

Scientific Considerations Concerning Salvia Divinorum and Salvinorin A:
Implications for Proposed Legislation

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We are psychopharmacology researchers at Johns Hopkins University School of Medicine who conduct clinical pharmacology studies on a variety of drugs of abuse. As described below, research with salvinorin A (the active constituent of Salvia divinorum) has potentially important implications for understanding a variety of disease states, including Alzheimer's disease, schizophrenia, bipolar disorder, dementia, and drug dependence. We have federal grant funding from the National Institutes on Health (NIH), and Food and Drug Administration (FDA) approval, to study the effects of salvinorin A in a controlled clinical laboratory trial.

We are concerned that recently proposed Maryland House (HB 8) and Senate (SB 9) bills intended to control Salvia divinorum may impede scientifically important academic research at Johns Hopkins and other institutions in Maryland. In addition to providing potentially important information relevant to a variety of disease states, our research will provide scientific information on the potential harms of Salvia divinorum use. It would be unfortunate if legislation designed with the intent of eliminating harm from Salvia divinorum use actually prevented the scientific assessment of its potential harms. The following is a summary of what we believe are the relevant scientific concerns surrounding Salvia divinorum and salvinorin A.

Background

The Salvia divinorum mint plant has been used in traditional spiritual practices by the Mazatec Indians of Oaxaca, Mexico to produce "mystical" or hallucinogenic experiences (Valdes, 1994; Ott, 1995, 1996; Siebert, 1994). Although the indigenous use of salvinorin A dates back hundreds of years, a recognition of the psychoactive effects of salvinorin A by American hallucinogen users dates back only about a decade (Siebert, 1994; Ott, 1995). Although in traditional Mexican use, the leaves of Salvia divinorum were chewed or made into an infusion and swallowed (Valdes, 1994; Siebert, 1994, Ott, 1995), contemporary use commonly involves either smoking or buccal (tincture)

administration. Effects include motor impairment, sensory alteration, vivid hallucinations, “out-of-body” experiences, and feelings merging with inanimate objects.

Pharmacology of salvinorin A

Salvinorin A, a neoclerodan diterpene, is a naturally occurring, potent, nonnitrogenous kappa opioid agonist, with no other known activity across 50 other receptors, transporters, and ion channels, including the 5-HT_{2A} serotonin receptor, which is the principal site of activity of classic hallucinogens such as LSD and psilocybin (Roth et al., 2002; Prisinzano, 2005). Recent studies have begun to characterize structure-activity relationships and the molecular mechanisms for salvinorin A binding to the kappa opioid receptor (Chavkin et al., 2004; Yan et al., 2005; Munro et al., 2005). Studies in monkeys show salvinorin A produces discriminative stimulus effects similar to other high efficacy κ agonists (Butelman et al., 2004). A kappa-like profile of antinociceptive and behavioral effects has also been demonstrated in rodents (Fantegrossi et al., 2005; Wang et al., 2005; Zhang et al., 2005; McCurdy et al., 2006; Carlezon et al., 2006).

Addiction potential of salvinorin A

Although self-administration, the hallmark pre-clinical test of abuse liability, has not been studied, salvinorin A was shown to produce several effects *different* from classic drug reinforcers (e.g., cocaine, heroin, marijuana, methamphetamine): it elevates rather than decreases thresholds for intracranial stimulation (Zhang et al., 2005); it produces conditioned place aversion rather than conditioned place preference (Carlezon et al., 2006), and it decreases rather than increases dopamine levels in the caudate putamen in mice and nucleus accumbens in rats (Zhang et al., 2005; Carlezon et al., 2006). These results suggest the lack of reinforcing or rewarding effects in nonhuman animals. Therefore, salvinorin A does not appear to be a drug that would lead to addiction (compulsive drug seeking).

Given its lack of rewarding effects in behavioral and brain assays in animals, it is likely that use of salvinorin A in humans is motivated by the reported extraordinary sensory and perceptual effects elicited by the drug, rather than classic euphoric drug effects. Supporting this, a recent scientific survey of 500 *Salvia divinorum* users reported that only 0.6% of users reported every feeling addicted or dependent on the drug (Baggott et al., 2004). The study authors considered this rate of endorsement too low to consider significant. Furthermore, despite the popularization of *Salvia divinorum* use over the past 5 to 10 years, there are no case reports of addiction to *Salvia divinorum* in the scientific literature, and *Salvia divinorum* use has not been reported to be a problem in substance abuse treatment programs. Our research group at the Behavioral Pharmacology Research Unit of Johns Hopkins School of Medicine has treated drug abuse in Baltimore for several decades and has conducted pioneering research on pharmacotherapies for opioid dependence. We are aware of no reports from our treatment program or affiliated treatment programs that have indicated *Salvia divinorum* to be a drug abuse problem in Baltimore.

Impairment resulting from salvinorin A

Although addiction appears to be of low concern with *Salvia divinorum*, it is clear that some use of *Salvia divinorum* can legitimately be considered *abuse* (i.e. use in a way that risks the well being of the individual or others). For example, *Salvia divinorum* can lead to substantial motor impairment that could potentially lead to accidents, particularly if the user is in a hazardous environment or situation. It should be noted, however, that there is little evidence that such injuries are occurring because there are no emergency department case reports in the scientific literature suggesting such injuries. This is perhaps due to the extremely short time course of the drug when smoked, allowing little time for such injuries to occur. Users describe effects to be substantially resolved in approximately 5 to 10 minutes.

