ , average concentrations, area-under-the-curve or AUC) (27).

Understanding the pharmacokinetics of the supplement (i.e., the exposure) helps predict the potential for AE. From a drug perspective, animal data provide guidelines to what blood concentrations are associated

with AE or more precisely, the concentrations that are not associated with AE. Since the product quality of herbal supplements is not truly known, independent testing is needed to ensure dose amounts. Blood samples are needed to determine drug exposure and to relate how exposure relates to AE. In general, individuals that eliminate a compound slowly (i.e., lower renal function or slower metabolic enzymes) may have a higher systemic exposure to an active ingredient thus leading to an AE; this type of patient-specific information would not be known without quantifying exposure. Additionally, the clinical measurement of the dependent variable to assess AE (i.e., pharmacodynamic outcome) can be delayed or persistent with respect to blood levels as suggested earlier. This type of effect results in an exposure-response relationship with considerable hysteresis (loop effect). Even in this case, exposure-response relationships can be informative. Ephedra, for example, follows a clockwise hysteresis for blood pressure effects (10,39). A clockwise hysteresis is indicative of 'acute tolerance' (10,54) similar to the effects seen with cocaine, a pharmacologically related compound to ephedrine (70).

#### Herbal vs. Synthetic Preparations

Active ingredients have similar effects regardless if they are synthetic or herbal preparations as long as the molecular structure is identical. However, given herbal/dietary products contain other potential modulators, pharmacological effects may be enhanced or blunted. For example, from a pharmacodynamic standpoint (i.e., dose-response relationship) ephedrine will elicit the same pharmacological response (e.g., thermogenic or cardiotoxic) regardless of source of the ephedrine (i.e., plant or synthetic) unless another substance (e.g., caffeine, aspirin, pseudoephedrine) is also present. Therefore, as long as the concentrations are similar at the site of action, the extent of pharmacological/toxicological outcomes assuming other confounding molecules from the product are not present. For example Berlin et al. (10) found peak increases in blood pressure of ~15% after a 50 mg dose; Haller et al. (39) found nearly the same peak increases in blood pressure (~15%) with a smaller dose of ephedrine (17.3 mg) but that was given in herbal form with caffeine (175 mg caffeine). This suggests the combination of products typically seen in ephedra products may potentiate the cardiovascular effects beyond ephedrine alone.

The similarity in drug exposure for different products is the basis for the principle of bioequivalence of pharmaceutical products or proving one product is interchangeable with another product without loss of efficacy. Gurley et al. (36) found almost no difference in plasma concentration versus time profiles between synthetic ephedrine hydrochloride (HCl, 25 mg) and 3 herbal ephedra products with equivalent ephedrine content. Assuming these products are bio-equivalent, which is reasonable based on the standard errors of AUC and  $C_{MAX}$  in this study, exposure of the body to ephedrine is similar than the pharmacological/toxicological responses should be similar as well. Therefore, the side effect profiles for ephedrine, a FDA approved OTC product, should be similar for those of ephedra. It should be stressed that these are just effects from ephedrine alone and not the other ephedra alkaloids and caffeine which are typically included in ephedra products.

#### **Subjects Factors**

In a safety-type study, characterizing the study population and adequate screening of the subjects is of the utmost importance. Populations that use dietary supplements ranges from young, apparently healthy adults, to elderly adults whom are prescribed multiple medications, to obese persons with multiple co-morbidities. Subject characteristics can be used to identify factors that could potentially predispose the individual to an AE (e.g., age, gender, race, co-morbid illnesses). Subject descriptors should include gender, body size (and possibly composition), ethnicity, pre-existing medical conditions, medication use, and prior exposure to compounds being tested. Previous physical activity or fitness level as well as diet and previous meals may also be informative.

