

The Rise of a New Psychoactive Agent: *Salvia divinorum*

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Abstract Since the 1990s, there has been a rise in the availability and recreational use of a herbal plant called *Salvia divinorum*. Numerous internet websites have advertised it for sale as a legal herbal alternative to illegal hallucinogens. Initial data surveying use has indicated many young adults are obtaining and using this herb for its psychoactive properties. Reported methods of ingestion for the plant include chewing, and smoking leaves or fortified extracts. Subjective effects of the plant include, affect changes, psychedelic-like changes in perception, and even loss of consciousness. Although the pharmacological properties and possible antidepressant effects have been studied in recent years, little information is known about potential negative impact resulting from recreational use, and scant information about *Salvia divinorum* currently exists in the psychological and substance abuse literature. While *Salvia divinorum* appears to be a substance with some therapeutic potential, it also poses some significant dangers as a substance of varying legal status with a potential for abuse.

Keywords *Salvia divinorum* · *Salvia* · Drugs of abuse · Recreational drugs · Hallucinogen · Kappa-opioid receptor · Salvinorin-A · Herbal drugs

Introduction

Once a little known substance, *Salvia divinorum* has gained increasing awareness by two divergent groups of individuals: pharmacological researchers and recreational substance users. Although this substance has been around for centuries, it has entered the modern world only relatively recently. Since the early 1990s, there has been a rise in the recreational

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use of *S. divinorum* as a hallucinogen—which only recently had been recognized by law enforcement, educators, and health officials (Schaper 2006). While the availability and use of this drug appears to be increasing, scant publications exist in the psychological and substance abuse literature. It is now imperative that other therapeutic professionals and researchers examine the potential and possible dangers of this psychoactive agent. This article will give a brief history of this psychoactive agent, including its methods of ingestion, subjective effects, and its potential for use and abuse. This article will also review the evolving legal status of this substance.

History

Salvia divinorum is a member of a family of mint plants known as the Labiatae. *Salvia* is prevalent to the Sierra Madre Mountains in Oaxaca, Mexico. In this isolated region, it has been used by Mazatec folk healers (“curanderos” or “curanderas”) in different rituals (Valdés 1994). The plant is mostly used by these shamans for medicinal or spiritual purposes. The Mazatec Indians referred to this herb by a number of names, most commonly “ska Maria pastora” (“leaves of the Virgin Mary, the Shepherdess”). The Mazatecs employed this plant for medicinal divination (learning the cause or identification of an illness) as well as for the management of such conditions as headache, *Salvia* was also used to foretell the future, and obtain divine answers to questions about friends, enemies and relatives. The story of western scientific exploration of the plant began in the late 1930s, when R. Gordon Wasson and Albert Hoffman brought back material from Mexico for the American botanist Carl Epling to identify (Wasson 1962, 1963). *S. divinorum* (“diviner’s sage”) was the name given to this plant by Epling (Epling and Játiva-M 1962).

Salvia divinorum is a unique hallucinogen that is seeing increased use and availability in humans. In recent years the active ingredient of *Salvia divinorum* has been identified as Salvinorin-A. (Valdes et al. 1984; Siebert 1994). Salvinorin-A is responsible for *S. divinorum*’s mind-altering effects. While *S. divinorum* (and Salvinorin-A) has been banned in a number of countries across the world, it is not currently a federally controlled substance in the United States, where it is used as a legal alternative to controlled substances (González et al. 2006).

Methods of Ingestion and Subjective Effects

Traditionally, Mazatec shamans used two methods of ingestion. They would crush the leaves to extract the leaf juices, which they then drink (usually mixed with water). Sometimes they simply ate the fresh leaves by chewing and swallowing them (Wasson 1962). Outside of Mexico, the plant material is either chewed or smoked (Baggott et al. 2004). When chewed, leaf mass and juice are maintained within the cheek area with absorption occurring across the lining of the oral mucosa (buccal). Dried leaves, as well as extracts (purported to be enriched with an increased concentrated levels of Salvinorin-A), are smoked. Smoking (in a water pipe or by inhaling the vapor) reportedly provides a more “intense” experience than other oral methods (González et al. 2006). The mechanism of action of Salvinorin-A is at the k-opioid receptor within the central nervous system (Sheffler and Roth 2003; Prisinzano 2005). It has been reported that for recreational users of the plant, smoking the fortified extract was the preferred form of administration (González et al. 2006). Subjective effects of *S. divinorum* have been described as potent but short-lived. Smoking pure Salvinorin-A, at a dose of 200–500 micrograms, results in effects within 30 s and lasts about 15–30 min. When the leaves

