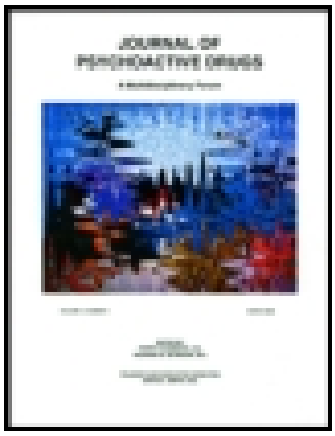

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The Association of Salvia divinorum and Psychotic Disorders: A Review of the Literature and Case Series

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The Association of *Salvia divinorum* and Psychotic Disorders: A Review of the Literature and Case Series

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Abstract — The association of substance abuse and psychotic disorders is of interest to clinicians, academics, and lawmakers. Commonly abused substances, such as cannabis, cocaine, amphetamines, and alcohol, have all been associated with substance-induced psychosis. Hallucinogens can induce desired psychedelic effects and undesirable psychomimetic reactions. These are usually transient and resolve once the duration of action is over. Sometimes, these effects persist, causing distress and requiring intervention. This article focuses on the hallucinogenic substance *Salvia divinorum*, the use of which has been observed, particularly among youth worldwide. We present background information based on a review of the literature and on our own clinical encounters, as highlighted by two original case reports. We hypothesize that consumption of *Salvia divinorum* could be associated with the development of psychotic disorders. We propose that clinicians routinely inquire about the use of Salvia in patients with substance use disorders or psychotic illnesses. More research is required to assess any relationship between *Salvia divinorum* and psychosis. Additionally, we advocate increased public and medical awareness of this substance and other emerging drugs of abuse.

Keywords — hallucinogen, psychosis, *Salvia divinorum*, Salvinorin A, substance-induced psychosis (SIP)

The association of substance abuse and psychotic disorders has been subject to speculation in the psychiatric literature for decades. Psychosis and substance abuse co-occur frequently (Cantor-Graae, Nordström, and McNeil 2001; Regier et al. 1990). This may be because substance abusers are at a higher risk of developing psychosis or because patients diagnosed with a psychotic disorder are at a higher risk of abusing substances than the normal population. A causal relationship remains elusive and information given to patients and caregivers by healthcare professionals is often confusing.

Estimates of the prevalence of comorbid substance use and psychotic disorders vary significantly. The 2011 USA National Survey reveals that 17.5% of adults with a mental disorder had a co-occurring substance use disorder (US Department of Health and Human Services 2011). Comorbidity for substance abuse appears higher for psychotic disorders with a 47% reported prevalence (Kessler et al. 1994). It is even higher in specialist and inpatient services, with one German study estimating a 74% lifetime prevalence and 62% point prevalence at the time of admission (Lambert et al. 2005). Alcohol, nicotine, and cannabis were among the substances most predominantly abused by patients with psychotic disorders (Kavanagh et al. 2004). The presence of a family history of psychotic disorders, a younger age of onset of substance use, in addition to

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longer duration and severity of use, are all risk factors for developing psychosis (Thirthalli and Benegal 2006).

Widely abused substances, such as cannabis, cocaine, amphetamines, and alcohol, have all been associated with substance-induced psychosis (SIP). Thirthalli and Benegal (2006) found the prevalence of psychotic symptoms lasting at least one month in a population of substance abusers to be highest for hallucinogens (85%) and lowest for sedatives (32%). These were patients presenting at various stages of their substance use, including chronic abuse, intoxication, and withdrawal. Cannabis has also been closely linked with the development of psychosis (Arseneault et al. 2004), particularly in a subgroup of vulnerable individuals whose experience of cannabis is characterized by distorted perceptions, thoughts, and feelings rather than euphoric effect (Verdoux et al. 2003). Prolonged psychotic symptoms following hallucinogens use have also been reported and include spontaneous recurrences of lysergic acid diethylamide (LSD)-like states with visual hallucinations and flashbacks that can occur up to five years after the last drug use (Abraham and Aldridge 1993).

A diagnosis of substance-induced psychosis carries a further risk for schizophrenia and related disorders. The risk of conversion varies from one substance to another, as supported by Niemi-Pynttari et al. (2013) in their review of Finnish inpatient records over more than a decade. An individual hospitalized with an initial diagnosis of cannabis-induced psychosis had a 46% chance of being diagnosed with schizophrenia in the eight years following his discharge. The rates for other substances were lower: amphetamines (30%), hallucinogens (24%), opioids (21%), and alcohol (5%).