Although the rate of injuries from use of *Salvia divinorum* is apparently low, one suicide by a Delaware teenager was claimed by his parents to be due to his intermittent use of *salvia divinorum* during some period of time before the suicide. Although the incident is certainly tragic and we understand and sympathize with the parents' efforts to prevent similar tragedies, the attribution of the teen's suicide to *Salvia divinorum* is not clear. Although reported ambiguously in many media reports, the earliest news reports made clear that there was no evidence that he was intoxicated on the drug when he committed suicide. In addition, there is an absence of any larger trend from other case reports of *Salvia divinorum* use that link use to depression or suicide. In fact, one case report in the medical literature describes the case of an adult whose treatment-resistant depression was purportedly *alleviated* by her self-experimentation with *Salvia divinorum* (Hanes, 2001). The high rate of suicide among youth (over 4,000 teen and young adult suicides per year in the U.S. alone, Center for Disease Control and Prevention, 2007) contributes further to the uncertainty of attributing the tragic Delaware suicide to *Salvia divinorum* use. The high publicity that this incident has received, partly due to the understandable anguish expressed by the teenager's parents, appears to be a prime moving force in the passage of new drug regulations controlling *Salvia divinorum*. Publicity has also surrounded the cases of a 12 year old Ohio boy who was killed by another child who had unsupervised access to a handgun. Although it is unclear whether the children had been using *Salvia divinorum*, *salvia* has been implicated in the case because of earlier use by the shooter. Although tragic, as with the Delaware case, the role of *Salvia divinorum* in this case appears unclear.

Importance of continued research with salvinorin A

Research with salvinorin A, a selective kappa agonist, has the potential for identifying novel opioid receptor modulators which may have therapeutic applications in the treatment of certain psychiatric disorders (e.g. Alzheimer's disease, schizophrenia, bipolar disorder, and dementia) (Sheffler and Roth, 2003) and in the treatment of pain. Also, a better understanding of opioid receptor mediated phenomenon may have relevance to treatment of drug dependence, and it has been proposed that research on novel compounds acting on the kappa system including salvinorin A may lead to the development of novel medical treatments for drug dependence (Mello & Negus, 2000; Prisinzano et al., 2005).

Chemists, pharmacologists, and behavioral scientists at several universities across the nation are conducting research with salvinorin A and related analogues that has

important implications for the treatment of Alzheimer's disease, schizophrenia, bipolar disorder, dementia, pain, and substance dependence. We are now conducting clinical research with salvinorin A which would allow for Johns Hopkins scientists to be among the first in the nation to characterize the clinical effects of salvinorin A in humans. It is our hope that the new state legislation would not inadvertently impose limitations or delays on FDA and Johns Hopkins approved research with salvinorin A.

A potential significant problem with the proposed legislation

A Johns Hopkins government relations liaison has indicated that section 5-304(c) of the Criminal Law provides language about exclusion for research conducted on Schedule I. However, this section is ambiguous. Specifically, the section provides an exclusion "...if the authorized provider is registered under federal law to conduct research with a controlled dangerous substance listed in Schedule I and gives evidence of the registration to the Department." The ambiguity rests on the fact that Salvia divinorum is not listed as a Federal Schedule I substance, and therefore it is not possible for a provider to be registered under federal law to conduct research with Salvia divinorum. DEA grants approval to conduct research with Schedule I substances on a drug-by-drug basis. DEA does not provide "blanket" approval for conducting research with all Schedule I drugs. Thus, although we are approved to conduct research with other DEA Schedule I drugs, we believe the proposed legislation will inadvertently preclude our continued research Salvia divinorum

Legislative options that minimize constraints on academic research

The federal DEA has been conducting a detailed evaluation using well-accepted procedures for determining whether Salvia divinorum should be scheduled. Indeed, the DEA employs a body of scientists from various scientific and medical disciplines specifically for engaging in such evaluations. Therefore, one option is to not schedule Salvia divinorum at the state level, and instead allow the analyses to be conducted by DEA scientists and drug control experts to determine the relative merits of scheduling Salvia divinorum. If Salvia divinorum is to be controlled at the state level, our hope is that a variety of options would be considered that would minimize constraints on academic research. One option would be to only ban the sale of the substance rather than possession. Another would be to ban possession by those under 21 years of age. A final option would be to explicitly exempt legitimate research. However, as stated previously, there is ambiguity over whether this is possible for a drug that is scheduled at the state level but is not scheduled federally.

Summary of considerations relevant to the potential scheduling of Salvia divinorum

While we take no advocacy position on the legal control of Salvia divinorum, our hope is that legislators consider the full scope of available scientific evidence and carefully consider both the advantages and disadvantages of regulatory action. The scientific evidence suggests that addiction to Salvia divinorum is not likely, and in this respect the drug differs from such legally controlled drugs as heroin, cocaine, marijuana, and methamphetamine. Therefore, it is not likely to become a widely popular emerging drug of abuse such as methamphetamine. However, Salvia divinorum use can cause substantial behavioral and motor impairment, and thus its use may potentially lead to

accidents. In this respect, use of Salvia divinorum appears more similar to sniffing glue, inhaling gasoline fumes, or taking high doses of diphenhydramine (Benadryl), than to addictive drugs such as heroin, cocaine, marijuana, and methamphetamine. A potential advantage of regulatory control would be to prevent such abuse and potential accidents. A potential disadvantage is that highly restrictive regulatory control would inevitably constrain scientific advancement because such restrictions decrease access and increase bureaucratic burdens to conducting scientific research with these compounds, which has importance for research on the biology of Alzheimer's disease, schizophrenia, bipolar disorder, dementia, pain management, and drug dependence. An additional potential disadvantage of regulatory control is that it will further encumber already overburdened drug enforcement efforts, ultimately distracting from the control of scheduled drugs with very clear and substantial public health burdens (e.g., heroin, cocaine).

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