HUMAN PSYCHOPHARMACOLOGY
*Hum. Psychopharmacol Clin Exp* 2013; **28**: 403–412.
Published online 23 June 2013 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2304

*REVIEW ARTICLE*

# *Salvia divinorum*: from Mazatec medicinal and hallucinogenic plant to emerging recreational drug

Jolanta B. Zawilska* and Jakub Wojcieszak

*Department of Pharmacodynamics, Medical University of Lodz, Lodz, Poland*

*Salvia divinorum* is a sage endemic to a small region of Mexico and has been traditionally used by the Mazatec Indians for divination and spiritual healing. Recently, it has gained increased popularity as a recreational drug, used by adolescents and young adults as an alternative to marijuana and LSD. Salvinorin A, the major active ingredient of the plant, is considered to be the most potent known hallucinogen of natural origin. This review surveys the current state of knowledge on the neurochemical, pharmacokinetic, and pharmacological properties of salvinorin A, the trends and motivation behind *S. divinorum* use, and the health problems among users of the plant's products. *S. divinorum* induces intense, but short-lived, psychedelic-like changes in mood and perception, with concomitant hallucinations and disorientation. Many websites have misinterpreted the limited existing research-based information on the side effects of salvia as evidence for its safety. However, data accumulated over the last few years indicate that potential health risks are associated with the use of *S. divinorum*, especially by teenagers, users of other substances of abuse, and individuals with underlying psychotic disturbances. Taken together, the data presented in this review point to the need for further basic and clinical studies to create a basis for the development of well-addressed prevention and treatment strategies. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—*Salvia divinorum*; salvinorin A; herbal highs; hallucinogenic drugs; kappa opioid receptor

## INTRODUCTION

*Salvia divinorum* is a rare member of the mint family (Labiatae), endemic to a small region of Oaxaca, Mexico. Similar to cannabis, *S. divinorum* can be also cultivated indoors or in any humid and semitropical environment. Shamans of the Mazatec Indians of Oaxaca have used the plant for centuries for divinatory and religious purposes as well as in medicinal practices to treat diarrhea, headache, rheumatism, anemia, and a semimagical disease known as panzón de Borrego, or a swollen belly, believed to be caused by an evil sorcerer. In ethnomedical use, the fresh leaves of *S. divinorum* are chewed or ground into a blend and consumed by ingesting the liquid (Cunningham *et al*., 2011). Recently, *S. divinorum* (usually referred to as salvia) has received increasing attention for its recreational use due to its unique psychomimetic effects as well as its accessibility, legality in some areas, perception of relative safety, and lack of detectability upon routine drug screening (Giroud *et al*., 2000; González *et al*., 2006; Lange *et al*., 2008, 2010; Miller *et al*., 2009; Baggott *et al*., 2010; Casselman and Heinrich, 2011; Ford *et al*., 2011; Kelly, 2011; Wu *et al*., 2011; Perron *et al*., 2012; Sumnall *et al*., 2012). *S. divinorum* is frequently promoted as a safe and legal alternative to scheduled hallucinogenic drugs, such as cannabis, LSD, and mescaline (Hoover *et al*., 2008; Cunningham *et al*., 2011; Sumnall *et al*., 2012). Contrary to the traditional use, inhalation is the primary method of *S. divinorum* intake for recreational purposes. Some users expect philosophical and/or mystical insights and experiences when on salvia. The aim of this survey was to present the current state of knowledge on the neurochemical, pharmacokinetic, and pharmacological properties of salvinorin A, the analytical methods for its detection and quantification, the trends and motivation behind *S. divinorum* use, and the health problems seen among users of the plant's products.

*Correspondence to: J. B. Zawilska, Department of Pharmacodynamics, Medical University of Lodz, 1 Muszynskiego St., 90-151 Lodz, Poland. Tel: +48-42-677-9294; Fax: +48-42-678-8398 E-mail: jolanta.zawilska@umed.lodz.pl



*Received 16 August 2012*
*Accepted 19 February 2013*

## SALVINORIN A, THE MAIN PSYCHOACTIVE INGREDIENT OF *SALVIA DIVINORUM*

### *Chemical structure and mechanism of action*

The principal active component of *S. divinorum* is the neoclerodane diterpene salvinorin A. Although a number of other compounds have been isolated from the plant, including salvinorins B–I, salvidivins A–D, salvinicins A and B, and divinatorins A–E, their biological activity, if any, remains to be elucidated (Cunningham *et al*., 2011). The reported contents of salvinorin A in dried leaf products were found to be (in μg/mg) 0.89–3.70 (Gruber *et al*., 1999), 3.2–5.0 (Tsujikawa *et al*., 2008), and 7.6–7.8 (Medana *et al*., 2006). The concentration of salvinorin A in leaves collected from separate plants, even genetically identical ones, can vary considerably (Gruber *et al*., 1999). More importantly, although Wolowich *et al*. (2006) demonstrated that the salvinorin A content of "concentrated extract" products with a labeled potency of 5–20× ranged from 0.126 to 0.951 μg/mg, an analysis of concentrated products with similar labeled potency (2–25×) performed by Tsujikawa *et al*. (2008) revealed a much higher concentration of salvinorin A: 4.1–38.9 μg/mg.

*In vitro* and *in viv*o studies have demonstrated that salvinorin A is a selective and potent agonist of κ-opioid receptors (KOR), more efficacious than either U69,593 or U50,488, two prototypical KOR agonists (Roth *et al*., 2002; Nemeth *et al*., 2010; Cunningham *et al*., 2011). Salvinorin A is the sole KOR agonist present in *S. divinorum*. The compound is the only known non-nitrogenous KOR agonist, and has no structural resemblance to any known hallucinogens but exhibits some structural homology to enadoline, a selective KOR agonist (Roth *et al*., 2002; Cunningham *et al*., 2011) (Figure 1). Salvinorin A is distinguished from U69,593 and dynorphin A (1–13), an endogenous peptide agonist of KOR, in that it requires unique amino acid residues within a binding pocket of KOR for binding, stabilization, and activation of the receptor (Cunningham *et al*., 2011). It is not known whether this property is related to the unique psychoactive effects exerted by salvinorin A, and if so, to what extent. Detailed studies have revealed that salvinorin A has negligible activity against numerous receptors, transporters, and ion channels (Roth *et al*., 2002; Cunningham *et al*., 2011). Of particular importance is the fact that salvinorin A has no affinity for other known receptors for psychoactive compounds, such as μ-opioid and δ-opioid receptors, sigma receptors, cannabinoid receptors, cholinergic receptors, glutamate receptors, and serotonin (5-HT) receptors, including 5-$HT_{2A}$, which represent the main molecular target for classical hallucinogens, such as LSD, *N*,*N*′-dimethyltryptamine, psilocybin, and mescaline (Roth *et al*., 2002; Cunningham *et al*., 2011).

