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National surveillance of herbal dietary supplement exposures: the poison control center experience†

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SUMMARY

Purpose—The purpose of this report is to characterize reports to poison control centers (PCCs) involving two widely used herbal dietary supplements (HDSs), *Echinacea*, and St. John’s wort (SJW).

Methods—We purchased data from the American Association of Poison Control Center’s (AAPCC) toxic exposure surveillance system (TESS®) on reports made to PCCs in 2001 involving *Echinacea* or SJW. Analyses were limited to those cases in which *Echinacea* or SJW were the only associated products, and in which these HDSs were deemed primary to observed adverse effects. Descriptive statistics were generated for selected demographic and exposure-related variables.

Results—During 2001, PCCs were contacted regarding 406 exposures involving *Echinacea* and 356 exposures involving SJW. Most of the reported exposures for both HDSs occurred among children 5 years and younger, and the majority of exposures were coded as unintentional. For both HDSs, exposures among patients ≥20 years old were more likely to be associated with adverse effects. Intentional exposures accounted for 21% of SJW cases and 3% of *Echinacea* cases, with 13% of SJW exposures reported as ‘suspected suicidal’.

Conclusions—TESS® represents a potentially important means of assessing and characterizing HDS-related adverse effects. Detailed studies validating the clinical events and outcomes of a sample of exposures reported to TESS® might offer substantial insights into adverse events (AEs) that could be systematically studied with other, established pharmacoepidemiological study designs.

Keywords

herbal dietary supplements; post-marketing surveillance; alternative medicine; complementary medicine; integrative medicine

INTRODUCTION

The 1-year prevalence rate of herbal dietary supplement (HDS) use has increased dramatically in the US, from 2.5% of the population in 1990, to 12.1% in 1997;¹ a more recent survey reports HDS use in the previous week at 13.9% in 2002,² and consumers spent nearly \$4.4 billion on HDSs in 2001.³ While many consumers of HDSs perceive them to be ‘natural’ and

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therefore ‘harmless’,⁴ research on the marketing of these products,⁵ herb–drug interactions,⁶ and adverse effects linked to HDSs⁷ has raised concerns about their efficacy, quality, and safety.^{8,9}

Current law dictates that HDSs are regulated like foods,^{10,11} and manufacturers are not required to demonstrate therapeutic efficacy, quality, safety, or to perform pre-marketing clinical trials and research.¹² Product standardization and quality are evolving and voluntary.¹³ Attempts to characterize adverse events (AEs) associated with dietary supplements (DSs) are generally limited to clinical observation and voluntary reporting mechanisms. Voluntary or ‘spontaneous’ reporting systems often contain incomplete information on various aspects of the reported AEs, including the product in question, adverse effect management, and clinical outcome.¹⁴ However, such systems can both act to alert clinicians and researchers of rare AEs, and can generate hypotheses to be tested in clinical and epidemiological studies.¹⁵

American association of poison control centers statement on AAPCC data

The American Association of Poison Control Centers (AAPCC; <http://www.aapcc.org>) maintains the national database of information logged by the country’s 61 poison control centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

In the absence of required pre-marketing trials and pending the implementation of mandatory post-marketing reporting by DS firms, the AAPCC toxic exposure surveillance system (TESS[®]) represents one potentially important source of information on consumer experiences with HDSs.¹⁶ In 2001, the AAPCC began collecting reported exposures involving botanical products separately from other DSs, comprising 12 219 exposures.¹⁷

Here we describe reports to PCCs in 2001 that involved the HDSs *Echinacea* or St. John’s wort (SJW). These two HDSs were selected due to their wide use among US adults,¹⁸ and because they are the signal herbs under study by the Iowa Botanical Supplements Research Center. In 2002, an estimated 38% of the civilian, non-institutionalized population in the US reported using *Echinacea* in the past 12 months.¹⁹ Three species of *Echinacea*—*E. purpurea*, *E. angustifolia*, and *E. pallida*—typically are used to treat and/or prevent the common cold and other infections. Eleven percent of the adult US population reported using SJW in 2002.¹⁹ SJW (*Hypericum perforatum*) historically has been used to treat a variety of ailments, including ‘fever, coughs, and bowel complaints’,²⁰ malaria, and insomnia, although in the US and Europe it is primarily used to treat depression.²¹

Prior research on AEs associated with DS exposures using PCC data has been reported,^{22–24} but to the best of our knowledge this is the first paper to utilize national TESS[®] data to report on exposures associated with specific HDSs.

