

The state of dietary supplement adverse event reporting in the United States

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SUMMARY

Purpose The Dietary Supplements Information Expert Committee (DSI-EC; the Committee) of the United States Pharmacopeial Convention (USP) reviews safety profiles of dietary supplements before development of *USP–National Formulary (USP–NF)* quality monographs. Because the veracity of dietary supplement adverse event reports (DS AERs) directly affects DSI-EC safety reviews, the Committee reviewed the current status of DS AER reporting in the US.

Methods DSI-EC reviewed PubMed searches, information from the US Food and Drug Administration's (FDA) MedWatch program, the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers (AAPCC), and reports from US and other agencies. DSI-EC analyzed this information to identify key factors that affect the quality of DS AERs.

Results The overall incidence of DS AERs appears generally to be low. However, the primary reporting portal (FDA MedWatch) receives fewer AERs than do poison control centers (PCCs), and limited coordination exists among national and international surveillance programs for evaluating signals that may indicate potential public health risks. Both inadequate and poor-quality reporting of DS AERs are major limitations of DS safety monitoring in the US.

Conclusions Based on its assessments, the Committee advances recommendations to improve the quality of reporting, monitoring, and assessing DS AERs. These include (1) enhanced data collection approaches, (2) improved coordination of AER surveillance programs, (3) strengthening of educational programs for public and health care sectors, and (4) conduct of research concerning the safety of DS. If taken, these approaches are expected to improve the health and well-being of DS users. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS—dietary supplements; adverse event reporting

Received 4 January 2008; Revised 21 April 2008; Accepted 8 May 2008

INTRODUCTION

Dietary supplements (DS) are among the most commonly used complementary or alternative medical therapies in the United States.^{1,2} Legal recognition in the US for DSs and DS ingredients arises from the Dietary Supplement Health and Education Act (DSHEA) of 1994.³ Various national analyses have

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estimated that 10–52% of the US population use DSs for the promotion of health and treatment of a variety of health conditions.^{1,4–7} Sales reported by the DS industry for 2005 were \$20 billion, which is an indication of strong consumer interest.⁸ Yet despite the popularity of DS, their expanding use has raised concerns regarding product quality and safety.⁹

Started in 1820 by practitioners, the United States Pharmacopeial Convention (USP) is an independent nonprofit, standards-setting organization for drugs, DSs, and food ingredients.^{10,11} USPC has five expert committees in its standards-setting body, the Council of Experts, devoted to creating official standards for DSs. The USP DSs Information Expert Committee (DSI-EC, the Committee) is charged with evaluating the safety of dietary ingredients prior to the development of quality monographs in *United States Pharmacopeia–National Formulary (USP–NF)*. The Committee has established a classification that supports the Committee's determination of the acceptable safety¹² of a DS before it publishes an official monograph for the DS ingredient or product in *USP–NF*.

DSI-EC conducts extensive safety reviews of DSs and their ingredients by analyzing information gathered from human clinical case reports, adverse event reports (AERs), animal pharmacological and toxicological data, historical use, regulatory status, and global contemporaneous extent of use. The Committee collects information from numerous sources, including PubMed searches, the US Food and Drug Administration (FDA) MedWatch, and international regulatory agencies, including those of Canada, Australia, and Britain. Data about toxicological or pharmacological properties of many DS products are not always available, so AER systems are important for the early detection of possible toxicity signals.

Because of the importance of the quality of DS AERs for safety reviews conducted by DSI-EC, the Committee undertook an analysis of the current status of DS AERs with the goal of identifying shortcomings and areas for improvement. DSI-EC reviewed literature about DS AERs by PubMed searches, the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers (AAPCC), and reports from US and other agencies.^{1,13–19} Further, the Committee analyzed AER information from the US FDA MedWatch program concerning several DS ingredients for which USP monographs were developed. DSI-EC analyzed this information to identify key factors that affect the quality of DS AERs. In this paper, DSI-EC defines

important terminology, highlights unique factors that have a bearing on DS AERs, reviews recent legislation on the subject, and proposes recommendations to improve the status of AER reporting.

