



## Selected Topics: Toxicology

### SALVIA DIVINORUM: EXPOSURES REPORTED TO A STATEWIDE POISON CONTROL SYSTEM OVER 10 YEARS

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□ **Abstract—Background:** *Salvia divinorum*, a hallucinogenic herb, has in recent years become popular among teenagers and young adults. Salvia is presently marketed as a “legal” alternative to other drugs of abuse, but little is known about the clinical toxicity of this substance. **Objectives:** The purpose of this study is to describe the clinical and demographic features of this emerging substance of recreational abuse using data obtained from the records of a poison control center. **Methods:** We performed retrospective review of exposures to the herbal hallucinogen *Salvia divinorum* as reported to the California Poison Control System (CPCS) over the last 10 years. Demographic and clinical data were collected and compiled from the computerized records of the CPCS for the search terms “salvia” and “sage.” **Results:** There were 37 exposures to *S. divinorum* and 96 exposures to non-hallucinogenic *Salvia* species. Eighteen (49%) of the exposures were to *S. divinorum* alone. Intentional *Salvia* exposures resulted in a variety of neurologic, cardiovascular, and gastrointestinal effects. Notably, the use of concomitant substances of abuse was associated with a high rate of complications and psychomotor disturbances. **Conclusions:** Intentional use of *S. divinorum*, whether alone or in combination with alcoholic beverages and other drugs, causes neurologic, cardiovascular, and gastrointestinal effects. This poison-center-based review helps to characterize the clinical toxicity of *S. divinorum*, but more clinical and pharmacologic research is warranted for this rapidly emerging substance of abuse. © 2009 Elsevier Inc.

□ **Keywords—***Salvia divinorum*; hallucinogen; poison control center

#### INTRODUCTION

*Salvia divinorum* is a perennial species of sage with hallucinogenic properties originally found in Northern Mexico (Figure 1). Also known as “Diviner’s Sage,” “Mystic Sage,” and “Magic Mint,” *S. divinorum* was originally used by the Mazatec population for shamanistic purposes, and continues to be used in the religious rites of some indigenous Mexican cultures (1). Since the mid-1990s, *S. divinorum* has become more readily available for consumers. Various preparations are being sold openly at smoke (“head”) shops as well as through multiple Internet retailers, where it is sold as an herbal extract to be smoked for recreational purposes (Figure 2). *S. divinorum* use/abuse is becoming increasingly popular among both adolescents and adults (2,3). *S. divinorum* intoxication videos have become a popular type of submission on widely accessed open Internet sites such as “YouTube” (4,5).

At present, the clinical effects of *S. divinorum* are not well defined. A literature search in the PubMed database in December 2008 revealed no clinical case reports or case series on the acute toxic effects of *S. divinorum*. Despite this paucity of published data, many states in the United States, as well as international governing bodies, have proposed listing this plant as a scheduled or illegal substance (6,7). This retrospective study describes the clinical and demographic details of inquiries made to a



**Figure 1.** Picture of *Salvia divinorum*, a perennial sage species indigenous to Northern Mexico. Source: [http://www.cahuinadencul.com.ar/fotos/planta\\_salvia\\_divinorum.jpg](http://www.cahuinadencul.com.ar/fotos/planta_salvia_divinorum.jpg).

statewide poison control network regarding exposures to *S. divinorum* and non-hallucinogenic *Salvia* species over a 10-year period.

## METHODS

We performed a retrospective study of all *Salvia* species exposure cases reported to the California Poison Control System (CPCS) from January 1998 to May 2008. Information collected from the search results included: patient age and gender; the dose, formulation, and route of exposure to *Salvia divinorum*; other medications or substances coingested; symptoms reported; laboratory results; duration of effects; and length of stay for those patients treated in a health care facility. The data were collected and tabulated using a standardized spreadsheet template. Verbatim entries were made for qualitative or descriptive data, and when a data parameter was not reported, the entry was flagged as “NR.” Patients whose outcome or clinical course was unavailable or unreported at the time of the review were noted as “lost to follow-up.” Descriptive data included items such as unique physical examination findings as well as the content and nature of hallucinations or thought disturbances. These were noted in an attempt to further define a specific toxic

syndrome from *Salvia* exposure. The study was reviewed and approved by our institution’s Investigational Review Committee.