METHODS

TESS[®] includes information on patient demographics, substance information, medical outcomes and adverse effects, and other variables related to reported exposures, including exposure management. TESS[®] receives reports obtained via phone calls from health

professionals and the general public via a standardized form.²⁵ Follow-up contacts continue until it is determined that clinical manifestations have subsided.²⁶

We purchased TESS[®] data²⁷ from the AAPCC that contained reported human exposures (excluding information calls) in 2001 to mono-preparations of *Echinacea* or SJW HDSs that were intended for human consumption. Some cases involved exposure to one or more substances in addition to *Echinacea* or SJW HDSs. Using the Poisindex[®] database, we identified and categorized concomitant substances via the coding scheme employed in the Poisindex[®].

When concomitant substances were involved in a reported exposure, a TESS poison specialist ranked them in order of their relative contribution to observed adverse effects. We limited our analyses to (1) those cases in which *Echinacea* or SJW was the *only* substance identified in a particular case and (2) those cases involving multiple substances in which *Echinacea* or SJW was ranked as the *primary* substance contributing to observed adverse effects.

Variable definitions and coding

We employed AAPCC definitions²⁷ for variables used in our analyses: number and type of concomitant substances, patient age and gender, relative contribution of concomitant substances to adverse effects, route and site of exposure, place of exposure management, provision and type of therapy, exposure reason and chronicity, medical outcome, and duration and type of adverse effects. Any deviations from AAPCC definitions are described below.

Data on patient age were provided in the TESS[®] database both as specific years old (e.g., '23 years'), and age group (e.g., '40s', 'unknown child ≤19 years'). From these categories, we regrouped patient age into ≤5 years, 6–12 years, 13–19 years, and ≥20 years; we also created an age group of <20 years which combined cases that contained patient information expressed in specific years old as well as age group.

For cases that involved concomitant substances, we combined similar substance categories for each HDS for report purposes. Also, for those exposures that involved three or more concomitant substances, we combined these substances into a single category.

Route of exposure was classified as ingestion, ocular, dermal, or unknown route. Site of exposure was coded as the patient's own residence, another residence (not the patient's), workplace, school, public area (e.g., a park or theater), health care facility (HCF), or other site. Chronicity of exposure was defined as follows: An *acute exposure* is 'a single, repeated, or continuous exposure occurring over a period of 8 hours or less'. A *chronic exposure* is 'a single, repeated, or intermittent exposure to the same substance lasting longer than 8 hours'.

Reason for exposure was classified as unintentional or intentional, or as an adverse reaction. *Unintentional* exposures were those which resulted from an unforeseen or unplanned event: *Unintentional-general* exposures are 'all unintended exposures that are not specifically defined' by other unintentional categories (e.g., most of the unintentional exposures in children). A *therapeutic error* is 'an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administering of the wrong substance'. *Unintentional misuse* is defined as the 'unintentional improper or incorrect use of a non-pharmaceutical substance'. An *environmental* exposure is 'any passive, non-occupational exposure that results from contamination of air, water, or soil'. *Unintentional unknown* refers to 'an exposure determined to be unintentional but the exact reason is unknown'.

An *intentional* exposure is a purposeful action which resulted in an exposure: *Suspected suicidal* exposures were those resulting ‘from the inappropriate use of a substance for self destructive or manipulative reasons’. An exposure was defined as *intentional abuse* if it resulted ‘from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effects, or some other psychotropic effect’. *Intentional misuse* refers to ‘an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect’. An *intentional unknown* exposure is one ‘determined to be intentional but the specific motive is unknown’. *Adverse reaction* refers to a

‘category ... used to monitor adverse reactions to a variety of products, including drugs, foods, cosmetics, and industrial or household products. Adverse reactions are those that occur with normal, prescribed, labeled, or recommended use of the product, as opposed to situations involving overdose, misuse, or abuse of the product’.