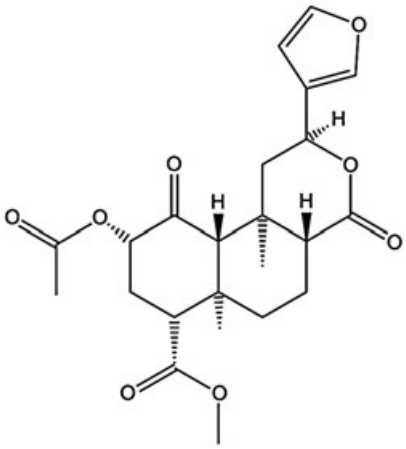

Figure 1. Chemical structure of salvinorin A

Recent studies performed by Hooker and coworkers suggest that salvinorin A might exert its psychoactive effects not only by direct and immediate actions on KOR. By using positron emission tomography, the distribution of [$^{11}$C]salvinorin A was analyzed in the brains of baboons. The obtained results showed that administration of naloxone, a nonselective antagonist of opioid receptors, did not reduce the overall concentration of [$^{11}$C]salvinorin A and had no effect on the regional distribution of the radioligand (Hooker *et al*., 2008). Furthermore, it was demonstrated that salvinorin A activated glucose metabolism not only in regions of the rat brain with high KOR density, such as the periaqueductal grey, the bed nucleus of the stria terminalis, and the cerebellar vermis, but also in regions that have little or no KORs, that is, the hypothalamus, the auditory, sensory, and frontal cortices, the left ventral pallidum, and the right lateral geniculate nuclei. A decrease in metabolic activity was observed in the caudate putamen, the superior colliculus, the hippocampus, and the medial brainstem (Hooker *et al*., 2009). From these results, it was concluded that the metabolic response to salvinorin A results not only from the immediate KOR effects but also from activation of neural circuit projection from the primary KOR sites to functionally and anatomically related regions of the brain (Hooker *et al*., 2009). It should be noted that at the present state of knowledge, it cannot be ruled out that salvinorin A may exert its actions through activation of one or more as yet undiscovered molecular target(s), in addition to the mechanisms described earlier.

### *Pharmacokinetic properties of salvinorin A*

Sublingual doses of 4 mg of salvinorin A were not found to be psychoactive in humans (Mendelson *et al*., 2011). Taken orally, the drug is minimally absorbed through the mucosa, and most of the dose is degraded in the



DOI: 10.1002/hup

gastrointestinal tract. On the other hand, when inhaled, salvinorin A exerts psychoactive effects within seconds that last only minutes (González *et al*., 2006; Lange *et al*., 2010; Cunningham *et al*., 2011; MacLean *et al*., 2013). There is a relationship between salvia dose and effect duration (Lange *et al*., 2010).

Animal studies demonstrating that salvinorin A is rapidly taken up and eliminated from the brain match the time course of visual hallucinations and behavioral impairment for smoked *S. divinorum* in humans. The earliest report investigating the pharmacokinetic properties of salvinorin A monitored a single dose of the drug in male and female rhesus monkeys following its intravenous administration (Schmidt *et al*., 2005b). The drug was rapidly distributed and eliminated. The kinetics of both processes appeared to depend on gender, being slower in female than in male monkeys, but overall, the elimination half-life was 56.6 min (Schmidt *et al*., 2005b). In another study, the central distribution of [$^{11}$C] salvinorin A was monitored in female baboons using positron emission tomography (Hooker *et al*., 2008). [$^{11}$C]Salvinorin rapidly entered the brain, reaching a maximum concentration, accounting for 3.3% of the total administered dose, in 40 s. Importantly, the observed input rate was nearly an order of magnitude faster than the previously reported input of [$^{11}$C]cocaine (cited in Hooker *et al*., 2008). Clearance of salvinorin A from the brain was also rapid, with a half-life of 8 min (Hooker *et al*., 2008). Assuming that doses of 200 μg are effective in humans when smoked, it was estimated that less than 10 μg of salvinorin A in the human brain is sufficient to elicit the drug's psychoactive effects (Hooker *et al*., 2008). Another study analyzed the pharmacokinetic parameters of intraperitoneally administered salvinorin A in Sprague-Dawley rats (Teksin *et al*., 2009). Consistent with previous reports, salvinorin A had a rapid uptake in the brain, displaying a $t_{max}$ of 10 min. Elimination from the brain was also fast with a $t_{1/2}$ of 36 min.

In rat plasma, salvinorin A is mainly degraded by carboxylesterase to salvinorin B (Tsujikawa *et al*., 2009). C-2 hydroxylated salvinorin B, an inactive metabolite of salvinorin A (Cunningham *et al*., 2011), has been demonstrated to be the major metabolite of salvinorin A in nonhuman primates (Schmidt *et al*., 2005b). In baboons, salvinorin A is presumably metabolized by at least two pathways; hydrophilic metabolites are excreted through renal filtration, and the lipophilic ones through biliary excretion (Hooker *et al*., 2008). Results of *in vitro* experiments suggest that in humans salvinorin A is metabolized by CYP450 (mainly CYP2D6, CYP1A1, CYP2C18, and CYP2E1 isoforms) and UGT2B7, with glucuronidation likely representing the major metabolic pathway of the drug (Teksin *et al*., 2009).

## EFFECTS OF SALVINORIN A

### *Effects of salvinorin A in animals*

Studies in rhesus monkeys show that salvinorin A produces discriminative stimulus effects similar to other high-efficacy KOR agonists, but not to those exerted by hallucinogenic compounds, such as psilocybin, a 5-$HT_2$ receptor agonist, and ketamine, an antagonist of NMDA receptors (Butelman *et al*., 2010). Similar results were obtained in rats (Baker *et al*., 2009; Killinger *et al*., 2010). In rhesus monkeys, salvinorin A induced ptosis and facial relaxation (Butelman *et al*., 2009). In a five-choice serial reaction time task in rats, salvinorin A produced disruptive effects associated with reduced motivation and deficit in processing (Nemeth *et al*., 2010). Furthermore, although salvinorin A did not affect short-term memory in rats, the drug impaired spatial long-term, episodic, and averse memories (Braida *et al*., 2011). In mice, salvinorin A caused conditioned place aversion and resulted in antinociception, hypothermia, sedation, motor incoordination, and lower locomotor activity (Fantegrossi *et al*., 2005; Zhang *et al*., 2005; Ansonoff *et al*., 2006; Cunningham *et al*., 2011). Antinociceptive and hypothermic effects of salvinorin A were abolished in KOR-1-knockout mice, an observation confirming that the drug is a functional KOR agonist (Ansonoff *et al*., 2006). Some of the behavioral changes described earlier, particularly facial relaxation, sedation, antinociception, and motor incoordination, resemble those observed in humans.