According to DSHEA, a DS is defined as: A product (other than tobacco) that is intended to supplement the diet and that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin,
- (B) a mineral,
- (C) a herb or other botanical,
- (D) an amino acid,
- (E) a dietary substance for use by humans to supplement the diet by increasing the total dietary intake,
- (F) a concentrate, metabolite, constituent, extract, or combination of any of these ingredients.³

ADVERSE EVENTS: DEFINITION AND TOOLS FOR ANALYSIS

Because of widespread consumer use and at times limited expertise on the part of practitioners in the safe and effective use of DS, DSI-EC identified a critical need for appropriate reporting and surveillance of DS AERs.^{20–22}

Definitions vary, but in general an adverse event is an unintended, undesired, or harmful effect associated with the use of a medication, intervention, or DS. A causal relationship does not have to be established between the DS and the adverse event in order for the AER to be useful for detection and analysis. Several causality algorithms, such as the Naranjo scale,^{23,24} the Kramer scale,²⁵ and the WHO scale¹⁹ are available for estimating the likelihood that a product caused an adverse reaction. Each of the methods analyses the AERs on the basis of different criteria including: a patient's previous experience with the substance, alternative etiologies, temporal correlation, correlation to dose, and dechallenge/rechallenge information. Each method scores the question strings to assign the likelihood of causation: doubtful/unlikely, possible, probable, and definitive/certain. The objective in choosing a causality scale is to provide a reproducible method of identifying and understanding causality of AERs and to assist in scientific judgment. The algorithms make clear that the more detailed the available information is, the more accurate and reliable the assessment of causality.

The core information of an AER consists of (1) the reporter, (2) the patient, (3) the suspect product, and (4) a narrative report of the adverse event. This core

information serves to provide the basic components to raise a signal of possible safety concern. Further, the core information provides a means to contact the reporter for additional information to assess the causality according to one of the algorithms mentioned above. However, while this makes it convenient to file a report with the core information, DS AERs often require additional information, as do many drug AERs, including details of the DS product (e.g., dose/amount taken and duration of use, brand name, manufacturer, exact names of ingredients as listed on the product label, and the time between product administration and the reaction), dechallenge/rechallenge information for all DS, over-the-counter (OTC) and prescription drugs, and patient characteristics (e.g., age, sex, concomitant use of other medications such as OTC and DS products, and medical and social history such as smoking and alcohol use). As noticed in the reports on products containing ephedra,²⁶ insufficiently documented case reports are the primary reasons that hamper informed judgment in evaluating relationships between an AER and a product. Table 1 lists minimal medical information required for a meaningful case report with essential attributes to facilitate causality assessment. The importance of providing complete case details in publications concerning AERs is stressed in other commentaries. For example, the International Society for Pharmacoepidemiology and the International Society of Pharmacovigilance have recently published guidelines for submitting AERs for publication.²⁷ If possible, the person filing the AER should retain a sample of the product, especially if the adverse event is severe, in case testing for adulteration or contamination is indicated.

THE CURRENT STATUS OF DS AER REPORTING IN THE US

Under DSHEA, DS manufacturers are not required to submit pre-market safety data about their products to FDA if the dietary ingredients were on the market before 1994. Although adverse events associated with DS generally are minor and may include allergic reactions (rash and urticaria) or gastrointestinal symptoms (nausea, diarrhea, and abdominal discomfort), rare but serious reactions such as death, hepatitis, renal failure, stroke, anaphylaxis, and seizures have been reported. According to DSHEA, FDA is responsible for ensuring the safety of DS and has the legal authority to take action if it determines that a product presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested on the DS product label. FDA relies primarily on its passive adverse events reporting system (MedWatch) to identify DS safety problems, which are triaged by the agency's Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS). However, an FDA-commissioned study estimated that the agency receives fewer than 1% of all AERs associated with DSs.¹³ Without appropriate reporting, FDA finds it difficult if not impossible to quickly and effectively identify the potential risk associated with the use of a particular DS. Without a reliable AER system, FDA cannot adequately act to ensure the public's health. After analyzing FDA's data, the Office of Inspector General (OIG) reported in 2001 that '...between January 1994 and June 2000, we were able to document only 32 safety actions that FDA took based on the adverse event reporting system—a period when