## RESULTS

A total of 133 cases were identified in the CPCS database. The average age of patients was 11 years (range 1–71 years), and 77 (58%) were male. The distribution of exposures by age (including both *S. divinorum* and non-divinorum exposures) were as follows: 86 exposures in children aged < 10 years old, 23 exposures in teenagers 15–20 years old, and 22 exposures in adults over 21 years old. (There were no exposures in patients aged 11–14 years, and ages were not noted in two case records).

One hundred cases were managed at home; 33 cases were evaluated in a health care facility, and 5 patients were admitted to the hospital.

The cases fell into two broad and demographically distinct categories: exposures due to *Salvia divinorum* (which is the only *Salvia* species known to be hallucinogenic), and exposures to non-divinorum *Salvia* species.



**Figure 2.** Picture of the herbal extract of *Salvia divinorum*. Note the concentration label “40×” with no other units of measurement provided. This is typical of available specimens of *Salvia divinorum*. Source: [http://www.salvia.uk.com/product\\_images/44/thumbs/1/salvia-40x.jpg](http://www.salvia.uk.com/product_images/44/thumbs/1/salvia-40x.jpg).

### Exposures to *S. divinorum*

There were 37 exposures to *S. divinorum*. All of these were in the context of recreational use of *S. divinorum* and were classified as “intentional” exposures (Table 1 lists demographic and clinical details and outcomes of these cases). There were no deaths. Sixteen of these 37 (43%) exposures were reported to have concomitant exposures to other psychoactive agents, and 18/37 (49%) exposures were only to *S. divinorum* (for the three cases, the presence of other ingested or inhaled drugs was unknown or not reported).

As indicated in Table 1, vital sign abnormalities were reported for some but not all of the cases of intentional *S. divinorum* cases. In cases where *S. divinorum* was the sole agent of exposure, vital sign anomalies were documented in 2 patients: systolic hypertension and tachycardia in one case, and only tachycardia in another (in the latter case, a 24-year-old patient denied concomitant intoxication but had used LSD, phencyclidine, marijuana, and amphetamine 2 days before smoking *Salvia*).

Table 2 lists the clinical symptoms and their frequency in cases of isolated *S. divinorum* exposures. The most common symptoms recognized after isolated *S. divinorum* use were confusion or disorientation, hallucinations, giddiness or dizziness, flushed sensation, and tachycardia. Symptoms related to mental or neurologic effects were prevalent in a majority of patients with intentional *Salvia* exposures. Of the patients with intentional exposures to only *S. divinorum*, 13 (72%) had evidence of psychotomimetic or neuromotor disturbances.

For 18 cases of intentional *Salvia* exposure, concomitant ingestions included the following: ethanol (5 cases); marijuana (5 cases); mushrooms (1 case); jimson weed (2 cases); MDMA or methamphetamines (2 cases); GHB (1 case); rootone (1 case); damina leaves and 2,5-dimethoxy-4-iodophenethylamine (1 case). Routes of exposure included oral ( $n = 8$ ), inhaled ( $n = 24$ ), or unknown/unreported ( $n = 5$ ). In the majority ( $n = 20$ ) of *S. divinorum* cases, the formulation used by the patient was unknown or unreported; when described, the formulations were: leaves/flowers ( $n = 13$ ), *S. divinorum* extract ( $n = 3$ ), or tablet form ( $n = 1$ ).

Interventions made for patients possibly exposed to *S. divinorum* are listed by case in Table 1. These included: benzodiazepines for agitation (5 cases), intubation (2 cases), pacemaker placement for 3<sup>rd</sup>-degree heart block (1 case, in which the history of recurrent syncope was suggestive of primary conduction system disease), calcium channel blocker for hypertension (1 case), activated charcoal (1 case), and oral challenge/dilution with fluids (4 cases).