From a clinical point of view, the effects of salvinorin A on the behavioral and molecular changes produced by cocaine appear particularly interesting. The drug has been shown to attenuate the cocaine-induced drug-seeking behavior in rats (Morani *et al*., 2009) and reduce the reward-potentiating effects of cocaine (Potter *et al*., 2011). Acute administration of salvinorin A blocked the cocaine-induced increase in locomotor activity and attenuated cocaine-induced c-Fos expression in the dorsal striatum (Chartoff *et al*., 2008). It appears likely that the aforementioned properties of salvinorin A may be used by cocaine addicts to suppress locomotor hyperactivity and achieve only the desired psychostimulatory effects.

At the neurochemical level, salvinorin A inhibits the stimulated release of dopamine from synaptosomes isolated from mouse striatum and prefrontal cortex. Furthermore, the drug inhibits the release of serotonin and stimulates the release of noradrenaline from hippocampal synaptosomes (Grilli *et al*., 2009). In *in vivo* studies, salvinorin A decreased extracellular concentrations of dopamine in the rat nucleus accumbens, a critical component of the reward system



DOI: 10.1002/hup

(Carlezon *et al*., 2006; Cunningham *et al*., 2011), but had no effect on concentrations of serotonin (Carlezon *et al*., 2006). An impairment of the mesolimbic dopaminergic pathway is postulated to be involved in salvinorin A-induced dysphoria (Grilli *et al*., 2009), whereas a decrease in serotonin bioavailability might underlie the sedative effects of the drug (Fantegrossi *et al*., 2005; Ansonoff *et al*., 2006). Acute salvinorin A treatment induced c-Fos expression in the rat nucleus accumbens shell (a brain region implicated in the regulation of mood), prefrontal cortex (a structure involved in cognition, self-knowing awareness, and morality), and central and lateral amygdala (key players in emotionality) (Chartoff *et al*., 2008). Further studies are needed to reveal whether these effects could be related to cognitive and behavioral disturbances observed in humans after the use of salvia.

### *Clinical effects and toxicity in humans*

Inhalation of the vaporized smoke of salvinorin A is considered as the most efficient method for achieving its psychoactive effects in humans. Salvinorin A induces intense, but short-lived, psychedelic-like changes in visual perception and mood, and somatic sensations, which appear in less than 1 min and last for 15 min or less (Table 1). Importantly, the rapid onset and high intensity of the effects of salvia can be disorienting and potentially dangerous to a new user, who may instead expect a marijuana-like experience. Characteristic vivid visual hallucinations include mainly perceptions of changes in bodily form, merging with objects in the environment, being relocated to a different setting, strong dissociate states in which the passage of time is altered, colorful visions of objects and designs (fractal, vine-like, and geometric patterns), and at higher effect intensity, complex three-dimensional scenes with a realistic appearance. Frequently reported positive effects of salvia are an increase in sensual and aesthetic appreciation, a creative, dream-like experience, increased calmness, and subjective well-being afterwards (González *et al*., 2006; Kelly, 2011; MacLean *et al*., 2013). Some users describe synesthesia, whereas others report an "out of body experience" and derealization/depersonalization (Baggott *et al*., 2010; Kelly, 2011). A highly modified perception of external reality and the self leads to a decreased ability to interact with oneself or with one's surroundings (González *et al*., 2006; Baggott *et al*., 2010; Kelly, 2011). Most of the reported effects of *S. divinorum* are pleasant (González *et al*., 2006; Casselman and Heinrich, 2011). Observation of YouTube™ videos of salvia use showed that 65% of them displayed people having good experiences, whereas only 12% of the videos revealed negative ones (Casselman and Heinrich, 2011). Interestingly, people were more likely to report positive effects if they declared their likelihood of using *S. divinorum* again and if they had smoked salvia to solve their psychological problems (Baggott *et al*., 2010). Effects of salvia could be also negative (Table 1), including loss of control over the experience, a feeling of heaviness in the head as if having smoked too many cannabis joints, tiredness, dizziness, grogginess, mental slowness, physical exhaustion, anxiety, social withdrawal, mental confusion, fear, terror, panic, amnesia, dysphoria, temporary language impairment, difficulty in integrating experiences, and increased perspiration (Lange *et al*., 2010;

Table 1. Main effects of *Salvia divinorum*/salvinorin A use

| Positive/desired effects | Negative effects |
|---|---|
| Relaxation and improved mood[a,b] | Loss of control over experience[a] |
| Calmness[a] | Difficulty in integrating experiences[a] |
| Intense but short-lasting psychedelic-like effects[a,b] | Racing thoughts[a] |
| Altered state of consciousness[a,b] | Tiredness, physical exhaustion, and sleepiness[a] |
| Vivid visual hallucinations[a,b] | Dizziness and drowsiness[a] |
| Auditory hallucination[a,b] | Irritability, anxiety, fear, panic attacks, and terror[a,c] |
| Dream-like experience[a,b] | Dysphoria[a] |
| Increased intrusive thoughts[b] | Acute psychosis and paranoia[c] |
| Feelings of dissociation, depersonalization, and derealization[a,b] | Psychomotor agitation[b,c] |
| | Temporary language impairment[a,c] |
| Increase in sensual and aesthetic appreciation[a,b] | Amnesia[a] |
| Floating feeling[a] | Lack of motor coordination[a] |
| Synesthesia[a] | Profound sweating[a] |
| Increased self-confidence[a,b] | Chills or gooseflesh[a] |
| Increased insight[a,b] | Nausea, vomiting, and abdominal discomfort[b,c] |
| Spiritual experiences[a,b] | |

[a]Data collected from self-assessment questionnaires or through Internet-based surveys (González *et al*., 2006; Baggott *et al*., 2010; Lange *et al*., 2010; Casselman and Heinrich, 2011; Kelly, 2011; Sumnall *et al*., 2012).
[b]Double-blind, placebo-controlled study (Addy, 2012; MacLean *et al*., 2013; Ranganathan *et al*., 2012).
[c]Case reports (Singh, 2007; Paulzen and Grűnder, 2008; Przekop and Lee, 2009; Meyer and Writer, 2012; Travis *et al*., 2012).