Relatively little has been written in the scientific literature on the psychogenic effects of the so-called "legal highs." Manufacturers and traders of recreational substances are always a step ahead in terms of the development and dissemination of products that are more potent and harder to detect. This article focuses on *Salvia divinorum*, a very potent natural hallucinogen (Ranganathan et al. 2012), the use of which has surged among subgroups of youth in Lebanon over the past year. We discuss its properties, common effects, and possible association with the onset of psychotic symptoms, illustrated by two recent clinical cases where we found the ingestion of *Salvia divinorum* to be potentially implicated.

SALVIA DIVINORUM: PATHOPHYSIOLOGY

Salvia divinorum is a naturally occurring species of the sage plant native to the Sierra Mazateca in Oaxaca, Mexico. Its remedial uses among the Mazatec Indians have included gastrointestinal problems, headaches, and rheumatism (Valdes, Diaz, and Paul 1983). The psychotropic active agent in *Salvia divinorum* was identified as the neoclerodane diterpene salvinorin A, the first hallucinogenic agent that is not an alkaloid.

While LSD, mescaline, and psilocybin all act through serotoninergic pathways, salvinorin A is believed to act as a selective and potent agonist at the kappa-opioid (KOPr) receptor in the absence of known affinity at the mu- and delta-opioid receptors. It also shows no affinity for targets of other hallucinogenic substances such as 5-HT_2, C B_1/CB_2, NMDA, or muscarinic receptors (Roth et al. 2002). Kappa-opioid receptors are present in the ventral tegmental area, nucleus accumbens, and prefrontal cortex (Shippenberg, Zapata, and Chefer 2007), brain regions involved in regulating mood and motivation. Other KOPr agonists have been reported to produce dysphoric and psychotomimetic effects (Carlezon et al. 2006; Pfeiffer et al. 1986). The impact of salvinorin A on dopamine levels in the brain is less understood. Salvinorin A has been shown, along with other hallucinogens (PCP, LSD, ketamine), to activate certain dopaminergic (D2) receptors in rat striatum, accounting possibly for its hallucinogenic effects (Seeman, Guan, and Hirbec 2009). This contradicts previous reports of inhibition of dopaminergic transmission in the nucleus accumbus in rodent brains (Shippenberg 2009; Simpson et al. 2009).

Salvia divinorum is usually ingested by chewing, swallowing, or smoking. It can be chewed as fresh leaves or in a quid and kept in the mouth. It can be eaten raw or drunk in a brewed liquid such as tea. It can be smoked in a similar fashion to marijuana, in a large bowled pipe, bong, or water pipe, or rolled into a "Sally D" cigarette. Usually, smoking or snorting results in an immediate effect. Chewing, sucking, or drinking results in a slower onset but a deeper and more sustained experience. The leaves are generally smoked alone and not mixed with tobacco. A quantity of 200 to 500 mcg of salvinorin A, smoked or absorbed orally, appears sufficient to cause hallucinations (Prisinzano 2005). It is not meant to be injected, although anecdotal intravenous injection has been reported on Internet drug forums.

The psychedelic experiences through consumption of *Salvia divinorum* include vivid visual hallucination and somatic sensations, a decreased ability to interact with the surroundings, a perception of overlapping realities, anxiety, discontent, and impaired speech. The "high" can last from under a minute to over two hours, depending upon the potency. When smoked, *Salvia divinorum* can cause a physical sensation of pressure, described as a pulling or pushing of the body in a particular direction. Some users find themselves pinned to the floor for the duration of their experience, a sensation described as "Salvia gravity." In terms of similarities with other substances, more than 50% of trial participants described it as unique, while a smaller number found it similar to other hallucinogens (Addy 2012). In a sample of students, the majority found

their experience similar to marijuana, even when they had not mixed the two substances. (Albertson and Grubbs 2009; Andréasson et al. 1989).

Research has been conducted to establish the immediate effects of *Salvia divinorum* consumption in controlled settings. In one study (Johnson et al. 2011), four healthy participants recruited from the community agreed to inhale 16 ascending doses of salvinorin A and four intermixed placebo doses under observation. Doses ranged from 0.375 μg/kg to 21 μg/kg, adjusted according to body weight. Subject-rated drug strength was assessed every two minutes for 60 minutes after inhalation. Subjective drug strength ratings were highest at two minutes following inhalation and were absent 20 minutes later. The subjective effect was almost exclusively positive in the absence of dysphoria, in contrast to what was expected based on previous research with kappa agonists where dysphoric effects predominated. In addition, salvinorin A produced an incremental dose-related effect on most subscales of the Hallucinogen Rating Scale (HRS; 99 Items) and on the Mysticism Scale that is used to rate the effect of hallucinogenic substances. No persistent effects were noted at follow-up.