Adverse reactions are classified by whether the exposure resulted from a drug (includes DSs), food, or other products (e.g., dermatitis associated with jewelry). Finally, *unknown* exposures are those in which ‘the reason for the exposure cannot be determined or if no other category is appropriate’.

Management site was also examined as it may provide an indication of the cost of exposure management. The exposure was managed *on-site* ‘if the patient is treated at home or any other non-health care site’. Management site was coded as *HCF* if ‘at the time of the initial contact with the center the patient is already in or *en route* to an HCF or was already treated or evaluated for the exposure in an HCF’. Cases that were referred to a primary care HCF as part of the management recommendation by the specialist were termed *referred to HCF*. *Other* ‘refers to any management site not identified above’.

Each case was coded for whether a therapy was provided or not. Cases in which therapy was not provided were coded as no therapy, the patient refused help, observation only, or unknown if any therapy was provided. Specific therapies were provided for each case in which therapy was recommended, performed, or recommended and performed, and multiple therapies could be indicated. *Administration of food/snack* was defined as the ‘administration of milk or other food as a demulcent or administration of sugar-containing food or drink or avoid hypoglycemia’. *Dilution/irrigation/washing* was defined by the AAPCC as:

1. Administration of water or fluid to decrease the concentration of a substance,
2. Removal of a substance from the eye or skin by flooding the area with water,
3. Cleansing with soap or detergent,
4. Using a solvent to aid removal,
5. Nasal or aural irrigation.

Those exposures followed to a known outcome were classified as having minor, moderate, or major adverse effects: For *minor effects*, ‘patients exhibited some symptoms as a result of the exposure, but they were minimally bothersome ... [and] usually resolve rapidly and usually involve skin or mucous membrane manifestations’. *Moderate effects* ‘are more pronounced, more prolonged or more of a systemic nature than minor symptoms ... [and] usually some form of treatment is or would have been indicated’. A *major effect* is the one in which ‘the patient has exhibited symptoms as a result of the exposure which was life-threatening or resulted in significant residual disability or disfigurement’.

Cases that were not followed to a known medical outcome were coded as resulting in potentially, minimally, or non-toxic effects: *Potentially toxic* refers to cases in which ‘the

patient was lost to follow-up ... and the exposure was significant and may have resulted in toxic manifestations with a moderate, major, or fatal outcome'. The outcome was coded as a *minimal effect* when 'the patient was not followed because ... the exposure was likely to result in only minimal toxicity of a trivial nature'. *Non-toxic* outcomes are those in which the poison specialist was 'reasonably certain that the patient will not experience any clinical effect from the exposure'.

Duration of adverse effects was provided for exposures that involved minor or moderate medical outcomes. Duration was categorized as ≤ 2 hours, > 2 hours to ≤ 24 hours, and > 24 hours.

The AAPCC defines 'clinical effects' as 'all reported signs, symptoms, and clinical findings associated with an exposure'. However, we employ the term *adverse effects* henceforth to describe such effects as described by AAPCC because all effects described are of an adverse nature. Thus, adverse effects were categorized according to the major organ system affected, and were available only for those cases in which the effects were deemed 'related' to the reported exposure by a poison information specialist. We separately calculated adverse effects for those cases coded as suspected suicides.

Data on other patient demographics and health care characteristics, such as race/ethnicity, household composition, marital status, employment and income, education, health insurance status, religion, and urban/rural residence, were not available in the TESS[®] dataset.

Analyses

Frequencies and percentages for variables described above were calculated using SAS 9.0²⁸ and calculations were performed separately for *Echinacea* and SJW exposures. For a subset of variables frequency and percentages were calculated by age group: gender, place of exposure management, provision and type of therapy, medical outcome, and duration and the type of adverse effects. Tabulations of concomitant substances involved in HDS-associated exposures were conducted manually.