are chewed, the first effects come on at about 15 min and gradually develop to peak about 30 min after ingestion. The peak level of effects for this method lasts 30 min to an hour, and gradually diminishes over an additional 30 min to an hour (González et al. 2006). The chewed effects are often reported as being more “subtle” than the effects of smoking *Salvia divinorum* or Salvinorin-A. (Baggott et al. 2004). Overall, the subjective effects described in self-reported experiments and case reports vary widely, from psychedelic-like changes in visual perception, somatic sensations, subjective perception of external reality and the self, increased relaxation, out-of-body experiences, loss of consciousness, and uncontrolled laughter (González et al. 2006).

The largest sampling of *S. divinorum* usage to date has been done by Baggott et al. (2004) who performed a web-based survey of 500 users. Those responding to the survey had used the plant for recreational purposes for a mean of 13.3 times (Standard Deviation= 22.9; range 1–250). Average age for respondents was 23.4 years old (range of 13–68). The reasons given were usually to explore altered consciousness or to have a spiritual/mystical experience. Users comprising 80.6% reported they would probably or definitely would use *S. divinorum* again. The 92.6% smoked *Salvia* with 61.4% using a concentrated extract and 37.3% using dried leaf; mean effects were estimated to last 14.1 min. Baggott et al. (2004) also report that common (>25%) after-effects of *Salvia* included feelings of increased insight (47%), improved mood (44.8%), calmness (42.2%), increased sense of connection with the universe or nature (39.8%), weird thoughts (36.4%), things seem unreal (32.4%), floating feeling (32%), increased sweating (28.2%) and body felt warm or hot (25.2%). Users composed of 25.8% reported persisting (>24 h) positive effects (usually an increased sense of well-being) on at least one occasion. Another 4.4% had persisting negative effects (most often anxiety). Some 0.6% had sought professional help for a *Salvia*-related problem. At some point, 0.6% felt addicted to or dependent upon *Salvia*; 1.2% reported strong cravings for *Salvia*; 0.4% endorsed three DSM-IV dependence criteria.

Pharmacological Action and Potential Therapeutic Use

Animal studies are consistent with in vivo pharmacological studies which demonstrate that Salvinorin-A is a highly potent and selective kappa or k- opioid receptor (KOR) agonist (Zhang et al. 2005). Salvinorin-A in contrast with the classical psychedelics, does not interact with the serotonin-2A receptor, but induces its psychotropic effects through this kappa-opioid receptor (KOR) activation, which likely accounts for the subjective mood and hallucinogenic effects of the drug in humans (Sheffler and Roth 2003). Animal research has indicated that k- opioid receptor (KOR) agonists may provide benefits in decreasing learned helplessness and depression (Ukai et al. 2002) and can lower dopamine levels in the brain (Di Chiara and Imperato 1988; Donzanti et al. 1992; Spanagel et al. 1992; Devine et al. 1993; Zhang et al. 2004). Kappa agonists have also been studied for the potential treatment of cocaine addiction (Glick et al. 1995; Kuzmin et al. 1997; Schenk et al. 1999; Walsh et al. 2001). Some researchers have noted that because of its pharmacological action on k-opioid receptors, drugs derived from Salvinorin-A may lead to novel medications for the treatment of mental disorders manifested by hallucinatory experiences (e.g., schizophrenia, affective disorders, and dementia) and may have a potential as an antidepressant or addiction treatment agent (Roth et al. 2002; Sheffler and Roth 2003; Chavkin et al. 2004). Therapeutic clinical action on humans has been reported in only one anecdotal report by Haynes (2001). This individual case study reports a 26-year old chronically depressed woman who had self-administered minimal oral doses of 0.5–0.75 g of *S. divinorum* leaves three times a week

with occasional intoxicating oral doses of 2–4 g. During this period she reported total remission of depressive symptoms as measured by the Hamilton Depression Scale. It was reported that she maintained improvement for 6 months after initial improvement. Even though these results are interesting, the lack of classic experiential design severely limits the generalizability of the results.