Concomitant use of prescription, over-the-counter, or illegal drugs can have a significant effect on AE. For approved drugs, drug interactions account for 25% of AE reports (48) and it is these interactions (i.e., drug-supplement) which may be partially responsible for AE seen in the dietary supplement literature. An example of a drug-ephedra interaction is a case study reported a relatively healthy male using ephedrine (Thermadrene<sup>®</sup>) who suffered an ischemic stroke (44). This patient smoked one pack of cigarettes per day for 12 years and was taking bupropion, a neurotransmitter reuptake inhibitor used for smoking cessation. The authors of this case report concluded that ephedra was responsible for the AE and did not address the

possible interaction with bupropion. Drug interactions for bupropion include cocaine, amphetamines and other stimulants – drugs with mechanisms of action similar to that of ephedrine. The drug interaction between bupropion and ephedra is more likely to be a cause of the AE than ephedra itself. This demonstrates the point that concomitant medications need to be noted and reported during safety studies.

Early clinical testing for drugs (i.e., Phase I Clinical Trials in drug development) generally uses healthy volunteers to reduce the possibility that a side effect or lab abnormalities could be caused by an underlying illness or other medications. As the side effect profiles are defined, testing moves into patient populations (Phase II and III). In the case of dietary supplements, initial safety studies should be conducted in normal healthy volunteers that are free from concomitant pathology/disease, use or abuse of drugs or alcohol and any other factors likely to confound the interpretation of test results. It is likely that many persons suffering from diseases are using dietary supplements despite a lack of studies documenting the safety of doing so in their disease-specific population. Recent studies have examined the efficacy and side effects of ephedra in ‘healthy’ yet overweight individuals (13,14).

Previous exposure to ephedra and ephedra/caffeine can confound AE studies as tolerance (or sensitivity) is noted for both ephedrine and caffeine (30,69). Further, an ephedrine or caffeine naive subject may have a larger pharmacological effect than an accustomed subject resulting in an AE where a frequent user who has built a tolerance may not demonstrate any side effects. Therefore, investigators should characterize subjects as users, excessive users, non-users, and sensitive users when screening subjects. While the benefits of studying one group over another are unclear, it seems prudent to include all groups in the same study. Recent ephedra studies excluded both excessive caffeine users (>500 mg/day) (13,14) and caffeine sensitive (45) subjects. Additionally, obesity, insulin resistance and stress contribute to chronic sympathetic activation (21) and therefore the addition of a sympathomimetic compound like ephedra may illicit AE at a more frequent rate than in normal, healthy populations.

There is no ideal study design or list of parameters needed to assess safety in dietary supplement research but study designs that follow a FTIH type design would provide valuable information on safety and tolerability of a dietary supplement. Table 2 lists some variables that are critical to measure and report in studies of this nature. Some variables such as age, gender, and body weight are commonly reported, but others such as timing of the AE in relation to dose or reason for subject dropout are addressed much less frequently.

**Table 2: Suggested parameters to be assessed in studies assessing dietary supplement safety.**

<i>Parameter</i>	<i>Example</i>
<i>Patient characteristics</i>	Age, race, sex, weight
<i>Adverse event</i>	Increased blood pressure, gastrointestinal disturbance, myocardial infarction
<i>Duration of adverse event</i>	Hours, months, years, permanent
<i>Severity</i>	Mild, moderate, or severe
<i>Seriousness</i>	Non-serious, life threatening, reversible
<i>Action taken</i>	None, dose reduced, treatment stopped
<i>Outcome</i>	Returned to normal, medical intervention, permanent disability, death
<i>Causality assessment</i>	Related, possibly related, not related
<i>Timing of onset in relation to dose</i>	Immediately after dose, days after dose, after several months of use
<i>Dose amount</i>	Mg/day, mg/kg body weight, mg/kg lean mass
<i>Duration of treatment</i>	Single dose, days, months
<i>Concomitant treatment during study</i>	Caffeine, other herbals, birth control pills, alcohol, illicit drugs, prescription and/or OTC medication

