

R. Bücheler<sup>1,2</sup>  
C. H. Gleiter<sup>1</sup>  
P. Schwoerer<sup>2</sup>  
I. Gaertner<sup>3</sup>

## Use of Nonprohibited Hallucinogenic Plants: Increasing Relevance for Public Health?

A Case Report and Literature Review on the Consumption of *Salvia divinorum*  
(Diviner's Sage)

**Introduction:** We want to call attention to a mint plant, called diviner's sage (*Salvia divinorum*), originally used in shamanic ceremonies of the Mazatec Indians of Mexico. On numerous websites of the internet, this ancient herbal drug and its extracts are offered as a legal means of widening individual awareness. Regarding its dose-response relationship, the active ingredient, salvinorin A, is one of the most potent naturally occurring hallucinogens. Laws on controlled substances, except for Finland, Denmark and Australia, do not prohibit cultivating, consuming or dealing with *Salvia divinorum*. Ingestion by smoking, vaporis-

ing or chewing, induces a short-lived inebriant state with intense, bizarre feelings of depersonalization. This article wants to be a signal for physicians or psychotherapists to take *Salvia* into consideration, when exploring young people for drug use. **Methods:** We report the individual perceptions of a young man consuming *Salvia divinorum*. We review the scarce scientific literature and consider relevant internet websites. **Discussion:** We define open issues for further investigations and try to discuss why *Salvia divinorum* may be of interest for teenagers and young adults in Europe.

### Introduction

In 2002 the number of offences, especially among children and adolescents involving the possession and purchase of cannabis, rose by more than 6% to 139 082/year in Germany [3]. Similar observations are documented from abroad [7,9]. These figures may reflect a changing attitude of young people towards drug use in general. Intoxication by nonprohibited drugs of herbal origin like *Datura* (*Datura Stramonium*) or Angel's Trumpet (*Brugmansia suaveolens* or *sanguinea*) plays an increasing role in emergency medicine [10,18,28].

We want to point out a newcomer among drugs of herbal origin: A Mexican mint, a sage plant, called "*Salvia divinorum*". For many centuries, it has been used by shamans of the Mazatec Indians in

the state of Oaxaca, Mexico, in healing and divination ceremonies. In 1962, however, it was characterized botanically for the first time by Epling and Játiva [13]. For ritual purposes, five up to 80 pairs of fresh leaves are chewed or crushed and prepared as a bitter tasting, foamy infusion [43]. To date, six different ingredients (salvinorin A-F) have been isolated from its leaves [27]. In 1982 the main psychoactive compound, salvinorin A (Divinorin A), was identified by two independent research groups [29,45]. Salvinorin A, which is not water-soluble, is only absorbed by the respiratory and, to a lesser extent, by the oral mucosa. Dried leaves of *Salvia divinorum* are smoked as a joint, consumed in water pipes or vaporized and inhaled. About 1.5 g of pure salvinorin A can be extracted from one kilogram of air-dried leaves, gained from about 8 kg of fresh leaves [37,43]. According to biochemical reports, it is easier to obtain salvinorin A than to extract

#### Affiliation

<sup>1</sup> Abteilung Klinische Pharmakologie, Universitätsklinikum Tübingen, Otfried-Müller Strasse 45, 72076 Tübingen, Germany

<sup>2</sup> Medizinischer Dienst der Krankenversicherung (MDK) Baden-Württemberg, 77933 Lahr, Germany

<sup>3</sup> Abteilung Allgemeine Psychiatrie und Psychotherapie mit Poliklinik, Universitätsklinikum Tübingen, Osianderstraße 24, 72076 Tübingen, Germany

#### Correspondence

Prof. Dr. med. Christoph H. Gleiter · Abteilung Klinische Pharmakologie · Universitätsklinikum Tübingen · Otfried-Müller-Strasse 45 · 72076 Tübingen · Germany · Fax: 07071 29 5035 · E-Mail: christoph.gleiter@med.uni-tuebingen.de

Received 1.10.2003 · Revised 11.3.2004 · Accepted 17.3.2004

#### Bibliography

Pharmacopsychiatry 2005; 38: 1–5 · © Georg Thieme Verlag KG Stuttgart · New York  
DOI 10.1055/s-2005-837763  
ISSN 0176-3679

lysergic acid diethylamide (LSD) or than to produce phencyclidine derivatives [44]. In minimum doses above 200 to 500 µg, purified salvinorin A has shown intense psychoactive effects [37].