This study was performed on anonymous data and there was no risk to the original participants. This study is part of a project that was approved by the University of Iowa Institutional Review Board.

RESULTS

The TESS[®] data included 516 reported exposures involving *Echinacea* and 488 reported exposures involving SJW. We excluded cases in which *Echinacea* or SJW were not deemed primary in terms of their contribution to observed adverse effects (as described above), resulting in 406 cases involving *Echinacea* and 356 cases involving SJW, which are the focus of the remainder of this paper. Among these, 352 reports involved *only Echinacea*, and 289 reports involved *only SJW*; 54 *Echinacea* cases and 67 SJW cases involved more than one substance (see Table 1).

Table 2 lists patient gender and age according to HDS exposure. Almost three-fourths of *Echinacea* exposures involved children 5 years and under, while just over one-half of SJW exposures involved children in this age range. Among persons 20 years and older, a greater proportion of exposures involved females. About 55% of all *Echinacea* exposures involved females; for SJW exposures the gender distribution was nearly evenly divided.

Table 3 presents concomitant substances involved in *Echinacea* or SJW exposures. Among *Echinacea* exposures involving concomitant substances, vitamins-electrolytes-minerals were

the most frequent concomitant substances, followed by prescription and over-the-counter medications and plants. Prescription and over-the-counter medications were the most frequent concomitant substances among SJW exposures.

All but two *Echinacea* exposures and four SJW exposures occurred via ingestion. Other exposure routes involving more than one case were ocular (*Echinacea*) and dermal (SJW). There were six cases involving two exposure routes, and two cases where the route was unknown (data not shown).

The majority of exposures to either HDS occurred in the patients' own residence (*Echinacea* - 95.8%; SJW - 91.9%). Eleven *Echinacea* exposures (2.7%) occurred at another residence, with public areas or health care facilities ($N = 2$, 0.5%) and other sites ($N = 4$, 1.0%) comprising the remaining locations. Other SJW exposure sites included a residence other than the patients ($N = 12$, 3.4%), workplace ($N = 6$, 1.7%), school ($N = 5$, 1.4%), and public area or HCF ($N = 4$, 1.1%). Two SJW exposure sites were unknown.

As presented in Table 4, *Echinacea* exposures were somewhat more likely to be acute compared to SJW exposures. Chronic SJW exposures were reported at nearly twice the rate of chronic *Echinacea* exposures.

The majority of exposures to either HDS were unintentional, with a greater percentage of *Echinacea* exposures (86.5%, vs. 65.7% for SJW) occurring in such a manner (Table 4). Likewise, unintentional -general exposures comprised the majority of cases. Adverse reactions accounted for about one-tenth of cases involving either HDS. Overall, intentional exposures accounted for 21% of SJW exposures, but only 3% of *Echinacea* exposures. Whereas only 2% of all *Echinacea* exposures were coded as suspected suicidal, this category accounted for 13% of SJW exposures.

Table 5 presents place of exposure management and distribution of therapy provision by age grouping (<20 years, ≥20 years) for both HDSs. Considerable variation emerged concerning where exposures were managed, both between HDSs and age groups. Exposures involving *Echinacea*, and persons under 20 years, were more likely to be managed at a residence or other non-health care site. A considerably greater percentage of SJW exposures were either referred to an HCF or were managed at or *en route* to one. Across *Echinacea* and SJW exposures, both age groups experienced highly similar patterns concerning whether any therapy was provided. Notably, therapy was provided for both HDSs at a moderately greater rate to patients under 20 years.