### Cases Attributed to *Salvia* Types Other than *S. divinorum*

The majority of exposures to the non-divinorum types of *Salvia* plants were exploratory ingestions in children. In adults, there was no indication that the non-divinorum sage plants were being used recreationally. Our study revealed that 96/133 cases involved exposures to non-divinorum species of *Salvia*. In this group, the average age of patients was 7 years (range 1–71 years). Routes of exposure were oral (90 cases), skin contact (2 cases), accidental inhalation of fumes from a burning sage plant (1 case), or unknown (2 cases). The majority (total 86, 65%) of these cases were ingestions by children aged 10 years or younger and involving species other than *S. divinorum*. These pediatric ingestions of ornamental or garden plants were categorized as unintentional (Table 3). The remaining patients were adults whose cases were reported to the poison control center after accidentally tasting non-divinorum *Salvia* species, or those who (in 2 cases) used *Salvia miltorrhiza* as a Chinese medicinal tea.

## DISCUSSION

*Salvia divinorum* is an increasingly popular recreational drug with a novel mechanism of action. Intoxication from *S. divinorum* for hallucinogenic or dissociative purposes can be achieved via the oral, sublingual, or, most commonly, inhalational route using leaves or dried extracts of the plant (8). According to self-reports by those who have used it, psychological effects occur within seconds to minutes and typically last for up to 1 h (9). Hallucinations and alterations or enhancements in sense perception are typically experienced. The active component in *S. divinorum* is thought to be salvinorin A, a diterpene with effects on the kappa opioid receptors found in the brain and spinal cord (10,11). Recent basic-science investigations have revealed that salvinorin A has a variety of neurologic effects, including psychotomimesis, analgesia, sedation, diuresis, and inhibition of gut motility (8,12). A recent survey estimates that 4% of college students have tried this substance for recreational intoxication in the last year (2).

Previous descriptions of *S. divinorum*'s psychological effects have been largely anecdotal, and many are firsthand accounts after recreational experimentation (4,5,12). Our study represents the first clinical case series of this emerging recreational drug.

In this study, we reviewed 37 cases in which *S. divinorum* exposure was intentional, defined as a case in which the patient was using the herbal *Salvia* plant or extract to achieve a recreational “high.” Roughly half of

Table 1. Exposures to *Salvia divinorum* Reported to CPCS, 1998–2008

Case #	Age, Years	Sex	Route	Coingestants	Vital Signs	Symptoms	Comments
1	15	M	Smoked	None	N/R	Excessive laughing, confusion	
2	15	M	Smoked	None	N/R	N/R	
3	18	M	Smoked	None	N/R	Anxiety	
4	18	M	Smoked	None	N/R	Hallucinations	
5	18	M	Smoked	None	Temp 36°C, pulse 75 beats/min, BP 153/80 mm Hg (24 h post-exposure)	Tachycardia, hyperthermia	
6	17	M	Oral	None	Afebrile, other vital signs N/R	Persistent anxiety, time disorientation	Ingested <i>S. divinorum</i> 1 week prior
7	18	M	Smoked	None	N/R	Dizzy, “spacey sensation”	Left against medical advice and lost to follow-up
8	16	M	Smoked	None	N/R	Mydriasis	Monitored in ED
9	18	M	Smoked	None	N/R	Confusion, psychosis, flushed skin	Left against medical advice and lost to follow-up
10	17	M	Smoked	None	N/R	“Not acting normal” s/p exposure 3 days prior	Left against medical advice and lost to follow-up
11	44	F	Oral	None	N/R	Burning mouth	
12	34	M	Smoked	None	N/R	“Feels like he has had a stroke”	Lost to follow-up, patient refused health care
13	22	M	Smoked	None	N/R	Lower GI bleed (unrelated)	GI bleeding unrelated to <i>S. divinorum</i>
14	23	M	Smoked	None	N/R	Hallucinations	
15	24	M	Oral	None	“stable”	Anxiety, palpitations	Left against medical advice and lost to follow-up
16	24	M	Smoked	None	“Tachycardic” (pulse not documented)	Hallucinations, tachycardic, confusion, mydriasis	Used LSD, phencyclidine and marijuana, and amphetamines 2 days before use of <i>S. divinorum</i>
17	22	M	Smoked	None	N/R	“Mind is blown,” confusion	Confusion noted three days after <i>S. divinorum</i> exposure
18	24	M	Smoked	None	N/R	Nausea, vomiting, diaphoresis ×4 days post-exposure	
19	17	M	Unknown	Unknown	N/R	Unknown	Lost to follow-up
20	20	F	Unknown	Unknown	Temp 39°C, pulse 119 beats/min, BP 155/100 mm Hg	Seizures, agitation, confusion	
21	21	M	Smoked	Unknown	“HTN” noted (BP not documented)	Agitation, HTN	Lost to follow-up
22	19	M	Smoked	Ethanol	Pulse 100 beats/min, BP 122/70 mm Hg	Anxiety	RBBB on ECG, monitored for 2–3 h in ED, then home
23	18	M	Smoked	Marijuana	N/R	Confusion, lethargic, responds to pain	Monitored in ED
24	19	M	Smoked	Mushrooms	Afebrile, pulse 70 beats/min, BP 148/86 mm Hg, Oxygen saturation 98% room air	Agitation, hallucinations	Monitored in ED
25	17	M	Smoked	Marijuana	“Tachycardia” noted (pulse not documented)	Combative	Monitored in ED
26	18	M	Smoked	Ethanol	N/R	Rapid eye movement (REM) activity while awake	Monitored in ED