Potential for Abuse and Harm

Since neither *Salvia divinorum*, nor any of its constituents, are listed in the federal Controlled Substances Act (CSA), a variety of Internet sites have appeared advertising *S. divinorum* or Salvinorin-A fortified extracts for sale as a legal alternative to illegal hallucinogens. *S. divinorum* sales have also been reported in “smart shops” or “head shops” across the United States and Europe with adolescents and young adults representing the largest group of consumers of this substance (González et al. 2006; Baggott et al. 2004). Nicknames or slang terms for *S. divinorum* include, “Sally D,” “Magic Mint,” “Lady Salvia,” “Purple Sticky” or simply, “Sage.” Almost nothing is known about either the long-term or short-term health issues relating to *S. divinorum*. This dearth of information can lead to some potentially dangerous assumptions being made. The assumption that because it can be purchased legally it is safe—may be an erroneous one. *S. divinorum* can sometimes affect motor co-ordination, balance, as well as awareness of surroundings (González et al. 2006). This can make it difficult to walk and perform simple tasks. The risk posed to the user can be quite significant. Even simple tasks such as walking down stairs could be dangerous if this effect is pronounced. Certainly more complex tasks, such as driving a car or operating machinery under the influence of *S. divinorum* could be quite disastrous. *S. divinorum*’s effects can continue well after the subjective effects have subsided (perhaps up to an hour when smoked). The long-term psychological effects of *S. divinorum* have not been studied, but given the research that people who start smoking cannabis as adolescents are at the greatest risk of later developing mental health problems (Rey and Tennant 2002); similar concerns about *S. divinorum*’s users would be prudent. Like other drugs, users with pre-existing mental illness or a latent predisposition to psychosis may be at risk to develop mental health problems as a result of *S. divinorum* use. It is impossible to say with confidence which users may be susceptible to drug induced psychosis as the effects of *Salvia* are not yet clearly understood. While Baggott et al. (2004) reported some identified pleasant effects of the substance (the same could be said of any drug of abuse), there was a subset that reported significant negative effects, and the formation of possible dependence.

Legal Status

S. divinorum is a federally unscheduled hallucinogenic plant. *S. divinorum* and Salvinorin-A are not currently controlled under the CSA. However, a number of states have placed controls on *S. divinorum* and/or Salvinorin-A. In 2005, Louisiana made it illegal to purchase or distribute *S. divinorum*. Both Delaware and Missouri have added *S. divinorum* and Salvinorin-A into Schedule I of the states’ drug regulations. Effective July 2006 in Tennessee, possession or distribution of Salvinorin-A will be illegal. Many other states including Alaska, Illinois, New Jersey, New York, Oklahoma, Oregon, Pennsylvania, Maine, and Wyoming are now moving towards proposed legislation to control the sale and distribution of *S. divinorum* and/or Salvinorin-A. It is currently controlled in Finland,

Denmark, Australia, Italy, and South Korea. The United States Drug Enforcement Agent (2007) (DEA) has placed *S. divinorum* on the list of “drugs of concern,” monitoring social indicators of impact (e.g. emergency rooms reports, illegal activity, accidents, etc.).

Conclusion

Although it appears that in indigenous use of the psychoactive agent called *S. divinorum* has existed for hundreds of years in a remote part of the world—its appearance as a recreational drug is a recent phenomenon. While initial research reveals its potential as a therapeutic agent, including possible antidepressant effects, there are significant risks related to recreational use. These risks include the potential for physical harm due to loss of awareness of surroundings under its effects, and unknown long-term physiological and psychological effects. Parents, educators, and therapists should be alerted to the existing and growing distribution networks that have formed across the internet and in communities and the easy access this has provided for youths. Substance abuse and mental health providers should be educated and alerted to the existence of this substance, diligently screening for negative indicators of use and abuse in client populations. As this substance gains attention, countries and individual states have moved toward strict legal controls. It is likely that further restrictions in the United States will continue, but further scientific research that objectively examines the potentials—while seriously assessing the risks of *Salvia divinorum*—is clearly warranted.

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