For exposures involving both HDSs, decontamination therapies accounted for the majority of therapies performed, or recommended and performed. Among patients under 20 years, dilution/irrigation/washing was performed or recommended and performed in 41.0% ($N = 132$) of exposures involving *Echinacea* and 50.4% ($N = 119$) of exposures involving SJW; administration of food/snack in this age group was performed or recommended and performed in 9.6% ($N = 31$) of *Echinacea* exposures and 8.9% ($N = 21$) of SJW exposures. Administration of a single dose of activated charcoal (*Echinacea*: $N = 30$; SJW: $N = 6$) was the next most frequently performed or recommended and performed specific therapy. Dilution/irrigation/washing and administration of food/snack were the most frequently recommended therapies for both HDSs.

The majority of *Echinacea* (92.5%) and SJW (84.3%) exposures in patients under 20 years were deemed non- or minimally-toxic, or resolved with no adverse effects (Table 6). Adverse effects were more likely to be present in patients 20 years and older. This pattern was sustained for moderate and potentially toxic effects as well, for both HDSs. Overall, adverse effects were more likely to be reported for SJW than *Echinacea* exposures.

In patients for whom minor or moderate medical outcomes were reported, some differences emerged as to the duration of adverse effects. For *Echinacea* exposures, around half of reported adverse effects lasted 2 hours or less (<20 years: 55%, $N = 5$; >20 years: 45%, $N = 9$). In comparison, a greater proportion of SJW exposures resulted in adverse effects that persisted greater than two and less than or equal to 24 hours (<20 years: 60%, $N = 15$; ≥ 20 years: 43%, $N = 16$). Minor or moderate adverse effects lasted more than 24 hours in seven cases (*Echinacea*—2; SJW—5). Among these, all but one SJW exposure occurred among patients 20 years or older.

Specific adverse effects associated with *Echinacea* and SJW exposures, and an explanation, are available at <http://www.public-health.uiowa.edu/epi/electronic-pubs/BG-Appendix0407.pdf>.

DISCUSSION

This article examined reports to 64 PCCs across the US in 2001 involving reported exposures to *Echinacea* or SJW HDSs. Patient demographics, exposure characteristics and management, medical outcomes, and adverse effects were described for these cases in an attempt to extend what is known about exposures and AEs associated with these HDSs. Only a minority of reported exposures to either HDS resulted in AEs, and all such medical outcomes were reported as minor or moderate effects. A considerable proportion of additional cases were deemed potentially toxic but were not tracked to the resolution of adverse effects.

We found that many reported exposures were coded by poison control specialists as intentional, especially those related to SJW. The FDA recently released a public health advisory on certain pharmaceutical anti-depressants, cautioning physicians to closely monitor patients taking these medications for worsening of depressive symptoms or suicide attempts.²⁹ A recent report documented a case of suicidal ideation and homicidal thoughts associated with the consumption of an SJW extract, which resolved upon the cessation of product use.³⁰ Future research could help clarify the relationship between SJW use and suicide. In particular, it would be important to know whether serious clinical outcomes are manifested in patients who consume high amounts of SJW. Such research could have implications for establishing safe dosing levels of SJW.

Rates of general pediatric HDS use are less than those of adult populations, and vary considerably depending on the population studied.³¹ In the present analyses, the majority (51–73%) of HDS exposures occurred among children 5 years and younger, but a considerably greater proportion of adult exposures resulted in an adverse effect. These findings are consistent with reporting patterns to PCCs, which historically involve young children,^{32,33} augmenting previous research on AEs associated with DS use among children utilizing PCC data.^{22–24} Most of the pediatric exposures were unintentional, suggesting that some children may have had unsupervised access to these HDSs. This raises the possibility that child-resistant DS containers should be considered. Pediatric exposures may also occur because parents or others offer children HDSs, believing them to be natural and safe. In this case, warnings on containers about the consequences of pediatric use, if indicated, should be provided.

Higher percentages of patients 20 years and older exposed to *Echinacea* or SJW initially were referred either to an HCF by a PCC specialist or were at or *en route* to an HCF when the PCC was contacted. In contrast, pediatric exposures were more likely to be provided therapeutic advice and management that took place in the home. It is possible that many of the unintentional exposures were not symptomatic, and thus were managed expectantly or with general approaches taken upon ingestion of smaller amounts of substances not known to be greatly toxic. Adults, however, may have been more likely to choose to seek medical care because the

advent of clinical signs and symptoms were perceived to be in need of diagnosis and management.