DOI: 10.1002/hup

Kelly, 2011; Sumnall *et al*., 2012). For some users, the experience was so intense that they discontinued use of the substance (Kelly, 2011). A headache and drowsiness for several hours after use was described by Kelly (2011). Vohra *et al*. (2011) analyzed 37 cases that had been reported over a 10-year period to the California Poison Control System after intentional *S. divinorum* exposure; half of these were associated with ingestion of *S. divinorum* alone. The most common symptoms recognized after isolated *S. divinorum* use were confusion or disorientation, hallucinations, dizziness, flushed sensation, and tachycardia. The listed effects of *S. divinorum*, especially changes in perception and mood, should be taken with caution, as they are based on retrospective self-reports collected through Internet-based surveys, with no quantitative measures used and no forensic analysis of the ingested *S. divinorum* product. In addition, one might expect that subjects with a history of using *S. divinorum* will report mainly positive effects. Similarly, users are more likely to video and share with others, *via* the Internet, their positive rather than negative *S. divinorum* experiences (Baggott *et al*., 2010; Casselman and Heinrich, 2011; Kelly, 2011; Sumnall *et al*., 2012).

As salvinorin A has been recently demonstrated to exert antidepressive effects in the rat anhedonia model (Harden *et al*., 2012), the question of whether *S. divinorum* can exert an antidepressant action in humans remains. Although several self-reports on relief from symptoms of depression with the use of salvia have appeared on the Internet websites and forums, only one published case report of antidepressant effects of preparation of *S. divinorum* leaves taken orally exists (Hanes, 2001).

To our knowledge, only a few double-blind, placebo-controlled studies on the effects of salvinorin A in humans have been performed. In one study, healthy hallucinogen-experienced volunteers were given the vaporized salvinorin A at increasing doses (0.375–21 μg/kg), and subjective effects (drug strength) and physical effects (safety, tolerability, heart rate, and blood pressure) were measured over a period of 1 h (MacLean *et al*., 2013). The drug did not significantly affect heart rate and blood pressure. No resting or kinetic tremors were observed. Salvinorin A strength ratings peaked at 2 min, and definite subjective effects were no longer present at approximately 20 min after inhalation (MacLean *et al*., 2013). The hallucinogenic and mystical effects of vaporized salvinorin A were dose dependent. In addition to intense hallucinations, spatial adjustments of the users' bodies, such as being dragged, pulled, or pushed in a particular direction, spinning, flipping, twisting, and stretching were described (MacLean *et al*., 2013). Addy (2012) analyzed acute and aftereffects of salvinorin A and found that inhalation of the drug increased talking, laughing, movement while sitting, and paranoid ideation. The reported experience was similar to that of dreaming (43%); using LSD (13%), psilocybin (10%), marijuana (10%), and MDMA (10%); and being in non-substance-facilitated altered states of consciousness, such as meditation, trance, or yoga (7%) (Addy, 2012). Eighty-seven per cent of participants reported aftereffects lasting less that 24 h after smoking, mainly reflection, empathy, intuition, and awareness of beauty, whereas 70% reported longer-lasting aftereffects. The molecular mechanisms underlying the delayed effects of salvinorin A are at present not known. Finally, in the recently published paper, the effects of inhaled salvinorin A (8 and 12 mg), administered through a vaporizer, were analyzed in 10 healthy individuals who had previously used salvia. The drug produced rapid and short-lasting (up to 30 min) psychomimetic effects and perceptual alterations, including feelings of dissociation and detachment, heightened awareness of visual and/or auditory stimuli, withdrawal into self, changes in concentration, and increased intrusive thoughts. The subjects compared the magnitude of salvinorin A-induced psychomimetic effects with those produced by ketamine and $\Delta^9$-tetrahydrocannabinol. In addition, salvinorin A increased plasma cortisol and prolactin levels and exerted psychophysiological effects, that is, a decrease in a broad-band resting-state electroencephalogram spectral power. The drug was well tolerated and did not produce changes in heart rate and blood pressure, euphoria, and cognition as evaluated by the digital forward, digital backward, and letter–number sequencing test (Ranganathan *et al*., 2012).

Although some aspects of the reported subjective effects of smoking *S. divinorum* or inhaling salvinorin A were similar to marijuana, ketamine, or high doses of classical psychedelics with 5-$HT_{2A}$ receptor agonist activity (Albertson and Grubbs, 2009; MacLean *et al*., 2013; Ranganathan *et al*., 2012), the hallucinogen-experienced participants found the experiences to be unique and particularly intense compared with other hallucinogens they had used (MacLean *et al*., 2013). The intense derealization and impairment appear to be characteristic of salvia. Furthermore, nearly all of the hallucinogen-experienced participants of the study conducted by MacLean *et al*. (2013) found salvinorin A to be "somewhat" or "completely" different to other hallucinogens, as the five most prominent hallucination themes were disruption in vestibular and interoceptive signals, contact with entities that often included communication and interaction, revisiting childhood memories, cartoon-like imagery, and recurring content across



DOI: 10.1002/hup

sessions. Of note, all of them rated salvinorin A sessions as personally meaningful and spiritually significant (MacLean *et al*., 2013).

The psychoactive effects of *S. divinorum* appeared to also depend on individual sensitivity, time of observation, and context of its use. It should be noted that expectations related to the previous use of psychomimetic drugs, individual interest in spirituality, and/or altered state of consciousness will lead *S. divinorum* users to report mainly positive experiences, thus limiting the outcome of the study.

Data on the toxicity of *S. divinorum* are sparse, and many Internet sites misinterpret the absence of scientific data on the possible toxicity or side effects of salvia as evidence for its safety (Hoover *et al*., 2008). Four case reports document that *S. divinorum* use was associated with extended psychotic-type reactions. A 15-year-old boy, with a history of salvia and marijuana use, was presented to psychiatric emergency services with acute onset of psychotic symptoms such as paranoia, déjà vu, blunted affect, thought blocking, and slow speech for a duration of 3 days (Singh, 2007). An 18-year-old woman was admitted to psychiatric services with acute onset of agitation, disorganization, and hallucinations shortly after smoking a herbal mixture containing cannabis and *S. divinorum* (Paulzen and Grűnder, 2008). In the third case, a 21-year-old man was hospitalized for acute psychosis and paranoia, which occurred shortly after smoking salvia. During transportation to the hospital, the patient became suspicious and attempted to jump from the vehicle. Upon presentation, he demonstrated echolalia, paranoia, flight of ideas, and psychomotor agitation (Przekop and Lee, 2009). It should be emphasized that interpretation of these cases was complicated by a concurrent use of another drug (Singh, 2007), injuries secondary to a medical treatment (Paulzen and Grűnder, 2008), and a suspected predisposition to schizophrenia (Przekop and Lee, 2009). A latest study presented the case of a 23-year-old man who experienced a rapid onset of psychosis and anxious dysphoria after smoking an unknown quantity of *S. divinorum* (Meyer and Writer, 2012). Travis *et al*. (2012) described gastrointestinal symptoms associated with withdrawal after chronic use of *S. divinorum* (three to five cigarettes daily for 3–4 months) by a 51-year-old woman, that is, initial nausea that progressed to diarrhea, abdominal discomfort, and vomiting.