## DETECTING RARE ADVERSE EVENTS

Pre-marketing drug trials (Phase I through III) are used to evaluate safety in healthy volunteers and patient populations (Table 1). However, these clinical trials do not have sufficient power to detect the more rare and sometimes more serious type B AE. Despite the time, money, and efforts put into this testing, AE are still reported post-marketing (Phase IV, post-FDA approval) and in some cases result in widely prescribed drugs being removed from the market (e.g. Pondimin<sup>®</sup> (fenfluramine) and Redux<sup>®</sup> (dexfenfluramine) – heart valve abnormalities; Seldane<sup>®</sup> (terfenadine) - fatal heart rhythm abnormalities; Renzulin<sup>®</sup> (troglitazone) – liver toxicity; OTC phenylpropanolamine - hemorrhagic stroke; Baycol<sup>®</sup> (cerivastatin) – rhabdomyolysis). The currently available system to study rare AE associated with dietary supplements on a population level after a product has been sold for several years is the United States' Medwatch system ([www.fda.gov/medwatch](http://www.fda.gov/medwatch)) or the United Kingdom's "yellow card" system. Two studies have used U.S. government databases to report AE associated with ephedra use (38,64). Using Medwatch, Haller and Benowitz (38) reviewed 140 reports of AE submitted to the FDA (1997 to 1999) and applied a rating system for assessing causation. Thirty-one percent of cases were considered definitely or probably related to the use of supplements containing ephedra alkaloids, and 31 percent were deemed possibly related. AE included hypertension (17 reports), palpitations, tachycardia, or both (13), stroke (10), and seizures (7). Ten events resulted in death, and 13 events produced permanent disability. Samenuk et al. (64) reviewed the now defunct FDA Adverse Reaction Monitoring System database for ephedra related AE. Of 926 AE cases reported to the FDA (1995 to 1997), use of ma huang in 37 patients was temporally related to stroke (16), myocardial infarction (10), or sudden death (11). Use of ma huang was reported within manufacturers' dosing guidelines in 36 of the 37 patients. The authors concluded that ma huang use is temporally related to stroke, myocardial infarction, and sudden death; underlying heart or vascular disease is not a prerequisite for ma huang-related adverse events; and the cardiovascular AE associated with ma huang were not limited to massive doses (64).

These studies provide strong circumstantial evidence indicating that ephedra alkaloids may be associated with serious medical complication, but do not establish a causal relationship. The AE reported by Haller and Benowitz (38), Samenuk et al. (64) and Shekelle et al. (65) are consistent with the expected AE of sympathomimetic drugs, supporting the validity of their findings. However, confounding factors such as underlying disease or drug interactions are not controlled which weakens the conclusions one can make from studies of this nature. Additionally, because these AE reports are voluntarily submitted significant under-reporting may occur, and so it is not possible to estimate the number of AE associated with ephedra ingestion on a population basis. The FDA Center for Food Safety and Applied Nutrition is currently developing a system to track and analyze AE associated with dietary supplements.

## REPORTING DATA

Most commonly, AE for supplements are case reports and for drugs the more serious AEs are first noted through this mechanism. The case study can serve as a twofold purpose: 1) case studies can act as a screening tool for future clinical investigations and 2) can report on more unusual or rare events that occur with long-term use. However, case reports are influenced by the rate which the AE occurs (i.e., frequency), the temporal relationship with respect to supplement exposure (i.e., did the AE occur during use or after cessation of use), and underlying lifestyle (i.e., cigarette smoking, alcohol use) and disease (16).

As mentioned earlier, side effects of supplements, like traditional drugs, can be segregated into rare and common occurrences. In rare events, each event is important and supports the need for case studies. For these events, ratios of people experiencing such events compared to the number of people exposed to the supplement become very useful. For example, two studies by Boozer et al. (13,14) reported side effects of ephedra/caffeine use during weight loss studies in a total of approximately 230 healthy but overweight individuals. These studies were 8 weeks to 6 months in duration and the supplement group had a higher incidence of side effects (69%) than a placebo control group (50%). An important note, subjects could have reported more than one side effect and would not be detectable in providing only frequency numbers. For that reason, use of a crude incidence rate such as (number of subjects with AE / number of subjects receiving supplement) factors out subjects with multiple AE but this calculation does not take into account

exposure nor severity and duration of the AE (19). For example, Figure 1 depicts the frequency AE based on the total study population and does not illustrate how many subjects reported AE. However, Table 3 is a contingency table that segregates AE based on number of subjects reporting AE, number of AE, and total subject number from which frequency data can be calculated.