In a recent double-blinded study (MacLean et al. 2013), eight "hallucinogen-experienced" participants were given salvinorin A in an incremental order with a single placebo dose included randomly over 20 sessions. Drug effect peaked at two minutes and rapidly decreased. All participants described dissociative effects similar to ones experienced with other hallucinogens, such as a range of somatic and proprioceptive hallucinations. All participants also reported encounters with "entities or beings," with which they were able to interact, and auditory and visual hallucinations with "cartoon-like images" often associated with their childhood. About half of the participants were seen and heard laughing by the researchers during peak drug effects. Follow-up assessments at one month showed no evidence of lasting negative effects such as depression, anxiety, psychiatric symptoms, or visual disturbances.

Randomized ingestion of salvinorin A over three days under strict observation led to psychomimetic effects usually associated with schizophrenia as measured on rating scales. A physiological response was also noted, including increased plasma level of prolactin and cortisol. All these changes were transient and no sequelaes were found at six months' follow-up (Ranganathan et al. 2012).

EPIDEMIOLOGY

The prevalence of *Salvia divinorum* use varies globally. The US annual National Survey on Drug Use and Health showed an 83% increase in lifetime prevalence from 0.7% of the population aged 12 and older in 2006 to 1.3% in 2008 (Wu et al. 2011). Overall, about 1.8 million persons admitted to having used this substance at least once in their lifetime. The US National Institute on Drug Abuse (NIDA 2013) estimates the prevalence of *Salvia divinorum* amongst American eighth graders, tenth graders, and twelfth graders in 2013 to be 1.2%, 2.3%, and 3.4%, respectively.

According to the United Nations Office on Drugs and Crime-World Drug Report (UNODC-WDR 2012), *Salvia divinorum* emerged as a substance of concern in Canada around 2009. In 2010, an estimated 1.6% of Canadians aged 15 years and over had used salvia in their lifetime and 0.3% reported having used it in the past year. However, its use is overrepresented among the younger generation, with 6.6% of those aged 15–24 reporting lifetime use.

A 2008 survey by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA 2011) in Romania revealed that 0.3% of Bucharest-based youth aged 15 to 34 who attend recreational settings had tried *Salvia divinorum* at least once in their life. In an online survey of UK club-goers carried out in 2009, 3.2% of respondents admitted to having consumed *Salvia divinorum* within the previous month, making it the fifteenth most commonly used drug in that country. Lifetime prevalence reached 29.2% (EMCDDA 2011). In Lebanon, there are no reliable statistics on the consumption of salvia. Anecdotally, salvia was virtually unknown among clinicians and local substance users until 2013, when a dramatic rise in use was noted in addiction services in parallel with recent increased availability on the streets.

ASSOCIATION WITH PSYCHOTIC SYMPTOMS

We performed a literature review of the terms "Salvia divinorum," "Salvinorin A," "Salvia divinorum and mental illness," "Salvia divinorum and psychosis," and "Salvia divinorum and schizophrenia" using PubMed and Google Scholar. It revealed three clinical references to a possible association between *Salvia divinorum* and persistent psychotic symptoms.

Przekop and Lee (2009) reported on a 21-year-old man in the US with no family history or personal history of psychiatric disorders, and with an unremarkable premorbid social, behavioural, and cognitive history, who was admitted to a psychiatric unit in an acute psychotic state shortly after smoking *Salvia divinorum*. His symptoms consisted of echolalia, paranoia, flight of ideas, and psychomotor agitation. He was started on a high dose of Risperidone with good initial response. He relapsed almost immediately once the medication was withdrawn. He was restarted on Risperidone and stabilized; however, after four months, he had not shown any noticeable progress. The authors hypothesize that the patient could have been genetically predisposed to schizophrenia, with *Salvia divinorum* abuse precipitating the first acute clinical manifestation. According to them, this may relate to salvia's ability

to influence dopamine levels in the brain and potentiate changes in the frontal lobe.

Paulzen and Gründer (2008) reported on an 18-year-old female patient admitted to the psychiatric emergency service in Germany with acute onset of agitation, disorganization, and hallucinating behavior after smoking cannabis. During admission, it was disclosed that she had also unknowingly smoked the leaves and leaf extracts of *S. Divinorum* for the first time. This was of particular interest as the patient had had a long experience of cannabis use without ever experiencing a psychotic episode. She was admitted to a general psychiatric ward with the presumptive diagnosis of a substance-induced psychotic disorder and subsequent schizophrenia-spectrum disorder. She displayed increasingly self-mutilating behavior, with a high level of disorganization and disorientation requiring commitment for involuntary treatment. After a number of attempts with typical and atypical antipsychotics. she finally responded to Clozapine and was stable on discharge. No information was provided on longer-term follow-up.

