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Case Series: *Salvia divinorum* as a Potential Addictive Hallucinogen

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Background and Objective: Recreational use of *Salvia divinorum* (salvia), a potent, naturally occurring hallucinogen, is on the rise internationally. Despite the paucity of information about its long-term health effects, salvia is readily available and generally portrayed as a safe non-addictive substance.
Methods and Results: We report on two patients who presented with an enduring and pervasive pattern of salvia use.
Discussion and Conclusions: Evaluating patients for salvia use during clinical assessment is strongly encouraged, especially among young polysubstance users.
Scientific Significance: Clinicians should be mindful of the multifaceted psychiatric effects of salvia, including the potential for a use disorder. (Am J Addict 2018;27:163–165)

INTRODUCTION

Salvia divinorum (salvia) is a naturally-occurring hallucinogenic plant of the Lamiaceae (Mint) family. It has been used for centuries by Mazatec shamans of Mexico for divination and spiritual healing.[1] In recent years, salvia has become a popular recreational drug[2] because of its potency, perceived safety, and ready availability,[3] particularly among young adults at-risk for polysubstance use.[4]

Consumption of salvia, usually through inhalation or oral ingestion, induces powerful cognitive, affective, and perceptual changes, including derealization, depersonalization, and an "array of delusional phenomena."[2] Salvinorin A is salvia's main psychoactive component. It is a highly selective, non-nitrogenous, potent kappa opioid receptor (KOR) agonist.[1] Its rapid onset of action, short half-life and dose-dependent hallucinogenic effects only partially overlap with those of classic hallucinogens, thereby providing users with a unique and intense experience.[5] The rewarding effects of salvinorin A seem to be mediated through the opioid and endocannabinoid systems in rats,[6,7] therefore providing a possible mechanism for dependence.

Salvia is legally sold in several countries in "smartshops" and its use is promoted online for recreational purposes.[8] Salvia is portrayed as a safe or legal substitute to other drugs with little information provided about its potential for harm.[9] Salvinorin A cannot be detected by commonly available toxicology kits,[10] making it more appealing to users in countries where cannabis or other hallucinogens are criminalized.

While acute effects of salvia such as psychotic experiences have been studied in laboratory and under natural conditions, chronic and heavy use leading to impairment has not yet been substantially described in the scientific literature. The recent popularity of salvia among substance users in Lebanon offers an opportunity for exploring the potential for clinical dependence. We report two cases where pervasive and enduring pattern of salvia use appears to have been a primary contributor for loss of functionality in two young males and a reason behind them seeking psychiatric treatment.

CASE A

A 16-year-old single adolescent male was brought to the Emergency department (ED) in January 2017 for symptoms of psychosis that had developed over several days, in the context of recent use of large quantities of salvia. Symptoms included paranoia, nihilistic delusions, thought insertion and thought broadcasting.

The patient reported a 3-year history of polysubstance use, mainly cannabis, alcohol, cocaine, and MDMA. First use of salvia was in April 2014 at age 14. He initially used salvia about once a month, whenever it was available among his peers. His use progressively increased to larger doses multiple times a week by the end of summer of 2016. Seven months prior to presentation, he had transitioned to exclusive daily salvia use. He reported that the main motivating factor behind the switch were the "salvia-specific" effects. These included a "decreased awareness of surroundings," feelings of euphoria and calmness, depersonalization, and visual distortions and

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illusions. He reported strong cravings for salvia becoming irritable and aggressive when not using. Protracted symptoms of tremors, nausea, headaches, irritability, and anxiety made his efforts to cut down unsuccessful. One month prior to presentation he reported depressive symptoms: low mood, anhedonia, loss of appetite, insomnia, and passive death wishes. He became socially isolated and withdrawn. His use of salvia had become continuous throughout the day. He dropped out of school and engaged in gambling and driving under the influence. He consulted a psychiatrist who prescribed mirtazapine 30 mg daily. He was admitted to the psychiatric inpatient unit a week later.

On first contact, he appeared anxious and avoided eye contact. Vital signs showed tachycardia. Medical history and investigations were unremarkable. Urine toxicology was positive for tetrahydrocannabinol (THC). He was started on olanzapine 10 mg daily, increased to 15 mg a week later. Elevated liver enzymes prompted a switch to risperidone 2 mg daily. Improvement was notable within days of olanzapine treatment and was sustained after switching to risperidone. While hospitalized, he presented symptoms suggestive of withdrawal: anxiety, irritability, headaches, nausea, insomnia, and cravings for salvia. He was started on diazepam 5 mg twice daily. He was discharged to a residential rehabilitation center on risperidone 2 mg once daily and escitalopram 10 mg once daily.

CASE B

A 32-year-old unemployed single male with a 13 year history of substance use disorder namely, alcohol and cannabis, with reported episodic use of tramadol and cocaine, was admitted voluntarily to our inpatient facility for management of depressive symptoms in the context of heavy regular salvia use. His admission was prompted by significant occupational and functional decline over the past several weeks.