Table 1. Minimal information that should be reported in MedWatch forms

Medical Information	<ul style="list-style-type: none"> • Medical history • Medical diagnosis • Dose and duration of use • Background on the patient (age, sex, chronic conditions, etc.) • Other medications (with prescribing information) • Pertinent findings from physical exam • Laboratory tests • Social history (smoking, alcohol use, other lifestyle factors) • Medical intervention, and de-challenge/re-challenge outcome
Product Information	<ul style="list-style-type: none"> • Contact information for the patient and health care professional • Label contents (dose, frequency, route, any safety recommendations, etc.) • Brand name and exact listing of ingredients • The type of extract, concentration, and/or strength of ingredients • Lot number • Expiration date
Manufacturer and Distributor Information	<ul style="list-style-type: none"> • Contact person • Address

more than 100 million people were taking supplements. With limited information to draw upon to generate and assess signals, FDA rarely reaches the point of knowing whether taking a safety action is warranted.¹³ FDA safety actions included issuing consumer safety alerts to warn against potentially risky supplements containing botanical ingredients of concern (like aristolochic acid), adulteration with drugs (PC SPES), interactions with prescription drugs (St. John's wort), adverse reactions (kava, LipoKinetix), and warnings regarding false claims to prevent or treat diseases (such as anthrax). In few cases, FDA enforced product recalls or import detentions and sent letters to health care practitioners and stakeholders.

In the US, four major groups are involved in the reporting and assessment of DS AERs: health care professionals (HCPs), consumers, PCCs, and DS manufacturers.

Health care professionals (HCPs)

The OIG's report noted 20% of DS AERs submitted to FDA came from HCPs, and many were incomplete.¹³ Before an HCP can report an adverse event, a patient must reveal that s/he is experiencing symptoms and is using a DS. US survey data clearly indicate that patients do not always report use of DS to their HCP; for example, 60–69% of patients who use DS and prescription medication concomitantly do not disclose this information to their HCP.^{4,28} Although patients may not be forthcoming about DS use, practitioners similarly may not be asking about such use.²⁹ Many HCPs believe they lack adequate information or education about DS either to recommend such products to their patients or to detect an adverse event associated with DS use.^{20,21,30–33}

Other members of the health care team appear to have similar concerns. A systematic review of the literature found strong agreement among US and Canadian pharmacists regarding the need for additional training about DS, increased regulation of DS, and unbiased quality information about DS.³⁴ Although an increasing number of educational programs attempt to bridge this knowledge gap, more effort is needed to educate HCPs in clinical practice, as well as those in medical, pharmaceutical, and allied health fields.

Reports of adverse events to DS may be filed by HCPs through the MedWatch form FDA-3500 for voluntary reporting,³⁵ and medication errors may be reported through the USP MEDMARX or MER (Medication Error Reporting) programs.³⁶

Consumers

According to the 2001 OIG report, at least half of the AERs submitted to FDA come from consumers.¹³ However, when consumers report an adverse event they usually do not inform or involve their HCP, who would be in a better position to provide objective and medically relevant information. Without this information, FDA may find it difficult to determine causality. Two clear examples are kava and ephedra. Though many case reports were filed by consumers, most were incomplete, which made an accurate safety assessment of these botanicals difficult. As noted in Section 'Adverse Events: Definition and Tools for Analysis' above, the missing information related to the details of the DS product (e.g., dose/amount taken and duration of use, brand name, manufacturer, exact names of ingredients as listed on the product label, and the time between product administration and the reaction), dechallenge/rechallenge information for all DS, OTC and prescription drugs, and patient characteristics (e.g., age, sex, concomitant use of other medications such as OTC and DS products, and medical and social history such as smoking and alcohol use). Consumers may have been unaware of FDA's role in regulating supplements, and FDA made only limited outreach to the public regarding MedWatch.¹³

Poison control centers

In contrast, AAPCC TESS data show that US PCCs have extensive penetration into the consumer and HCP base and historically have recorded substantially higher numbers of DS AERs compared to FDA's MedWatch system.^{37–40} During the 10-year period from 1993 to 2002, US PCCs received reports of 21 533 toxic exposures with definitive medical outcomes in which a botanical product was the only substance involved. Of these, 4306 (19.9%) had moderate or major medical outcomes including 2 deaths.⁴¹ PCCs are located predominantly in hospitals and academic health centers, which are designed to manage undesirable exposures, toxicity, and overdoses. The outreach programs by these centers provide better visibility of the PCCs to the general public and local health centers and pharmacies and provide an avenue for the public to report incidence of adverse effects including poisoning. The reason for the significantly higher submissions to the PCCs is likely due to the fact that a reporter may be more inclined to file an adverse event and seek information on its management than to file a passive report with MedWatch.