**Table 3: Adverse events reported during an efficacy comparison of dexfenfluramine to ephedrine/caffeine (E+C) in overweight individuals. Data summarized from Breum et al. (15).**

	<i>Number of Events / Number of Subjects</i>								Total AE	Total Subjects with AE	Total Subjects
	CNS		CV		GI		Other				
<i>Dexfenfluramine</i>	25	14	0	1	9	9	1	6	35	30	53
<i>E+C</i>	26	23	4	4	1	2	2	6	33	35	50
<i>Total</i>	51	37	4	5	10	11	3	12	68	65	103

## DISCUSSION

Lack of adequate knowledge of the information on a dietary supplement by the public and medical practitioners or misuse by users are probably the major contributing factors to the occurrence of AE. The confusion surrounding dietary supplements and the lack of available data concerning the safety of many supplements does not appear to have deterred consumers as supplement sales have increased in the United States from 9.8 to 14.7 billion dollars (1995 to 1999) and a projected 18.5 billion dollars in 2002; it is estimated that there are 12 million supplement users in the United States (1). The U.S. has seen the biggest growth over the past decade but worldwide sales have also been increasing (18). As such, the U.S.'s National Institutes of Health's (NIH) Office of Dietary Supplements (ODS) released a mission statement in 1998 in which two of its goals were to "improve scientific methodology as related to the study of dietary supplements" and "inform and educate scientists, health care providers, and the public about the benefits and risk of dietary supplements." (59). Methodological considerations in regards to efficacy have been addressed elsewhere (40,62), however, some of the safety issues are not being adequately addressed and can be summarized in Table 4.

**Table 4: Summary of major points in determining adverse events associated with dietary supplements**

<i>Major Points</i>	<i>Relevant Questions</i>
<i>Outcome Measurements</i>	What are the expected AE? Can they be reliably measured? What is the optimal frequency and time of assessment?
<i>Sample Size and Study Population</i>	What is the a priori effect size? What frequency do the AE occur? Healthy volunteers or target population? Ethnicity, gender? Exclusion/inclusion criteria?
<i>Study Design</i>	<ul style="list-style-type: none"> <li>• Placebo group (or compared vs. a standard treatment)?</li> <li>• Study duration?</li> <li>• Dose amounts?</li> <li>• Single dose or multiple dose?</li> <li>• Testing product purity?</li> <li>• Crossover or parallel?</li> <li>• Blinding?</li> <li>• Blood collection for exposure measurements?</li> </ul>
<i>Reporting Data</i>	<ul style="list-style-type: none"> <li>• Contingency tables?</li> <li>• Graphical?</li> <li>• Tabular?</li> </ul>

- Verbal?
- Number of events?
- Number of subjects?
- Segregation by body system?
- Amount of AE over time?

In the face of a media frenzy that challenges the safety of dietary supplements in the United States, the general population wants greater certainty regarding safety concerns from dietary supplement products as is provided by the FDA with prescription and OTC drugs (12,49,52). However, government intervention fuels the debate between those wanting to protect an individual's right to self-treat and those who prioritize public safety. Mistrust between researchers, government, and supplement manufacturers have made it difficult to develop a systematic method of for testing the safety of dietary supplements. In a recent commentary (49), C. Everett Koop, former United States General Surgeon, stated "...the natural products industry has kept its distance from medical research and from clinical medical practice, focusing instead on the short-term marketing advantages derived from keeping herbal and nutritional remedies exempt from any FDA review...". Further, the mistrust of researchers for industry-sponsored dietary supplement research has reduced the believability of industry-sponsored studies (40,71). Because of this mistrust, it is suggested that the nutrition research community be responsible to assess the long-term impact of dietary supplements (58).

Safety is a relative rather than an absolute term that is based on risk to benefit ratios and its assessment needs to be established to demonstrate the benefits for a particular supplement clearly outweigh the risks. Factors such as metabolism, genetics, user demographics (e.g., age, gender, race), interactions with concomitant medications, or physiologic and pathophysiologic states (e.g., hepatic or renal disease) need to be addressed as these factors can be evaluated and quantified and should serve as the fundamental basis of dietary supplement AE assessment. Efficient assessment, monitoring and verification of AE can lead to a better understanding of factors that impact the development of AE. Determination of safety and efficacy needs to be made available so consumers can make informed choices on the use of these supplements. This section needs to provide enough data and interpretations from past research to clearly identify the need for doing your study. However, it should not be too long. Focus the content on being able to answer several important questions.

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