Table 1. (Continued)

Case #	Age, Years	Sex	Route	Coingestants	Vital Signs	Symptoms	Comments
27	17	M	Oral	Possible jimsonweed, ecstasy (MDMA), phencyclidine	Temp 40.0°C, pulse 107 beats/min, BP 200/150 mm Hg	Hypertension, tachycardia, mydriasis, hyperthermia, nystagmus, agitation,	Serotonin syndrome vs. anticholinergic delirium vs. steroid-induced psychosis (wrestler), patient extubated on hospital day 2
28	19	M	Unknown	Gamma hydroxy butyrate (GHB)	Afebrile, other vital signs stable	Vomiting, agitation, confusion, sedated	Monitored in ED
29	17	M	Oral	Possible marijuana, jimsonweed (datura stramonium)	Afebrile, pulse 110 beats/min, BP wnl	Confusion, hallucinations, mydriasis, dry skin, flushed	Monitored in ED, patient stated Salvia baked in brownies
30	18	M	Unknown	Ethanol	N/R	Agitation	Left against medical advice and lost to follow-up
31	15	M	Unknown	Ethanol, protein supplements	Blood pressure 100s systolic, pulse 70–80 beats/min	Syncope, 3 <sup>rd</sup> -degree heart block	Symptoms due to preexisting cardiac disease
32	35	M	Oral	Rootone	N/R	Weak, LBP	
33	30	M	Smoked	Ethanol, marijuana	N/R	N/V, wk, dizzy	
34	49	M	Oral	Amphetamine	Pulse 94 beats/min BP 164/110 mm Hg	Agitation, mydriasis, HTN, confusion	Admitted to hospital for observation
35	26	M	Oral	Damina leaves, ethanol, 2,5-Dimethoxy-4-Iodophenethylamine	Afebrile, pulse 111 beats/min, BP 128/71 mm Hg, respirations 18 breaths/min (on ventilator)	Seizures, coma	Admitted to hospital, intubated for 2 days and extubated without complications
36	Unknown	F	Smoked	Marijuana	N/R	Fasciculations of neck	Left against medical advice and lost to follow-up
37	20	M	Smoked	None	N/R	Abdominal pain, hypoglycemia (blood glucose 60 mg/dL)	

BP = blood pressure; ED = emergency department; N/R = not reported or recorded in the poison center database; GI = gastrointestinal; HTN = hypertension; RBBB = right bundle branch block; ECG = electrocardiogram; MDMA = methylene-deoxy-methamphetamine "Ecstasy"; wnl = within normal limits.