AAPCC's 2005 Annual Report included 2228 cases of adverse reactions attributed to DSs, excluding homeopathic and hormonal products.⁴² The AAPCC report defines an adverse reaction as one that occurs with normal, labeled, or recommended use of the product as opposed to overdose, misuse, or abuse. The report lists 1383 cases with moderate outcomes, 101 cases with major outcomes, and 11 deaths.

For comparison, between June 2003 and March 2005, FDA's CAERS received approximately 1145 AERs that were submitted voluntarily by industry, HCPs, and consumers,⁴³ but PCCs registered 1926 cases with moderate and major outcome in 2004 alone. The gap in reporting AERs to MedWatch requires urgent attention. The 2001 OIG report recommended that FDA work with PCCs and state health departments to identify signals of possible public health concern.

Dietary supplement manufacturers

DSHEA does not require the collection or record keeping of DS AERs by manufacturers, nor does it mandate reporting AERs to MedWatch. However, the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006⁴⁴ (DSNDCPA, the Act, provisions effective from 22 December 2007) makes it mandatory for all DS and nonprescription drug manufacturers or distributors to file serious AERs to MedWatch. The Act defines a 'serious adverse event' as one that results in (i) death, (ii) a life-threatening experience, (iii) in-patient hospitalization, (iv) a persistent or significant disability or incapacity, or (v) a congenital anomaly or birth defect; or requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above.⁴⁴

According to the Act, the DS manufacturer, packer, or distributor (the responsible party) must submit to FDA within 15 business days, any report received regarding a serious adverse event associated with the DS when the product is used in the US, accompanied by a copy of the label on or within the retail package of the product.

The new law addresses one of the important issues raised by the 2001 OIG report, which observed that FDA lacked the actual product labels for 77% of DS associated with adverse events and was unable to determine ingredients in 32% of AERs. Further, by requiring the contact information of the responsible party on the product label, the Act addresses another major concern of the 2001 OIG report, which found that FDA was unable to determine the manufacturer of DS products for 32% of the products involved in reports.¹³

UNIQUE FACTORS REGARDING DIETARY SUPPLEMENTS

DSs differ from prescription and OTC drugs in several ways that affect the reporting and analysis of AERs. Contamination, adulteration, substitution, or misidentification of a dietary ingredient can occur.^{19,45–48} DeSmet and D'Arcy reported that 'many of the cases where herbal products have been associated with actual human poisoning were not in fact caused by herbs alleged to be in the product but resulted from substitution or contamination of the declared ingredient, intentionally or by accident, with a more toxic botanical, a poisonous metal, or a potent nonherbal drug substance'.⁴⁹ This situation may be ameliorated by the recent release of FDA's current Good Manufacturing Practices (cGMPs) for DSs. The DS cGMPs require proper manufacturing controls to be in place so that DS are processed in a consistent manner and meet quality standards.⁵⁰ Other standards to ensure product quality are in place. For example, *USP General Information Chapter Manufacturing Practices for Dietary Supplements <2750>*⁵¹ includes recommended cGMPs and discusses procedures, facilities, and controls that can be used in the manufacture of a DS product to ensure that it possesses the necessary quality attributes.