Differences in adverse effect severity between younger and older age groups may also reflect varied reporting practices. Poisonings involving children, especially children 3 years and younger, are associated with high rates of PCC consultations.¹⁶ While we are unaware of research that specifically examined PCC reporting rates for DS exposures involving adults, some research suggests that adults are less likely to consult a physician following adverse effects to HDSs compared to prescription or over-the-counter medications.³⁴

As with adverse drug reactions, AEs involving DSs can be categorized into three broad categories: Effects occurring immediately after exposure, effects materializing after long-term use, and effects presenting in the distant future after an exposure has ceased.³⁵ Using data from 11 PCCs, Palmer *et al.*²² reported that more severe adverse outcomes were associated with the chronic use of DSs. In our analyses, the majority of exposures associated with either HDS occurred within 8 hours after exposure. It may be that persons who experience adverse effects shortly after exposure to these herbs are more likely to contact PCCs, compared to those cases resulting from long-term use or involving a lengthier time interval between exposure and onset of adverse effects. Persons in these latter exposure categories may be more likely to visit their physician rather than contact a PCC, or they might not attribute adverse effects to the DS.³⁴ This latter scenario is perhaps more likely with SJW, similar to other anti-depressants, in which effects (beneficial and adverse) may not become apparent for several months.²² Unfortunately, detailed information on the scenarios surrounding these exposures was only available for a small number of case reports and thus was excluded from our analyses.

Thirty-five *Echinacea* exposures and 39 SJW exposures were characterized as encompassing adverse drug reactions. *Echinacea* generally is thought to have a favorable adverse effects profile, at least with short-term use.^{36,37} Reported adverse effects associated with *Echinacea* use include asthma, hepatitis, anaphylaxis,⁷ recurrent erythema,³⁸ and rash.³⁹ Additionally, there is some evidence suggesting that persons with certain pre-existing diseases or conditions, such as atopic disease, are more likely to develop adverse effects upon exposure to *Echinacea*.⁴⁰ Adverse effects associated with SJW are thought to be comparable or more favorable to those observed in prescribed anti-depressants.^{41,42} Overall, adverse effects are estimated to occur in 1–3% of those taking SJW.⁴³

Medical outcomes for several cases, especially those involving SJW and older patients, were coded by a poison control specialist as potentially toxic. Although no conclusions can be drawn from these cases, they do raise the possibility that more serious adverse effects involving *Echinacea* and SJW HDSs were experienced but not tracked or fully reported.

Limitations

The limitations of TESS[®] data need to be considered when interpreting results of the above analyses. The structure of data collection methods used in TESS[®] restricts its epidemiological applicability. Ultimately, TESS[®] is subject to the limitations of any reporting system in which collected data are not verified. Calls are made to PCCs on a voluntary basis, and the exposure experiences and distribution among demographic variables described in TESS[®] may not be indicative of experiences in the general population.

Overall, TESS[®] data are likely to underestimate ‘known’ exposures.^{25,44} For example, it has been documented that poisoning deaths are substantially under-reported to PCCs.⁴⁵ Certain socio-demographic characteristics are associated with under-utilization of PCCs, and thus, TESS[®] data are likely to under-represent exposures among these groups. Studies have documented PCC underutilization among lower income and racial/ethnic minority households,

and in population-dense areas.^{46–49} It should be noted, however, that these studies were based on local or regional data, and thus it is not known whether the differential utilization patterns identified are specific to the respective sites studied, or by extension, to TESS[®] as a whole.

In TESS[®], reported, putative associations between substances and medical outcomes are only documented in part. Thus, reported substances associated with AEs cannot be deemed causative agents. In addition to the circumstances of HDS exposure, factors such as when and where the plant was grown, which part of the plant was used, processing and extraction techniques, the form and storage of the HDS, and the presence of other ingredients all may affect the relative safety and efficacy of HDSs.^{50,51} While more than four-fifths of reported exposures involved only single-ingredient *Echinacea* or SJW HDSs, it cannot be ruled out that some reported adverse effects stem from exposure to concomitant substances or underlying co-morbidity. Finally, it is possible that some HDSs requested in TESS[®] were not included in the data we received due to data transcription or coding errors.