As the content of salvinorin A in one gram of dried leaves may vary from 0.9 to 3.8 mg [19], only 0.1–0.5 g of these leaves are required for a hallucinogenic trip, when inhaled. Fortified plant-extracts however, can also be ordered via the internet. They contain up to 25 mg salvinorin A per gram. On the internet, esoteric websites or ethnobotanical shops openly offer *Salvia* as a means of improving the air in rooms or as a legal hemp alternative at an affordable price [e.g. 2,16,25,31]. Five grams of dried *Salvia* leaves cost between 5 to 12.50 €, not including shipping charges.

The cultivation of *Salvia divinorum* has spread from South and North America to Canada and Europe. Recently, the plant was identified in the greenhouses of a Swiss horticulturist [17].

As clinical effects of *Salvia divinorum* in adolescents have not been described in medical literature, we would now like to recount the psychedelic experiences of a teenager. We have also reviewed available scientific articles as well as trip reports and accessible sites of the internet.

### Case report

In February 2003, the mother of a 19-year old high school student preparing for his A-levels consulted the Department of Clinical Pharmacology of the University Hospital Tuebingen for information concerning the potential health risks of *Salvia divinorum*. She had accidentally noticed a dreadful offensive odour coming from her son's room. While smoking the dried leaves, the young man hardly reacted to her approach and seemed to suffer from a reduced awareness. His face had a strange, transcendental and mask-like expression. The young man was a good student. Apart from habitual smoking, no other drug use was reported by the parents who thought him to be "normal" regarding his social and academic skills. His IQ was tested as above 140.

A standardized psychiatric interview revealed neither personal nor family histories of major psychiatric disorders. The young man reported that he had been chewing or inhaling dried leaves of *Salvia divinorum* twice a week for about six months, alone or in the company of friends. His most important motivation to consume *Salvia* is the unique sensation of being disconnected from his own body during the trip. This extracorporeal existence in a new "astral body" gives him a very "good" feeling of recreation. He also describes vestibular hallucinations that provide an illusion of hovering above the floor, or penetrating the natural limits of his own room. In these moments, he believes to gain a more mature insight not only into his own personality but also into philosophical or ethical problems. Almost immediately – he estimates in less than five minutes after inhaling – the peak of psychotropic effects seems to be reached. During the trip, he experiences somatic sensations like prickling of the skin, fever-like hot flashes, muscular tremor, and a sort of ringing in the ears. All these effects, including the desired feeling of changing his personality and an increased status of self-consciousness, complete-

ly disappear within 30 minutes. For some hours afterwards, he reports shivering and exhaustion that render him unable to learn or memorize school assignments. The young student attributes this lack of concentration not to a prolonged drug effect but to the need of reflecting the overwhelming perceptions during the trip.

He denies having optical or verbal hallucinations, "bad trips" nor fits of panic. During the last months, his trips seemed to follow similar patterns as described above. Nevertheless, he reports his impression that the amount of *Salvia* material, necessary for one trip, will have to be increased gradually in order to maintain the original effective strength. The young man says that he has a good feeling about the safety of *Salvia divinorum*. He is convinced to be well informed by numerous websites on the internet which do not describe severe short term nor long term health risks such as intoxication or an induction of psychoses.

### Discussion

#### Sources of information on *Salvia divinorum*

Reliable, systematic observations on the psychotropic activities of *Salvia divinorum* or its ingredients in human beings are scarce: Searching databases like MEDLINE or BIOSIS, we found a publication on psychotropic effects following the use of fresh *Salvia* leaves in six human volunteers, as well as after the application of purified salvinorin A in 20 volunteers [37]. In another paper, two ethnobotanical researchers report their own observations after drinking a *Salvia* infusion in two different concentrations [43].

On the internet however, "*Salvia divinorum*" is linked to numerous websites of ethnobotanical shops, consumers and "experienced specialists" that provide details on botanical cultivation, on dosing and sometimes even publish "guidelines" for a safe and satisfying use of "the magic mint" [e.g. 1,16,35,42]. In chat-rooms such as [33], users communicate and discuss their experiences during the trips. Amateur researchers even publish the results of their private "double-blind" and "placebo-controlled" tests in search of the optimal *Salvia* dose for meditation [40].