Although there is some concern for abuse and drug-induced psychosis, salvia's short-term and long-term effects have not been sufficiently examined to determine its definitive dangers. Several reports suggest that, by analogy to other KOR agonists, salvinorin A has low addiction liability (Baggott *et al*., 2010; Ranganathan *et al*., 2012; Sumnall *et al*., 2012). However, a study by MacLean *et al*. (2013) was the first to indicate the possible abuse liability of salvinorin A due to the increase of "good" effects and drug "liking" ratings across doses, whereas drug "disliking" and "bad" effects were low across all doses.

## PREVALENCE, PROFILE, AND MOTIVATION FOR *SALVIA DIVINORUM* USE

Recreational *S. divinorum* products, leaves, and seeds are all available for purchase at online websites and in shops that sell drug use paraphernalia, that is, head or smart shops in countries or states in the case of the USA where salvia is not prohibited. They are frequently marked as "herbal/legal highs" (Halpern and Pope, 2001; Miller *et al*., 2009; Currie, 2013). By analogy to other novel psychoactive substances, users typically use Internet websites and forums as sources of information on *S. divinorum*. The plant has several street names, including, among others, magic mint, Sally D, diviner's sage, lady sally, Maria pastora, ska Maria pastora, puff, and incense special. In smoke shops, it has been sold under the popular brand name Purple Sticky™ (Lange *et al*., 2008). Typically, recreational salvia products are commercially available in packages that include either the leaf or another absorbent material impregnated with an extract of salvinorin A (Halpern and Pope, 2001; Miller *et al*., 2009). In 2009, salvia products were the most popular among "legal highs" marketed by UK-based Internet retailers (Schmidt *et al*., 2011). Furthermore, a recently published report from the 2-year Psychonaut Web Mapping Project (2008–2010) on trends in recreational drug use in seven European countries put *S. divinorum* on the list of 30 the most common products or substances identified (Deluca *et al*., 2012).

It is estimated that the lifetime prevalence of *S. divinorum* is similar to that of other hallucinogens (Khey *et al*., 2008). The lifetime use of salvia reported by Ford *et al*. (2011) was 1.66% in the group of American adolescents 12–17 years old and 5.08% in adults at the age of 18–34 years. Data obtained from a sample of 42 179 Canadian adolescents aged 12–17 years who responded to the 2008–2009 Youth Smoking Survey revealed that 3.8% and 6.3% of them had used *Salvia* in the past year and their lifetime, respectively (Currie, 2013). The prevalence rates of *S. divinorum* use among undergraduate students of a large public university in the State of Florida were as follows: lifetime use 6.7%, use within the last year 3.0%, and use within the last month 0.5% (Khey *et al*., 2008). Lange *et al*. (2008) found that approximately 4.4% of 1571 college students had reported using salvia



DOI: 10.1002/hup

within the last year. Analysis of 166 453 public-use data files from the 2006–2008 US National Surveys on Drug Use and Health revealed an increase of the lifetime prevalence of *S. divinorum* use from 0.7% in 2006 to 1.3% in 2008 (Wu *et al*., 2011).

The reported lifetime use of *S. divinorum* products is 13 days, and the number of days salvia was used in the last year and month is 7.5 and 1.5, respectively (Baggott *et al*., 2010). Users will typically inhale *S. divinorum* smoke from a pipe and hold it in their lungs for an average of 24 s, similar to smoking marijuana; they may repeat this maneuver several times (Baggott *et al*., 2010). In an average session, users smoke an estimated 0.25–0.75-g leaf material (Baggott *et al*., 2010). The main effects of the *S. divinorum* leaf or extract were estimated to last by an average of 15 min when used in this manner. Those who chewed or otherwise buccally absorbed the *S. divinorum* products reported keeping it in their mouth for an average time of 18 min before spitting or swallowing it. When used in this manner, effects were estimated to last approximately 31 min (Baggott *et al*., 2010). Most users reported primarily using salvia in home settings such as apartments and houses. Some of them emphasized a need for a safe environment to facilitate a smooth hallucinogenic trip (Kelly, 2011).

According to epidemiological data, typical users of salvia are young-adult White men whose parents have higher income than parents of nonusers. The use of alcohol, tobacco, marijuana, and other illicit drugs (namely LSD, ecstasy, heroin, phencyclidine, and cocaine); misuse of prescription drugs; and self-control are all positively and significantly correlated with salvia use (Khey *et al*., 2008; Albertson and Grubbs, 2009; Miller *et al*., 2009; Baggott *et al*., 2010; Nyi *et al*., 2010; Ford *et al*., 2011; Wu *et al*., 2011; Currie, 2013). Importantly, polydrug use was the strongest determinant for recent and former *S. divinorum* use (Perron *et al*., 2012). *S. divinorum* use is also common among individuals who are engaged in risk-taking behaviors, such as selling illicit drugs and stealing (Perron *et al*., 2012). Self-reported depression and anxiety were also associated with salvia use (Perron *et al*., 2012). Recent and former *S. divinorum* users had greater odds of having past-year depression and a substance use disorder (alcohol or drugs) than past-year alcohol or drug users who did not use *S. divinorum*. Approximately 15% of *S. divinorum* users had self-reported depression in the past year compared with 7.2% of nonusers of *S. divinorum*. Moreover, 43% of the past-year users and 28.9% of former users had a drug use disorder compared with only a 2.5% of nonusers of salvia (Wu *et al*., 2011). Whether the increased rate of salvia use in the population of depressed patients reflects the antidepressive effect of salvinorin A or only users' expectations as to the drug's action remains to be elucidated.