Singh (2007) reported on a 15-year-old male who presented to psychiatric emergency service with a three-day history of paranoid ideas, multiple episodes of déjà vu, and a dull affect, thought blocking, and mental slowness. The patient had been concurrently using marijuana for 11 months and *Salvia divinorum* for eight months. He had used marijuana only hours before his acute episode, while the last use of *Salvia divinorum* was unknown. During his hospital stay, his symptoms improved. Details of a timeline and any treatment were not provided. Investigations ruled out organic causes, including temporal lobe lesions.

We report below on two cases we encountered of a psychotic illness developing in the context of *Salvia divinorum* abuse.

CASE STUDY 1

Mr. A. is a 19-year-old Lebanese male patient who was brought to the emergency department by his family in March 2014 with acute onset of manic and psychotic symptoms. These had developed within a matter of days upon returning from a trip abroad, where he reported having consumed unknown quantities of *Salvia divinorum* and cannabis.

This was his second admission to the hospital in two years. His only preceding admission, in August 2012, lasted three months and had been similar in presentation, with a combination of severe mood and psychotic symptoms. It had also been acute and associated with the abuse of a combination of substances (cannabis regularly and MDMA occasionally) and a brief course of the non-stimulant ADHD treatment Atomoxetine. Mr. A's symptoms had disappeared within three months of discharge on a combination of an antipsychotic (Olanzapine) and a mood stabilizer (Valproic Acid). He complied with regular medical follow-up until December 2013, but stopped all medication gradually around that period.

The relapse in March 2014 was abrupt with psychotic symptoms of delusions of mind control, persecutory and grandiose delusions, some of which were congruent with an elevated manic mood. It was characterized by a decrease in need for sleep, restlessness, overactivity, irritability, increased libido and sexual disinhibition, in addition to homicidal ideas. During his hospitalization, Mr. A required increasing doses of antipsychotics and mood regulators to contain his irritability and agitated behavior brought on by delusions of persecution and thought control. A re-challenge with valproic acid was stopped when he developed disproportionate sedation and hyperammonemia.

Mr. A. was switched to therapeutic doses of lithium carbonate and carbamazepine in addition to olanzapine 30 mg daily. On discharge, improvement of mood symptoms had been noted with decreased but persistent paranoid persecutory delusions. On follow-up, complaints over the sedative effects of olanzapine led to a crossover switch to aripiprazole, while carbamazepine was tapered and stopped. At six months' follow-up, he remained on 800 mg of lithium carbonate and 10 mg of aripiprazole. His family ensured that he was compliant with medication. No active positive psychotic symptoms were detected. However, loss of motivation and a degree of global impairment in executive functioning persisted.

CASE STUDY 2

Mr. D is a 24-year-old Lebanese male with a history of substance abuse who was brought to the outpatient psychiatric clinic in an emergency by his family in April 2014. He had no formal psychiatric history and had never consulted a mental health professional. However, he had a family history of unspecified psychotic disorders. On mental state examination, he appeared perplexed and was exhibiting distressed behavior in response to paranoid persecutory delusions. Evidence of moderate formal thought disorder was also observed.

The patient and his accompanying relatives informed the clinical team of his history of at least 12 months prior to presentation of daily cannabis use (varying between one and five joints per day), in addition to twice-weekly cocaine sniffing. He also smoked *Salvia divinorum* two to three times a week. The direct experience consisted of a transient dissociative state and visual hallucinations of up to 20 minutes duration. These were sometimes pleasant and at other times not.

The patient continued this pattern of substance use until five days prior to presentation, when he developed delusions of reference, persecutory paranoia with intense behavioral changes dominated by social avoidance, and

restlessness. A routine urine drug screen under strict conditions was negative for any of the main substances of abuse (opiates, cocaine, amphetamines, THC, benzodiazepines). The test does not cover salvia. Due to the level of distress, immediate inpatient treatment was advised but refused due to financial reasons. He was started on risperidone 2 mg twice daily and alprazolam 0.5 mg twice daily.