#### Clinical effects

The young boy, who lives about 100 km away from our clinic told us about his trip experiences in a clinically drug-free condition. As *Salvia* and its ingredients cannot be detected by usual drug-screening methods, we did not perform blood or urine analysis. We excluded the concomitant use of other hallucinogens by interview. The student reported *Salvia* effects like depersonalization, widening of consciousness, the subjective illusion of rapid movements, flying or hovering, as being comfortable feelings. They seem to outreach negative side effects of *Salvia* use such as impaired vigilance and coordination. Although horror-trips appear to be rare, on the internet, some consumers delineate frightening attacks of panic, mostly due to the loss of self-control and to the profound experience of losing contact with consensual reality. As this is "nothing for beginners", most of the websites recommend the presence of a sober "trip sitter" [14,35]. He should also protect the *Salvia* consumer against injury due to somnambulistic activities or to coordination disturbances [38].

Onset and duration of the young man's trips correspond to the data reported on websites and in a scientific publication: After inhaling a bolus of the active ingredient, hallucinogenic feelings are intense but very short-lived. They occur rapidly after 30 seconds and disappear within one hour [38]. Hallucinogenic effects after oral ingestion of salvinorin A begin within 3–5 minutes. These perceptual distortions may return for up to 4 hours, sometimes experienced as “flashbacks” [43]. Hysterical laughter is observed, but *Salvia divinorum* is said to have only a weak influence on the prevailing mood of the consumer and rarely changes it [37]. This is an important difference to LSD or hallucinogenic mushrooms.

Salvia provides the experience of voyages leading the individual to places of the past, especially from childhood. It may cause vivid illusions of a self-metamorphosis into things like water or animals, culminating in the individual conviction of having definitely abandoned human existence [37].

Doses of salvinorin A needed for hallucinogenic effects, vary from one individual to the other. Different Salvia websites report that about 10 to 15% of the consumers do not experience any psychotropic effects at all! In doses exceeding 1 mg salvinorin A, out-of body experiences, i.e. advanced “trip levels”, are frequent [37]. On awakening after very high trip levels, the consumer may completely have lost his recollection of having taken any drug [35].

These psychotomimetic effects of *Salvia divinorum* closely resemble schizophrenia symptoms induced by other distinct classes of drugs: Serotonergic agonists (e.g. LSD) and especially antagonists of the NMDA (*N*-methyl-*D*-aspartate) glutamate receptor like phencyclidine (PCP, Angel dust) or ketamine [21,22]. Indeed, web-reports describe similarities of Salvia associated perceptions with LSD or Ketamine [1,34], but it is often emphasized, that the depersonalization caused by Salvia has a unique and specific character [37]. In 2002, the active ingredient, salvinorin A, has been shown to be a potent and strong agonist of cerebral kappa-opioid receptors (KOR) [6,32,36]. This interaction may cause the reported vegetative reactions to Salvia like sweating, chill and increased diuresis, which may be related to the interaction with KOR. The same effects were shown by synthetic agents stimulating KOR like spiradolone in humans [46]. Salvia induced illusions are intensified by rest and darkness [43]. The afterglow of former Salvia trips as well as the concomitant intake of other psychoactive agents like ethanol, cannabis, LSD or hallucinogenic mushrooms have been mentioned to determine the individual feeling [35].

#### Pharmacokinetics and pharmacodynamics of the active ingredient, Salvinorin A

Salvinorin A, a neoclerodane diterpene, is the only known non-alkaloidal hallucinogen [6]. Beside the fact, that it is not easily absorbed by the gastrointestinal system [37], data on bioavailability, on metabolism or excretion and on interactions with food, drugs or narcotic agents are not published. In terms of its psychoactive effects doses of above 200  $\mu\text{g}$ , salvinorin A rivals in potency with the synthetic hallucinogen LSD acting in doses of 50–250  $\mu\text{g}$  [44].

Pharmacodynamic aspects of salvinorin A and its derivatives have been studied more exactly in the last decade [6,32,36]. In human and nonhuman cell cultures, salvinorin A has proven to be a selective, full and very efficacious agonist for KOR [6,32]. It does not interact with 5-hydroxytryptamine 2A-receptors, like classical hallucinogens such as LSD, psilocybin or mescaline do, and shows no affinity to  $\mu$ - or  $\delta$ -opioid receptors nor did it interact with binding-sites for norepinephrine, dopamine, glutamine and GABA-transporters [32]. Psychotropic effects of salvinorin A appear to be the result of KOR stimulation. This hypothesis is supported by the recently published behavioral effects of salvinorin A in primates [4]. Salvinorin A is the first naturally occurring non-nitrogenous agent and stimulates KOR to the same extent like dynorphin, the endogenous KOR-agonist [6].