**Table 2. Signs/Symptoms Associated with Isolated Use of *Salvia divinorum***

Clinical Feature	Frequency
Altered mental state (confusion, disorientation)	7
Hallucinations	3
Excessive laughter/giddiness	1
Dizziness	1
Mydriasis	2
Flushing/warm sensation	3
Diaphoresis	1
Tachycardia	2
Palpitations	1
Hypoglycemia	1

these cases also involved exposure to other psychoactive agents, confounding the assessment of *S. divinorum*'s particular contribution to toxicity. In cases where only *S. divinorum* was inhaled or ingested, neurologic symptoms and signs of intoxication were noted and compiled. According to this analysis, *S. divinorum* intoxication is characterized by a constellation of symptoms and signs: anxiety, bizarre and vivid hallucinations, giddiness, space-time disorientation, nystagmus, palpitations, hypertension, tachycardia, nausea, and vomiting. As with many recreational substances, not all patients experience all of the symptoms listed, and more clinical information is necessary to fully depict the range and severity of signs and symptoms of this emerging recreationally used substance. Clinicians caring for patients intoxicated by *S. divinorum* are encouraged to pay close attention to possible psychiatric, neurologic, gastrointestinal, and cardiovascular effects.

From this study, it seems that the concomitant use of multiple psychoactive agents is more likely to result in more serious adverse effects (e.g., seizures, intubation) than the use of *S. divinorum* alone. For example, vital sign abnormalities were noted in 2/18 cases in which *S. divinorum* was the sole agent of intentional intoxication; in contrast, abnormal vital signs were reported in 6/16 cases in which additional psychoactive substances were also involved. Furthermore, in those cases with more significant adverse effects, other psychoactive substances besides *S. divinorum* were reported in at least one, and possibly three, of the four cases. Two of these cases experienced seizures. Despite a small sample size, these data suggest that polysubstance abuse is a risk factor for more severe adverse clinical outcomes in the setting of intentional *S. divinorum* use.

A dose-response relationship was not possible to establish from this case series. There was an overall paucity of data about the doses and formulations used by patients in this case series. In the vast majority of cases, information about quantity consumed was either unreported, unavailable, or unreliable. For instance, in many

cases, there was a lack of caller certainty about the amount or strength utilized, even when the exposures were intentionally undertaken. Indeed, much of the ambiguity about doses consumed is a consequence of herbal manufacturing practices; *S. divinorum* extracts are usually marketed as concentrations such as “5×,” “10×,” or “50×,” without listing milligram equivalents (Figure 2). Each manufacturer determines the strength rating based on subjective criteria such as the age and water weight for a particular batch. This marketing practice, compounded by the paucity of physiologic data on this plant, currently challenges attempts to establish a clinically useful dose-response relationship for this substance. A robust estimation of dose-response for this plant product will have to wait until doses can be more precisely determined of *Salvia* consumed in recreational settings. Analytical laboratory methods such as liquid chromatography-mass spectroscopy have been employed recently to detect Salvinorin in both commercial samples and biological fluids, but these techniques have not gained wide acceptance in common clinical practice (8,13,14).

Using our search criteria, we were surprised to learn that the majority of calls about “*Salvia*” species referred to plant species not known to have hallucinogenic or psychoactive effects. Poison center specialists and clinical toxicologists may be asked to provide advice on both hallucinogenic and non-hallucinogenic varieties of *Salvia* plants, and this study highlights the need to distinguish the exact species of *Salvia* to help make appropriate triage and therapeutic decisions. Consistent with prior research on household plant exposures, our study confirmed that pediatric, exploratory, or low-dose exposures to non-hallucinogenic *Salvia* varieties have a benign clinical course, as demonstrated by the asymptomatic outcomes of children < 6 years old who ingested

**Table 3. Species of Non-hallucinogenic *Salvia* or Sage Plants Implicated in Pediatric Ingestions of “*Salvia*”**

<i>Salvia albocaerulea</i>
<i>Salvia coccinea</i>
<i>Salvia columbriæ</i> (chia)
<i>Salvia farinacea</i>
<i>Salvia fruticosa</i>
<i>Salvia lavandulifolia</i>
<i>Salvia lavandulifolia</i>
<i>Salvia leucantha</i>
<i>Salvia longystyla</i>
<i>Salvia meloxylon/albocaerulea</i>
<i>Salvia microphelia</i>
<i>Salvia miltiorrhiza</i>
<i>Salvia paleafolea</i>
<i>Salvia splendens</i>
<i>Salvia triloba</i>
<i>Abronia fragrans</i> (Red Lantana)

leaves, flowers, or other parts of non-hallucinogenic *Salvia* plants (15).