Race/ethnicity, income, educational level, religion, health insurance status, patient history and co-morbidities, and other important demographic variables and medical history were not available through TESS[®]. We believe that it would be of value if AAPCC reporting protocols could be revised to make such variables available, although the resources required to do so may be considerable.⁵²

Despite these limitations, TESS[®] data can provide new insights into adverse experiences with individual HDSs. TESS[®] incorporates a structured data collection system, and individual PCC reports that ultimately become part of TESS[®] are subject to multiple quality control reviews mechanisms.⁵³ Also, chart reviews and individual PCC site visits are conducted periodically to ensure compliance with data collection protocols.²⁵ TESS[®] can serve as an important tool in generating hypotheses⁴⁴ concerning links between DSs and AEs.

In order to detect a rare AE associated with a particular DS, a prohibitively large sample of persons exposed to a particular DS may be necessary to obtain statistically significant observations.¹⁵ The PCCs that contribute data to TESS[®] serve nearly the entire US population, and thus TESS[®] data may be able to detect rare AEs involving DSs.¹⁷ Finally, firmly establishing causality between specific DS use and AEs, while desirable, is usually unlikely without further data collection. Despite this, as a recent Institute of Medicine report suggests, a ‘prominent degree of suspicion’, may be a sufficient standard on which to base decisions pertaining to DS safety regulatory decisions.⁵⁴

KEY POINTS

- Some exposures involving *Echinacea* and SJW HDSs occurred intentionally, and a subset of these were coded as ‘suspected suicidal’.
- Unintentional pediatric exposures involving HDSs may warrant consideration of child-resistant containers for these products.
- Despite its limitations, the TESS[®] represents an important means of assessing and characterizing HDS-related adverse effects.

Under the Dietary Supplement Health and Education Act of 1994, there is no requirement that DS manufacturers report AEs received from the public or health professionals to the FDA. However, the recently passed ‘Dietary Supplement and Non-prescription Drug Consumer Protection Act’ requires DS firms to report, beginning in December 2007, any serious AE to the FDA within 15 days of receiving the report.⁵⁵ It also requires firms to submit any new medical information to FDA received within 1 year of the initial reports, and to maintain records

on all AEs it receives for 6 years. Still, data from PCC reports offer important contributions to the surveillance of DS outcomes.

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Table 1Number of additional substances in exposures involving *Echinacea* or St. John's wort

Number of additional substances	<i>Echinacea</i>		St. John's wort	
	%	<i>N</i>	%	<i>N</i>
None	86.7	352	81.2	289
One	9.6	39	12.4	44
Two	2.5	10	3.9	14
Three or more	1.2	5	2.5	9
Total	100.0	406	100.0	356

Gender and age* among *Echinacea* and St. John's wort reported exposures

Column totals in this and subsequent tables may not add to exactly 100 due to rounding error.

Table 3
Concomitant substances reported among herbal dietary supplement exposures

Substance category	<i>Echinacea</i> (N = 54)		<i>St. John's Wort</i> (N = 67)	
	%	N	%	N
Vitamins/electrolytes/minerals	31.3	26	4.8	5
Prescription and over-the-counter medications*	24.1	20	55.2	58
Plants	21.7	18	7.6	8
Other dietary supp./herbals/homeopathic	15.7	13	17.1	18
Stimulants and street drugs	3.6	3	3.8	4
Other chemicals/products**	2.4	2	1.0	1
Alcohol (beverage)	1.2	1	10.5	11
Total (% within all cases)	100.0	83 [†]	100.0	105 [‡]

* Includes analgesics, anti-depressants, hormones and hormone agonists, sedatives, hypnotics, anti-anxiety, anti-psychotics, cold/cough preparations and anti-histamines, cardio-vascular drugs, muscle relaxants, nose/nasal preparations, gastro-intestinal preparations, anti-microbials, anti-convulsants, and 'miscellaneous' and 'unknown' drugs.