Unlike most prescription medications, many DS products contain multiple ingredients, which limits or precludes attribution of adverse events to a single ingredient. Some traditional medical systems, such as Ayurveda and Traditional Chinese Medicine, occasionally include heavy metals and toxic herbs as part of their therapeutic approach. Studies have shown that certain DS products from India and China contained significant levels of heavy metals, toxic herbs, and undeclared pharmaceuticals.^{52–56}

Practitioners who evaluate DS AERs also must consider the potential for drug–DS interactions. Working with an underdeveloped AER coding system for DS makes it difficult to record and retrieve data regarding particular ingredients. The lack of a well-developed coding system (*cf.* MedDRA)⁵⁷ for DS could be a major limitation in the performance of pharmacovigilance and pharmacoepidemiology. FDA and PCCs could undertake an important public health initiative by developing a standardized coding terminology for DS or by adopting the classification system developed by the WHO Uppsala monitoring center.⁵⁸

CONCLUSION AND RECOMMENDATIONS

During its review of safety information for DS ingredients, DSI-EC noted that many AERs are

Table 2. Some recommendations from different organizations to improve the status of DS adverse event reporting

Professional organization	Recommendations
Inspector General Report (OIG): adverse event reporting for dietary supplements—an inadequate safety valve ¹³	<ol style="list-style-type: none"> 1. Facilitate greater detection of adverse events. Contract with PCCs to obtain their adverse event reports about DS. Inform health professionals and consumers about the adverse event reporting system for dietary supplements 2. Obtain more information about adverse event reports in order to generate stronger signals of public health concerns. Educate health professionals about the importance of including medical information in adverse event reports. Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party. Develop a new computer database to track and analyze adverse event reports 3. Obtain vital information to adequately assess signals generated by the adverse event report system. Issue guidance on the type of safety information that manufacturers should include in the 75-day premarketing notification requirement for some new DS ingredients 4. Explore the possibility of a DS monograph system that would contain safety information about particular ingredients 5. Collaborate with the National Institutes of Health in setting a research agenda that addresses safety issues 6. Assist industry and USP in standardizing DS ingredients, particularly botanicals
Institute of Medicine (IOM): dietary supplements—a framework for evaluating safety ¹⁴	<ol style="list-style-type: none"> 1. FDA should maintain and refine a prospective, systematic monitoring and tracking mechanism for DS 2. Congress must provide adequate resources to protect the consumer under DSHEA 3. AERs: FDA should continue to work with PCCs as a source of adverse event reports, and Congress should provide sufficient resources to support this activity. FDA should increase efforts to inform health care professionals and consumers about the MedWatch adverse event reporting program with respect to DS 4. To initiate the 75-day premarketing review period, Congress should require both the distributor and manufacturer to provide FDA with all available data—favorable and unfavorable—regarding the safety of the product 5. When a manufacturer changes the formulation or processing of a DS ingredient, the substance should be considered a new dietary ingredient and should be subject to regulatory oversight as such 6. IOM recommends the continued development of effective working relationships and partnerships among FDA, other federal agencies, and interested groups regarding research to further evaluate safety concerns associated with DS 7. IOM believes that all federally supported research on DS efficacy should be required to include the collection and reporting of safety data <p>This publication provides helpful guidelines for adverse event reporting</p>
International Society for Pharmacoepidemiology (ISPE) and the International Society of Pharmacovigilance (ISoP)—guidelines for submitting adverse event reports for publication ¹⁶	
The American Society of Health-System Pharmacists (ASHP) ¹⁷	<ol style="list-style-type: none"> 1. ASHP believes that DS, at minimum, should receive FDA approval for evidence of safety and efficacy; meet manufacturing standards for identity, strength, quality, purity, packaging, and labeling; and undergo mandatory postmarketing reporting of adverse events including drug interactions 2. ASHP urges pharmacists and other health care practitioners to integrate awareness of DS use into everyday practice and encourages pharmacists to increase efforts to prevent interactions between DS and drugs 3. ASHP supports the education of pharmacists and other health care practitioners regarding the taxonomy, formulation, pharmacology, and pharmacokinetics of DS
American Society for Clinical Pharmacology and Therapeutics (ASCPT): position statement on dietary supplement safety and regulation ¹⁸	<ol style="list-style-type: none"> 1. Provide legislation and funding to enable FDA to establish procedures to improve detection of AEs associated with dietary supplements, obtain better data about AE reporting, improve the assessment of AER data, and improve the dissemination to consumers of AERs associated with dietary supplements 2. Implement FDA's DS cGMPs because they promote and protect public health 3. Implement the recommendations of the Department of Health and Human Services Inspector General regarding the template for labeling DS, and provide additional contact information on DS labels for consumers 4. Provide enhanced education about DS to health care professionals and consumers 5. Enhance research opportunities about the potential adverse effects, as well as possible efficacy, of DS