For 3 months prior to presentation, he reported consuming between 25 and 30 salvia joints daily as he progressively renounced all other substances, including alcohol. His first experience of salvia occurred 3 years prior, with resulting effects described as "at least four times better than cannabis." He progressed quickly to regular use, resorting to cannabis when salvia was not available, and experiencing only partial relief for his craving. In February 2015, he was temporarily arrested for possession of illicit substances. He remained abstinent for 1 year under regular judicial monitoring including drug testing, He relapsed in 2016 due to interpersonal stressors. On relapse he initially smoked only salvia and the experience was recalled as less intense, leading to escalation in consumption. Within months he had lost his job; a long-term relationship failed and he accumulated debts through gambling. In the weeks leading to presentation he was spending most of his time isolated at home, smoking joints of salvia "every 15–20 minutes." Two months prior to presentation he developed feelings of sadness, worthlessness and guilt, as well as fragmented sleep. He consulted a psychiatrist who prescribed clomipramine 75 mg daily. Improvement in mood symptoms did not affect salvia consumption. He experienced occasional paranoia during salvia use but no protracted psychosis. Medical history and routine investigations were unremarkable. Urine toxicology was positive for THC. He received intravenous clomipramine 75 mg daily for 3 days. On day 4, he was switched to oral paroxetine 20 mg daily and carbamazepine 300 mg twice daily. While hospitalized, he experienced insomnia, irritability, malaise, and cravings for salvia. He received as needed acetaminophen, quetiapine, and diazepam. On discharge, he was directed to an outpatient substance abuse rehabilitation program with psychiatric follow-up.

DISCUSSION

The DSM-V specifies four criteria domains that represent a "pathological pattern of behavior" related to substance use: (i) impaired control; (ii) social impairment; (iii) risky use; and (iv) pharmacological criteria. Both cases meet criteria for "other hallucinogen Use Disorder."[11]

Both patients gradually used salvia in larger amounts over longer periods than was intended, both made repetitive unsuccessful efforts to control consumption. They consistently craved salvia and prioritized using it, seeking it or recovering from it.

Pattern of use resulted in failure to fulfil major role obligations leading to exacerbation of social and interpersonal problems. This includes inability to complete schooling (case A) and loss of employment (case B). Both progressively isolated themselves and abandoned recreational activities. Repetitive use in physically hazardous conditions occurred such as driving while intoxicated (case A). Both patients continued to use salvia regardless of the emergence of psychiatric symptoms and despite awareness the substance may be causing or compounding their depressive symptoms.

Both patients required increasing amounts of salvia to achieve desired levels of intoxication. They reported subjective symptoms of withdrawal, mainly anxiety irritability and malaise. Corresponding signs were clinically observable during hospitalization.

Several studies endorse a potential anti-addictive role for KOR agonists; as salvinorin A modulates rats' cocaine-seeking behavior[12] and decreases operant responding for cocaine or remifentanil in monkeys.[13] However, other studies found chronic salvinorin A to actually contribute to increased sensitivity to cocaine's stimulant effects.[14] One study by Ehrich et al. found that, depending on the timing of KOR activation and cocaine administration, KOR activation may actually potentiate cocaine-induced increases in dopamine release.[15] If KOR activation can both increase and decrease drug self-administration depending on timing, this decreases KOR agonists' potential for "real world" treatment of addiction.[16]

Both patients denied cannabis use in the weeks preceding admission, however toxicology assays were positive for THC. Voluntary cannabis use or adulteration of a non-regulated substance cannot be ruled out. In habitual cannabis users, THC and 11-OH-THC may be detected in urine for up to 24 days.[17] Another limitation is the difficulty of testing for salvia. Methods available to detect salvinorin A include thin layer chromatography and gas chromatography—mass spectrometry.[18]However they are not routinely used,[19]due to the need for specialist laboratories and their high cost.

Salvia samples that fitted the substance's known description were however visualized. The signs and symptoms of withdrawal that were observed, namely malaise, nausea, headache, irritability, and anxiety are also seen in cannabis withdrawal. This is an additional confounding factor.

Salvia use on a large scale is a somewhat recent occurrence.[9] Rates of depression are higher among users compared to nonusers[4] and case reports have documented a possible association with psychosis[20] thereby highlighting its potential link with psychiatric conditions in vulnerable persons.[4]

As is the case for many substances, long-term consequences appear limited to a subgroup. The association with psychiatric comorbidities needs further evaluation, given the overlapping symptoms with depression and anxiety illustrated in our cases. Cross-tolerance with other substances and neurocognitive impact of heavy regular use remain understudied. Evidence-based treatment strategies, whether pharmacological or psychological are lacking. In line with previous recommendations[4,19] our experience supports addressing salvia use in high risk groups of young polysubstance users.

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Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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