There are different reasons that underlie the motivation for *S. divinorum* use, such as curiosity, the wish to explore altered consciousness, or to try a new experience, spiritual or mystical reasons, personal growth or self-understanding, contemplation or meditation, relaxation or enjoyment, for fun, to get high, to increase enjoyment of other activities, to help resolve psychological problems, or interest in drug-induced states of consciousness (Baggott *et al*., 2010; Sumnall *et al*., 2012). An Internet-based survey of 219 *S. divinorum* users revealed that users who were young adults (≤21 years) at first use favored salvia for fun or to relieve boredom, whereas users who were adults (≥22 years) at first use favored salvia for its spiritual effects (Nyi *et al*., 2010). Furthermore, Sumnall *et al*. (2012) noted that spiritual purposes, a desire to feel close to nature, enhanced creativity, and personal psychotherapy were more frequently present in the most recent use than in the first use.

As the primary drive of *S. divinorum* use is the pursuit of altered states of consciousness, it is suggested that legal controls would do little to discourage existing users from purchasing salvia products (Sumnall *et al*., 2012). Several authors pointed out that repeated intentional salvia use for the purpose of obtaining positive psychomimetic effects could pose a health concern or increase the likelihood of medical and other psychiatric conditions for those users who have been affected by other substance use or psychiatric disorders (Singh, 2007; Przekop and Lee, 2009; Vohra *et al*., 2011; Wu *et al*., 2011). Furthermore, the high prevalence of substance use disorders among recent *S. divinorum* users emphasizes the need to study the health risks of drug interactions.

Taken together, accumulating epidemiological data on the prevalence, profile, and motivation for *S. divinorum* use will allow a precise definition of the risk groups to which future educational, prevention, and treatment strategies should be addressed.

## ANALYSIS OF SALVINORIN A

At present, neither salvinorin A nor its metabolites can be detected by standard and extended drug tests. However, because *S. divinorum* is controlled in several countries, including Australia, Belgium, Canada, Denmark, Estonia, Finland, Italy, Japan, Poland, Russia, Spain, and Sweden, and in several USA states, various highly advanced methods for forensic analysis of suspected products and biological fluids have been developed in recent years.



DOI: 10.1002/hup

*Salvia divinorum* cannot be distinguished from other *Salvia* species on the basis of morphological features. However, as salvinorin A is present only in *S. divinorum*, the plant is usually identified by detection of this psychoactive compound. Common methods of salvinorin A detection in the plant material are based on gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry preceded by extraction using various solvents (e.g., Pichini *et al*., 2005; Schmidt *et al*., 2005a; Wolowich *et al*., 2006; Barnes and Snow, 2012; Willard *et al*., 2012). Willard *et al*. (2012) found dichloromethane the most suitable, as this solvent extracts the greatest mass of salvinorin A, with the least extraction of other plant compounds, and has the highest interday precision.

Barnes and Snow (2012) compared two methods of extraction of salvinorin A from plant material and urine and water solutions, that is, liquid–liquid extraction (LLE) with chloroform and solid-phase microextraction (SPME) using 85-μm polyacrylate fiber. They found SPME more precise than LLE, with a limit of detection for SPME at least one order of magnitude lower than for LLE. SPME was proposed for clinical or physiological samples, as unmetabolized salvinorin A is present in urine, whereas LLE is better suited for higher concentrations that may be found in products containing salvinorin A.

Another way to identify *S. divinorum* is by DNA identification using short orthologous standard DNA sequences, known as DNA bar coding, and polymerase chain reaction. DNA bar coding enables rapid and accurate identification of unidentified plant organisms whose DNA barcodes have been already registered in a sequence library (Ogata *et al*., 2012). Amplification of the chloroplast *rbcL* gene allows differentiation of *S. divinorum* from other commonly smoked plants, that is, *Nicotiana tabacum* and *Cannabis sativa*, whereas amplification of *trnL* gene using trnLF3 and trnLR2 primers allows *S. divinorum* to be distinguished from other *Salvia* species, excluding *Salvia venulosa*, a close relative of *S. divinorum*. However, *S. venulosa* is a very rare plant that is unlikely to be present in seized products. By sequencing three regions of the chloroplast genome (*trnL–trnF*, *matK*, and *rbcL*) and one of the nuclear genome (an internal transcribed spacer combination), *S. divinorum* was identified in a sample of herbal products that also contained *Mitragyna speciosa*. Gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry analyses of this sample revealed the presence of not only salvinorin A and mitragynine (an active component of *M. speciosa*) but also synthetic cannabinoids, such as JWH-250 and JWH-122 (Ogata *et al*., 2012).

## SUMMARY AND CONCLUSION

Although *S. divinorum* has been traditionally used for centuries for spiritual and medical practices, its appearance as a recreational drug is a recent phenomenon. Because of its potent and unique hallucinogenic activity, ready availability, perception of relative safety, and lack of detectability upon routine drug screening, the plant has gained increasing popularity, especially among adolescents and young adults. Users typically use Internet websites and forums as sources of information on *S. divinorum* where the plant is promoted as an anti-addictive, an effective tool in psychotherapy, and a herb that may be used in the treatment of different diseases, such as depression, bipolar disorder, posttraumatic stress disorder, anxiety, schizophrenia, and chronic pain (http://www.salviatruth.com). Many of the sites misinterpreted the lack of scientific evidence on toxic and negative side effects of salvia as evidence for its safety. However, experimental and clinical data accumulated over the last few years highlight the potential health risk of using *S. divinorum*, especially by teenagers, who are particularly vulnerable for experimentation with new psychoactive substance promoted by the Internet, users of other substances of abuse, and individuals with underlying psychotic disturbances. Taken together, the evidence presented in this review points to the need for further basic and clinical studies creating a basis for the development of efficient, well-addressed educational, prevention, and treatment strategies.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

## REFERENCES

Addy PH. 2012. Acute and post-acute behavioral and psychological effects of salvinorin A in humans. *Psychopharmacol* **220**: 195–204.

Albertson DN, Grubbs LE. 2009. Subjective effects of Salvia divinorum: LSD– or marijuana-like?. *J Psychoactive Drugs* **41**: 213–217.

Ansonoff MA, Zhang J, Czyzyk T, *et al*. 2006. Antinociceptive and hypothermic effects of salvinorin A are abolished in a novel strain of kappa-opioid receptor-1 knockout mice. *J Pharmacol Exp Ther* **318**: 641–648.

Baggott MJ, Erowid E, Erowid F, Galloway GP, Mendelson J. 2010. Use patterns and self-reported effects of *Salvia divinorum*: an Internet-based survey. *Drug Alcohol Depend* **111**: 250–256.