The patient presented to the emergency department on the following day, having developed acute neck dystonia, which led to his admission to the psychiatric unit for further management. He was stabilized and started on olanzapine 20 mg total and symptoms progressively decreased over the following five days. They were still present on discharge. He was subsequently reviewed in clinic two weeks later, where persistence of overvalued ideas of persecution was noted. On continuous follow-up the psychotic symptoms remitted, and olanzapine was tapered and stopped after two months. He exhibited signs of depression and was started on sertraline 50 mg, later increased to 100 mg. Mr. D restarted using substances three months after hospital discharge, including *Salvia divinorum* up to eight cigarettes twice weekly, cannabis eight joints twice a week, and one gram of cocaine twice a week. He did not report any psychotic symptoms and none were elicited on examination. However, depressive symptoms persisted, and he was gradually switched to venlafaxine 150 mg and aripiprazole 5 mg.

DISCUSSION

The association of the hallucinogen *Salvia divinorum* with psychosis remains underinvestigated. The scarcity of clinical references to it in the literature could be the result of a lack of association, but also could be due to lack of awareness and underreporting. Salvinorin A cannot be tested for by widely available toxicology tests. It can only be detected by liquid chromatography mass spectrometry in blood and urine, or by gas chromatography mass spectrometry in blood, urine, and saliva. A third method is the high-performance liquid chromatography-atmospheric pressure chemical ionization in blood and urine (Willard and Anne 2011; McDonough et al. 2008; EMCDDA). This is a major limitation in all of the case reports, including our own.

In the cases presented earlier, the consumption of *Salvia divinorum* coincided with the onset of an acute psychotic episode in young individuals who either had no confirmed diagnosis of mental disorder or had been previously treated for a substance-induced illness. In two case reports in the literature, and in our observed cases, the concurrent consumption of cannabis and *Salvia divinorum* made it difficult to draw conclusions on the role of either substance in precipitating the acute episode or shaping its presentation.

Nonetheless, it is noteworthy that often the introduction of *Salvia divinorum* to their drug repertoire had been more recent. Both of our patients, once orientated and able to reflect on the days preceding their admission to the hospital, subjectively identified salvia as a possible cause for their symptoms. Predisposition to psychotic disorders seems relevant, whether through a positive personal psychiatric history or a family history. This is consistent with the accounts of *Salvia divinorum* users who perceive it as a "problematic" drug for those with a mental disorder (Kelly 2011). While no causal relation can be implied, the role of *Salvia divinorum* in at least precipitating the psychiatric presentation in our cases appears more than coincidental. This is despite the fact that small experimental studies mentioned earlier do not show any persistent effects from the consumption of average to high doses of its active component salvinorin A. The perceived absence of long-term effects even led to suggestions for a therapeutic role in depression (Hanes 2001). Better understanding of action at the kappa-opioid receptor on mood and perception may provide some answers. From that perspective, the association between *Salvia divinorum* and psychotic disorders could be similar to the one between cannabis and these disorders, where a relatively small number of individuals are susceptible to developing a persistent psychosis following use. This is despite the differences in action at the brain receptors level between cannabis and salvinorin A. The challenge, given the high prevalence of cannabis use among substance abusers in general, will be to isolate cases of psychosis where the consumption of both substances does not overlap.

There is need for more research into the possibility of persistent psychotic symptoms after single or multiple uses of substances containing Salvinorin A. Until its association with psychotic phenomena is established or dismissed, we propose to err on the side of caution through raising public and medical awareness of this substance, which appears attractive to young users and offers an alternative to criminalized drugs. This may be particularly important for those who already suffer from an underlying mental illness or have a strong family history of psychotic and mood disorders. Establishing guidelines on diagnosis, detection, and treatment of *Salvia divinorum* abuse would encourage doctors to inquire about this substance, at least among high-risk populations. Traditionally, there had been conflicting opinions on whether *Salvia divinorum* could become a drug of widespread abuse (Kelly 2011; Valdes 1994), but the current situation in Lebanon confirms that possibility. This might be due to specific local circumstances, such as the tight regulation of cannabis and the sudden influx of the herb on the market. There is no reason why these specific circumstances cannot be found elsewhere. The trend is for increased use in the developed world (Addy 2012).

The lack of consensus over the nocive effects of *Salvia divinorum* has also translated into confusion in legislation, whereby no federal regulation exists in the United States (Griffin, Miller, and Khey 2008). This is replicated on a

global level, with different European countries adopting contradictory strategies (Dalgarno 2007).

A coordinated effort from clinicians, researchers, and law enforcement agencies on an international level is required to establish the safety profile of newly proliferating psychoactive substances. We are concerned that avoidable new cases of psychotic illnesses may be presenting to psychiatric units across the world, without due attention being given to potential causative or associated agents, such as *Salvia divinorum.*

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