** Includes food products, cosmetics, and 'other chemicals'.

[†] Excludes one case in which the 'substance' took the form of a question about a food product.

[‡] Excludes four cases for which substance category information was unavailable.

Table 4
Circumstances surrounding *Echinacea* and St. John's wort exposures

	<i>Echinacea</i>		St. John's wort	
	%	N	%	N
Chronicity				
Acute	91.6	372	85.4	304
Chronic	3.2	13	6.2	22
Acute-on-chronic	4.3	18	7.0	25
Unknown	0.7	3	1.4	5
Total	100.0	406	100.0	356
Reason for exposure				
Unintentional	86.5	351	65.7	234
Unintentional—general	80.8	328	60.4	215
Therapeutic error	4.2	17	3.9	14
Unintentional misuse	1.5	6	0.8	3
Unintentional unknown/other *	0.0	0	0.6	2
Intentional	3.2	13	21.1	75
Suspected suicidal	2.0	8	13.2	47
Intentional abuse	0.0	0	3.1	11
Intentional misuse	1.0	4	2.8	10
Intentional unknown	0.2	1	2.0	7
Adverse Reaction	10.1	41	11.8	42
Drug (includes DSs)	8.6	35	11.0	39
Other **	1.5	6	0.8	3
Unknown	0.2	1	1.4	5
Total	100.0	406	100.0	356

* Includes one unknown, unintentional exposure and one case involving an environmental exposure.

** Includes food and dermatological exposures.

Table 5
Place of management and provision of therapy among *Echinacea* and St. John's wort exposures, by age*

	<i>Echinacea</i>				<i>St. John's wort</i>			
	<20 years		≥20 years		<20 years		≥20 years	
	%	N	%	N	%	N	%	N
Place of management								
On-site	94.1	303	63.9	53	78.0	184	41.1	46
HCF**	3.4	11	22.9	19	9.7	23	36.6	41
Referred to HCF	1.9	6	6.0	5	11.9	28	21.4	24
Other	0.0	0	4.8	4	0.0	0	0.0	0
Unknown	0.6	2	2.4	2	0.4	1	0.9	1
Total	100.0	322	100.0	83	100.0	236	100.0	112
Provision of therapy								
Yes	47.8	154	34.9	29	53.8	127	32.1	36
No	16.8	54	24.1	20	11.0	26	19.6	22
Observation only	19.3	62	26.5	22	19.1	45	23.2	26
Patient refused help	0.0	0	0.0	0	1.3	3	8.0	9
Unk. if therapy provided	16.2	52	14.5	12	14.8	35	17.0	19
Total	100.0	322	100.0	83	100.0	236	100.0	112

* Age information not available for one and eight cases involving *Echinacea* and St. John's wort, respectively.

** HCF, health care facility.

Table 6
Reported medical outcomes of exposures to *Echinacea* and St. John's wort, by age*

Medical outcome	<i>Echinacea</i>			St. John's wort		
	<20 years		≥20 years	<20 years		≥20 years
	%	N	%	%	N	%
Any adverse effect	3.4	11	28.9	14.4	34	46.4
Minor effect	2.8	9	18.1	8.5	20	17.9
Moderate effect	0.0	0	6.0	2.1	5	15.2
Potentially toxic	0.6	2	4.8	3.8	9	13.4
Non-/min. toxic**	68.6	221	38.6	50.0	118	25.0
No effect	23.9	77	8.4	34.3	81	9.8
Unrelated effect	4.0	13	24.1	1.3	3	18.8
Total	100.0	322	100.0	100.0	236	100.0

* Age information not available for 8 and 24 cases involving *Echinacea* and St. John's wort, respectively.

** Refers to those exposures deemed non-toxic or minimally toxic and for which no follow-up call was made.