Barnes BB, Snow NH. 2012. Analysis of salvinorin A in plants, water, and urine using solid-phase microextraction-comprehensive two-dimensional gas chromatography–time of flight mass spectrometry. *J Chromatogr A* **1226**: 110–115.

Baker LE, Panos JJ, Killinger B, *et al*. 2009. Comparison of the discriminative stimulus effects of salvinorin A and its derivatives to U69,593 and U50,488 in rats. *Psychopharmacology* **203**: 203–211.

Braida D, Donzell A, Martucci R, Sala M. 2011. Learning and memory impairment induced by salvinorin A, the principal ingredient of *Salvia divinorum*, in Wistar rats. *Int J Toxicol* **30**: 650–661.

Butelman ER, Prisinzano TE, Deng H, Rus S, Kreek MJ. 2009. Unconditioned behavioral effects of the powerful κ-opioid hallucinogen salvinorin A in

nonhuman primates: fast onset and entry into cerebrospinal fluid. *J Pharmacol Exp Ther* **328**: 588–597.
Butelman ER, Rus S, Prisinzano TE, Kreek MJ. 2010. The discriminative effects of the kappa-opioid hallucinogen salvinorin A in nonhuman primates: dissociation from classic hallucinogen effects. *Psychopharmacology (Berl)* **210**: 253–262.
Carlezon WA Jr, Béguin C, DiNieri JA, *et al*. 2006. Depressive-like effects of the kappa-opioid receptor agonist salvinorin A on behavior and neurochemistry in rats. *J Pharmacol Exp Ther* **316**: 440–447.
Casselman I, Heinrich M. 2011. Novel use of *Salvia divinorum*: unobtrusive observation using YouTube™. *J Ethnopharmacol* **138**: 662–667.
Chartoff EH, Potter D, Damez-Werno D, Cohen BM, Carlezon WA Jr. 2008. Exposure to the selective kappa-opioid receptor agonist salvinorin A modulates the behavioral and molecular effects of cocaine in rats. *Neuropsychopharmacology* **33**: 2676–2687.
Cunningham CW, Rothman RB, Prisinzano TE. 2011. Neuropharmacology of the naturally occurring κ-opioid hallucinogen salvinorin A. *Pharmacol Rev* **63**: 316–347.
Currie CL. 2013. Epidemiology of adolescent *Salvia divinorum* use in Canada. *Drug Alcohol Depend* **128**: 166–170.
Deluca P, Davey Z, Corazza O, *et al*. 2012. Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project. *Prog Neuropsychopharmacol Biol Psychiatry* **39**: 221–226.
Fantegrossi WE, Kugle KM, Valdes LJ 3rd, Koreeda M, Woods JH. 2005. Kappa-opioid receptor-mediated effects of the plant-derived hallucinogen, salvinorin A, on inverted screen performance in the mouse. *Behav Pharmacol* **16**: 627–633.
Ford JA, Watkins WC, Blumenstein L. 2011. Correlates of *Salvia divinorum* use in a national sample: findings from the 2009 National Survey on Drug Use and Health. *Add Behav* **36**: 1032–1037.
Giroud C, Felber F, Augsburger M, Horisberger B, Rivier L, Mangin P. 2000. *Salvia divinorum*: a hallucinogenic mint which might become a new recreational drug in Switzerland. *Forensic Sci Int* **112**: 143–150.
González D, Riba J, Bouso JC, Gómez-Jarabo G, Barbanoj MJ. 2006. Pattern of use and subjective effects of *Salvia divinorum* among recreational users. *Drug Alcohol Depend* **85**: 157–162.
Grilli M, Neri E, Zappettini S, *et al*. 2009. Salvinorin A exerts opposite presynaptic controls on neurotransmitter exocytosis from mouse brain nerve terminals. *Neuropsychopharmacology* **57**: 523–530.
Gruber JW, Siebert DJ, Der Marderosian AH, Hock RS. 1999. High performance liquid chromatographic quantification of salvinorin A from tissues of *Salvia divinorum* epling and játiva-m. *Phytochem Anal* **10**: 22–25.
Halpern JH, Pope HG Jr. 2001. Hallucinogens on the Internet: a vast new source of underground drug information. *Am J Psychiatry* **158**: 481–483.
Hanes KR. 2001. Antidepressant effects of the herb *Salvia divinorum*: a case report. *J Clin Psychopharmacol* **21**: 634–635.
Harden MT, Smith SE, Niehoff JA, McCurdy CR, Taylor GT. 2012. Antidepressive effects of the κ-opioid receptor agonist salvinorin A in a rat model of anhedonia. *Behav Pharmacol* **23**: 710–715.
Hooker JM, Xu Y, Schiffer W, Shea C, Carter P, Fowler JS. 2008. Pharmacokinetics of the potent hallucinogen, salvinorin A in primates parallels the rapid onset, short duration of effects in humans. *NeuroImage* **41**: 1044–1050.
Hooker JM, Patel V, Kothari S, Schiffer WK. 2009. Metabolic changes in the rodent brain after acute administration of salvinorin A. *Mol Imaging Biol* **11**: 137–143.
Hoover V, Marlowe DB, Patapis NS, Festinger DS, Forman RF. 2008. Internet access to *Salvia divinorum*: implications for policy, prevention, and treatment. *J Subst Abuse Treat* **35**: 22–27.
Kelly BC. 2011. Legally tripping: a qualitative profile of *Salvia divinorum* use among young adults. *J Psychoactive Drugs* **32**: 46–54.
Khey DH, Miller BL, Griffin OH. 2008. *Salvia divinorum* use among a college student sample. *J Drug Education* **38**: 297–306.
Killinger BA, Peet MM, Baker LE. 2010. Salvinorin A fails to substitute for the discriminative stimulus effects of LSD or ketamine in Sprague–Dawley rats. *Pharmacol Biochem Behav* **96**: 260–265.
Lange JE, Reed MB, Croff JM, Clapp JD. 2008. College student use of *Salvia divinorum*. *Drug Alcohol Depend* **94**: 263–266.
Lange JE, Daniel J, Homer K, Reed MB, Clapp JD. 2010. *Salvia divinorum*: effects and use among YouTube users. *Drug Alcohol Depend* **108**: 138–140.
MacLean KA, Johnson MW, Reissig CJ, Prisinzano TE, Griffiths RR. 2013. Dose-related effects of salvinorin A in humans: dissociative, hallucinogenic, and memory effects. *Psychopharmacol (Berl)* **226**: 38–92.
Medana C, Massolino C, Pazzi M, Baiocchi C. 2006. Determination of salvinorins and divinatorins in Salvia divinorum leaves by liquid chromatography/multistage mass spectrometry. *Rapid Commun Mass Spectrom* **20**: 131–136.
Mendelson JE, Coyle JR, Lopez JC, *et al*. 2011. Lack of effect of sublingual salvinorin A, a naturally occurring kappa opioid, in humans: a placebo-controlled trial. *Psychopharmacol* **214**: 933–939.
Meyer EG, Writer BW. 2012. *Salvia divinorum*. *Psychosomatics* **53**: 277–279.
Miller BL, Griffin OH III, Gibson CL, Key DN. 2009. Trippin on Sally D: exploring predictors of *Salvia divinorum* experimentation. *J Crim Jus* **37**: 396–403.
Morani AS, Kivell B, Prisinzano TE, Schenk S. 2009. Effect of kappa-opioid receptor agonists U69593, U50488H, spiradoline and salvinorin A on cocaine-induced drug-seeking in rats. *Pharmacol Biochem Behav* **94**: 244–249.
Nemeth CL, Paine TA, Rittiner JE, *et al*. 2010. Role of kappa-opioid receptors in the effects of salvinorin A and ketamine on attention in rats. *Psychopharmacology* **210**: 263–274.
Nyi PP, Lai EP, Lee DY, Biglete SA, Torrecer GI, Anderson IB. 2010. Influence of age on *Salvia divinorum* use: results of an Internet survey. *J Psychoactive Drugs* **42**: 385–392.
Ogata J, Uchiyama N, Kikura-Hanajiri R, Goda Y. 2012. DNA sequence analyses of blended herbal products including synthetic cannabinoids as designer drugs. *Forensic Sci Int* doi: 10.1016/j.forsciint.2012.09.006.
Paulzen M, Grűnder G. 2008. Toxic psychosis after intake of hallucinogen salvinorin A. *J Clin Psychiatry* **69**: 1501.
Perron BE, Ahmedani BK, Vaughn MG, Glass JE, Abdon A, Wu LT. 2012. Use of *Salvia divinorum* in a nationally representative sample. *Am J Drug Alcohol Abuse* **38**: 108–113.
Pichini S, Abanades S, Farré M, Pellegrini M, Marchei E, Pacifici R. 2005. Quantification of the plant-derived hallucinogen salvinorin A in conventional and non-conventional biological fluids by gas chromatography/mass spectrometry after *Salvia divinorum* smoking. *Rapid Commun Mass Spectrom* **19**: 1649–1656.
Potter DN, Damex-Werno D, Carlezon WA Jr, Cohen BM, Chartoff EH. 2011. Repeated exposure to the kappa-opioid receptor agonist salvinorin A modulates extracellular signal regulated kinase and reward sensitivity. *Biol Psychiatry* **70**: 744–753.
Przekop P, Lee T. 2009. Persistent psychosis associated with *Salvia divinorum* use. *Am J Psychiatry* **166**: 832.
Ranganathan M, Schnakenberg A, Skosnik PD, *et al*. 2012. Dose-related behavioral, subjective, endocrine, and psychophysiological effects of the κ opioid agonist salvinorin A in humans. *Biol Psychiatry* **72**: 871–879.
Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S. 2002. Salvinorin A: a potent naturally occurring nonnitrogenous κ opioid selective agonist. *Proc Natl Acad Sci U S A* **99**: 11934–11939.
Schmidt MS, Prisinzano TE, Tidgewell W, Harding W, Butelman ER, Kreek MJ, Murry DJ. 2005a. Determination of salvinorin A in body fluids by high performance liquid chromatography–atmospheric pressure chemical ionization. *J Chromatogr B* **818**: 221–225.
Schmidt MD, Schmidt MS, Butelman ER, *et al*. 2005b. Pharmacokinetics of the plant derived κ-opioid hallucinogen salvinorin A in nonhuman primates. *Synapse* **58**: 208–210.
Schmidt MM, Sharma A, Schifano F, Feinmann C. 2011. "Legal highs" on the net—evaluation of UK-based websites, products and product information. *Forensic Sci Int* **206**: 92–97.
Singh S. 2007. Adolescent salvia substance abuse. *Addiction* **102**: 823–824.
Sumnall HR, Measham F, Brandt SD, Cole JC. 2012. *Salvia divinorum* use and phenomenology: results from on line survey. *J Psychopharm* **25**: 1498–1507.
Teksin ZS, Lee IJ, Nemieboka NN, Othman AA, Upreti VV, Hassan HE. 2009. Evaluation of the transport, *in vitro* metabolism and pharmacokinetics of salvinorin A, a potent hallucinogen. *Eur J Pharm Biopharm* **72**: 471–477.
Travis CR, Ray GA, Marlowe KF. 2012. A report on nausea and vomiting with discontinuation of chronic use of *Salvia divinorum*. *Case Rep Med* **2012**: 543747.