Due to their reduced affinity to KOR, therapeutically used opioid-antagonists like naloxone or naltrexone are not regarded as a very potent antidote for salvinorin A [15,23,24].

#### Pharmacotherapeutic potential

KOR mediated neurotropic effects are analgesia, sedation, dysphoria and perceptual distortions [12,15,30]. Selective stimulation of KOR by salvinorin A may be a pharmacological model to study the promotion of schizophrenia, dementia or bipolar depression. KOR-antagonists like nor-binaltorphimine, have shown antidepressant effects by ameliorating psychomotoric functions in rats [26]. Paradoxically, a case-report of a 26-year old woman documents the complete resolution of a perennial depression since ingesting 0.5–0.75 g of Salvia leaves three times per week sublingually [20]. This is surprising, since the dysphoric side effects of KOR-agonists normally form an obstacle to their use as analgesics, for instance, see [46].

Stimulation or blockade of cerebral KOR may also modulate cardiovascular functions. Experimental investigations in animals show an influence on blood pressure, on the ischemic tolerance of the myocardium and on the induction of cardiac arrhythmias [8,47,48].

#### User population and legal aspects

To date, the vast majority of *Salvia divinorum* consumers are younger adults and adolescents. As “Diviner's mint” is not a party-drug [35,43], it appeals to individual experimentalists. On the internet, they define themselves as a kind of community, ingesting the plant or its extracts not to satisfy an addiction, but as a tool for meditative introspection [5,42]. In international conferences, psychotherapists, artists, ethnobotanists, anthropologists, pharmacologists and consumers discussed, how the plant could serve modern people in daily life to perform meditation or healing rituals [40].

Salvinorin A fails to meet the criteria of chemical similarity to other hallucinogens. Therefore, in most of the countries the plant and its compounds are not banned by national laws for controlled substances. In Australia however, the possession of *Salvia divinorum* is illicit [14]. This is officially justified by concerns about its unknown addictive potential and long-term effects. In Europe, only Finland and Denmark have added Salvia to the list of controlled plants. In Norway, *Salvia divinorum* is not controlled, but has the status of a psychoactive drug. The American Drug Enforce-

ment Agency (DEA) has placed *Salvia divinorum* on a list of drugs or chemicals “of concern”, without legal implications at present. Consumers have meanwhile founded a “*Salvia Divinorum* Defense Fund” in order to prevent more restrictions on *Salvia* use [5,33].

## Conclusion

*Salvia divinorum* might become increasingly attractive to adolescents and young adults for several reasons:

- It can be easily ordered at an affordable price.
- The use of *Salvia divinorum* promises philosophical insights or escapism for young people seeking their own personality. Furthermore, adherence to an international “*Salvia* community” may be socially attractive.
- Numerous internet sources offer a mixture of esoteric advice, practical warnings and instructions on the use of the plant. The consumer may take this subtle promotion of *Salvia* products as “evidence-based” in a scientific sense and underestimate known and unknown health risks.

## Open issues

As a consequence, the following questions deserve more attention in research:

1. Unidentified, salvinorin-induced intoxications by an unintentional intake of more than 500–1000 µg salvinorin A may be more frequent than presumed, because salvinorin A in blood or urine is not examined by the drug screenings, available at the moment.
2. The influence of *Salvia* use on social behavior and on daily activities like driving a car or handling technical devices should be observed.
3. Psychotomimetic effects of *Salvia divinorum*, especially in teenagers and young adults should be documented systematically, e.g. by using a standardized questionnaire to assess altered states of consciousness [11].
4. Long term effects of Salvinorin A especially in combination with conventional hallucinogens or psychoactive drugs must be watched carefully. They might promote the manifestation of endogenous psychoses in predisposed persons.
5. The addictive potential of *Salvia divinorum* is still a matter of debate. Stimulated cerebral KOR may develop mechanisms of tolerance that mediate withdrawal behavior [39,41].
6. Pharmacokinetics and molecular mechanisms of salvinorin A as well as interactions with ethanol or psychoactive drugs should be investigated. Finally the potential of this naturally occurring KOR-agonist for exploring and alleviating psychiatric conditions, has to be determined.

## Acknowledgments

### Funding:

C.H. Gleiter is supported by the BMBF (Deutsches Bundesministerium für Bildung und Forschung), grant 01 EC 0001.

I. Gaertner is supported by the AKF-program in therapeutic approaches to opioid dependence (University of Tuebingen 2003).

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