### Limitations

Limitations of this study include the small sample size and retrospective design. These factors limit the completeness of clinical information available for review. A number of patients were ultimately lost to adequate follow-up by poison control center personnel, so any delayed signs and symptoms may have been missed. Incomplete documentation or reporting regarding the circumstances surrounding the exposures makes it difficult to draw many concrete conclusions such as dose-response relationship. Many laypersons and clinicians choose not to report asymptomatic or mildly symptomatic exposures of toxins to regional poison centers, so the available reports may be skewed to reflect a more ill population of patients. Even ill patients with poisonings are sometimes not reported to the poison control center, so our data were likely subject to a general under-reporting of *Salvia* exposure cases. Our small sample size and inability to review hospital records in detail also limit us from making firm conclusions about the potential interactions (synergism/antagonism) between *S. divinorum* and other psychoactive substances. Notably, because there are no laboratory tests or biological markers commonly available for the detection of Salvinorin A, its related metabolites, or specific physiologic effects of this substance, the exposure to *S. divinorum* was confirmed only by history or, more rarely, a specimen of the plant or labeled extract available for identification by health care providers. Finally, self-reporting bias limits the accuracy of the clinical findings, as patients may have been mistaken or confused about the agent(s) involved in their exposure at the time of the poison center inquiry.

### CONCLUSIONS

*Salvia divinorum* seems to be rising in popularity among adolescents and young adults. This poison-center-based case review adds to the expanding knowledge of *S. divinorum*'s clinical effects. In patients who intentionally used *S. divinorum* alone, psychiatric effects were most evident, while neurologic, cardiovascular, and gastrointestinal effects were loosely associated with the exposure. Clinicians should also note that patients who have intentional exposures to this agent frequently present

with concomitant exposures to other psychoactive substances, and the use of multiple agents seems to carry a higher risk of severe adverse effects. Because most clinical laboratories are not equipped to detect Salvinorin A or related metabolites, the diagnosis of *S. divinorum* intoxication must, at present, rely on historical details. Additional basic and clinical research will elucidate the pharmacokinetics, full spectrum of clinical effects, and any unique treatments required for this emerging substance of abuse. We encourage emergency physicians who care for patients exposed to *Salvia* plant species to enlist the assistance of clinical toxicologists and poison center personnel via regional poison control centers.

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### ARTICLE SUMMARY

#### 1. Why is this topic important?

The rapid rise in popularity and widespread availability of *Salvia divinorum* as a recreational substance of abuse represents a potentially significant emerging toxin. Emergency clinicians and poison center personnel may be asked to provide care for patients under the influence of this hallucinogenic plant, about which there are very few clinical and pharmacologic data currently available.

#### 2. What does this study attempt to show?

This study describes clinical and demographic details of exposures to *Salvia divinorum* and describes the symptoms likely to be encountered by emergency physicians in cases of isolated *Salvia divinorum* exposure. In addition, non-hallucinogenic species of *Salvia* (sage) plants are provided for reference, as these may be confused or mistaken for the recreationally used *Salvia divinorum* variety of sage.

#### 3. What are the key findings?

In patients who intentionally used *Salvia divinorum* alone, neurologic, cardiovascular, and gastrointestinal effects were evident. The concomitant use of multiple agents or drugs of abuse is more likely to result in more serious adverse effects (e.g., seizures, intubation) than the use of *Salvia divinorum* alone.

#### 4. How is patient care impacted?

Physicians caring for young adults or teenagers who manifest unexplained mental status changes or cardiovascular and neurologic symptoms should consider the diagnosis of exposure to *Salvia divinorum*. Patients who present with *Salvia divinorum* intoxication require aggressive monitoring and supportive care acutely, especially if exposed to multiple toxic agents.