difficult to interpret because of incomplete medical/case information, lack of product name or manufacturer, and confounding variables such as patients' alcohol use, concurrent medications, and other pre-existing risks. Major factors that influence the reliability of DS AERs are the identity and quality of the products. Regrettably, most DS products are not appropriately identified, analyzed, or characterized in the majority of AERs, which makes difficult the assignment of definitive causality to the product. DSI-EC has found that its concerns about the shortcomings of DS adverse event reporting systems are shared by other governments and professional organizations.^{13–19} Table 2 summarizes some of the recommendations from these organizations, and DSI-EC supports many of them.

Specifically, DSI-EC makes the following proposals to improve the quality of reporting, monitoring, and assessing DS AERs:

A. Recommendations for Educating HCPs:

- DSI-EC encourages all health care providers to contact MedWatch, their local PCCs, and/or the DS manufacturer when they suspect a DS adverse event.
- DSI-EC encourages health care providers to ask and counsel patients about their use of DS, as well as to document such use in the patient chart alongside prescription and over-the-counter products.
- DSI-EC encourages FDA to review the MedWatch program's user interface to ensure its user friendliness and capacity to collect appropriate data. (Table 1 shows a list of minimal medical information for an ideal MedWatch case report.)
- DSI-EC encourages MedWatch and the AAPCC to create appropriate DS coding systems that will allow accurate data recording and retrieval.
- DSI-EC recommends that MedWatch and the AAPCC collaborate to create guidelines that promote reporting of complete information in DS AERs.
- DSI-EC encourages hospitals and health systems to create internal hospital policies and train their staff about appropriate reporting of DS AERs.
- DSI-EC encourages educational services such as the Accreditation Council for Pharmacy Education and other qualified organizations to offer training during meetings and conferences and in cooperation with other stakeholders regarding reporting DS AERs. These courses could carry

continuing medical education/continuing education credits.

B. Recommendations for manufacturers:

- DSI-EC supports recent legislation concerning mandatory reporting to FDA by DS manufacturers and distributors when the later learn of serious adverse events associated with their products.
- DSI-EC supports implementation of DS cGMPs to address potential quality control issues in DS AERs and encourages the use of public standards to set specifications for dietary ingredients.
- In the event of a DS AER, DSI-EC recommends that the manufacturer should retain the product so that it can be tested if necessary.

C. Recommendations for safety research and monitoring:

- DSI-EC recommends that scientists include DS safety in their research programs (e.g., testing for herb–drug interactions and testing with use during pregnancy).
- DSI-EC recommends that the databases from MedWatch, PCCs, and other international agencies be analyzed by an interested governmental agency or private body periodically for DS AER signals and trends that may warrant formal safety reviews.

KEY POINTS

- The Dietary Supplement Health and Education Act of 1994 regulates DSs in the United States. Compliance with compendial monograph quality standards is voluntary.
- Many DS AERs are difficult to interpret because of incomplete information, and some unique confounding variables..
- A Food and Drug Administration (FDA)-commissioned study estimated that the agency receives fewer than 1% of all AERs associated with DSs..
- Although FDA has established MedWatch to collect DS AERs, poison control centers in the US apparently receive more such reports..
- In this report, Dietary supplement Information Expert Committee (DSI-EC) of the United States Pharmacopeia (USP) reviewed the status of DS AERs and made recommendations for improving the quality of reporting, monitoring, and assessing DS AERs.

- DSI-EC recommends the development of a validated quality scoring system to assess the quality of DS AERs.
 - To ensure proper compliance with these cGMP rules and to improve the safety of DS, FDA needs additional funding for the proper oversight functions.
- D. Tools for identification and standardization:
- DSI-EC supports the development and use of reference standards for establishing the identity and quality of DSs.

ACKNOWLEDGEMENTS

DSI-EC thanks Stefan Schuber, PhD, director, scientific reports, for his editorial assistance.

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