Tsujikawa K, Kuwayama K, Miyaguchi H, *et al*. 2008. Determination of salvinorin A and salvinorin B in *Salvia divinorum*-related products circulated in Japan. *Forensic Sci Int* **180**: 105–109.

Tsujikawa K, Kuwayama K, Miyaguchi H, Kanamori T, Iwata YT, Inoue H. 2009. *In vitro* stability and metabolism of salvinorin A in rat plasma. *Xenobiotica* **39**: 391–398.

Vohra R, Seefeld A, Cantrell FL, Clark RF. 2011. *Salvia divinorum*: exposures reported to a statewide poison control system over 10 years. *J Emerg Med* **40**: 643–650.

Willard MAB, McGuffin VL, Smith RW. 2012. Forensic analysis of *Salvia divinorum* using multivariate statistical procedures. Part I: discrimination from related *Salvia* species. *Anal Bioanal Chem* **402**: 833–842.

Wolowich WR, Perkins AM, Cienki JJ. 2006. Analysis of the psychoactive terpenoid salvinorin A content in five *Salvia divinorum* herbal products. *Pharmacotherapy* **26**: 1268–1272.

Wu L-T, Woody GE, Yang C, Li J-H, Blazer DG. 2011. Recent national trends in *Salvia divinorum* use and substance-use disorders among recent and former *Salvia divinorum* users compared with nonusers. *Subst Abuse Rehabil* **2011**: 53–68.

Zhang Y., Butelman ER, Schlussman SD, Ho A, Kreek MJ. 2005. Effects of the plant-derived hallucinogen salvinorin A on basal dopamine levels in the caudate putamen and in conditioned place aversion assay in mice: agonist actions at kappa opioid receptors. *Psychopharmacology* **179**: 551–558.