Synthetic Cannabis Substances (SPS) Use and Hallucinogen Persisting Perception Disorder (HPPD): Two Case Reports

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ABSTRACT

Hallucinogen Persistent Perceptual Disorder (HPPD) is a clinical syndrome characterized by the recurrence of distressing perceptual disturbances which previously emerged during primary hallucinogen intoxication, in the absence of recent use. Here we present two patients who developed HPPD following use of Synthetic Cannabis Substances (SCS), with no prior history of natural-occurring or synthetic hallucinogen use. Both cases had a prior history of cannabis dependence and current tobacco dependence. In both cases patients reported the presence of visual disturbances when smoking SCS and staring at stationary and moving objects. Both patients discontinued SCS use abruptly after suffering from a panic attack under the influence of SCS. Despite cessation of SCS, both patients continued to suffer from HPPD which was accompanied by significant anxiety. Following clonazepam treatment, both subjects reported significant improvement in symptoms and remained with a residual focal visual disturbance which was not accompanied by significant anxiety. To the best of our knowledge these are the first reports of HPPD following SCS use. In light of the increasing use of SCS, clinical psychiatrists should be aware of these perceptual side effects.

INTRODUCTION

The use of Natural Cannabis Substances (NCS), which are CB1 receptor partial agonists, has been associated with the appearance of perceptual disturbances during use and after total cessation (1). Thus it is plausible to expect that the intake of Synthetic Cannabis Substances (SCS) like JWH-018, JWH-073 and HU-210 which are generally CB1 full receptor agonists and were also associated with the appearance of perceptual disturbances during use (2) might affect some predisposed and susceptible users provoking a partial or total recapitulation of the previous perceptual experience in the absence of SCS use. We present the cases of two SCS users with prior history of NCS use who reported the presence of Hallucination Perception Persisting Disorder (HPPD) after stopping SCS consumption. To the best of our knowledge this is the first report of SCS-associated HPPD in the professional literature. Both patients gave informed consent for the publication of their cases.

CASE 1

Mr. R is a 26-year-old single, male college student who completed compulsory military service and did not have any prior police or criminal records. He had a five year previous history of almost daily "heavy" use of NCS (at least three times per day) (1). He also reported occasional social alcohol drinking and heavy tobacco smoking. He fulfilled DSM-IV-TR full criteria for cannabis and nicotine dependence (3). He denied other substance use including LSD or other natural-occurring or synthetic hallucinogens. He did not report the presence of visual disturbances during NCS use. For the two years prior to his evaluation Mr. R consumed SCS ("Nice Guy" and "Spice") on an almost daily basis (mainly at evening and night hours), without consuming other substances except tobacco. He explained his SCS use election and

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predilection to the availability and affordability of these substances.

Mr. R reported common visual disturbances when under the influence of SCS.

Perceptual disturbances have appeared when staring at stationary and moving objects. Staring at stationary objects was associated with **halos** (a circular band of colored light around a light source or object), **color intensification** (slightly more intensified), **color intensification of dimmed color** (slightly less intensified), **brightness** (source appears to be radiating or reflecting light), **visual snow** (literally visualizing particles of air), **positive afterimages** (an image continuing to emerge after the exposure to the original image has ceased) **and change in texture** (physical change of a static surface). Staring at moving objects was associated to **illusions of movement** (slow motion movement) and **trailing phenomena** (afterimage-like trail or perception of a series of slow-movement discrete positive afterimages in the wake of moving objects) (4).

These visual disturbances were experienced as benign and comfortable, a kind of psychedelic mind-broadening enriching and fruitful experience. They appeared sporadically during his two years of SCS consumption.

Following a severe panic attack during consumption of SCS, Mr. R abruptly discontinued SCS use. He described this panic attack as accompanied by visual disturbances and referred to it as being "a horrific trip." Forty-eight hours following the first panic attack Mr. R re-experienced the return of some of the visual disturbances experienced during SCS use along with anxiety features. Since the initial attack, he reported being continuously bothered by visual disturbances accompanied by anxiety features, and these complaints led to his psychiatric evaluation.

On psychiatric examination the patient reported visual occurrences which were similar to those experienced during SCS use and resembled intoxication-associated visual imagery. These almost daily episodes usually lasted between fractions of a second and a few minutes. The perceptual disturbances were sufficiently severe to cause significant distress, anxiety and impairment in social and occupational functioning. Mr. R fulfilled DSM-IV-TR diagnostic full criteria of HPPD (3). There was no previous neurological, ophthalmological or other comorbid medical diseases or co-occurring psychiatric history. A complete physical, neurological (including EEG), and laboratory examination was unremarkable.

Uncomplicated outpatient SCS withdrawal was unexpectedly mild and was treated with small doses of clonazepam (5-8). Dosage started at 0.25 mg bid gradually increased to 1 mg bid after two weeks. He reported high motivation for preventing relapse to SCS, and was very reluctant to consume "addictive chemical medications." During the two weeks following his initial psychiatric evaluation he reported the appearance of two additional panic attacks, milder in severity, accompanied by visual disturbances. Afterwards, no panic attacks were reported, and visual disturbances persisted. These HPPD-Type (HPPD II) (5-8) episodes slowly became more benign and less distressing. His condition dramatically started to improve. He continued taking clonazepam 1mg bid for the next five weeks. After completing two months of treatment, he refused to continue pharmacological treatment stating that he does not need more "chemicals in his body." He agreed to gradually stop clonazepam. After treatment suspension he continued to report considerable improvement in the frequency of perceptual disturbances and accompanying anxiety. At his six-month evaluation he reported that symptoms had disappeared almost completely. Despite the prominent amelioration, Mr. R continued to complain of focal visual disturbance known as trailing phenomena that remained without accompanying anxiety features.

CASE 2

Mr. B is a 24-year-old male waiter with a three-year history of previous daily use of NCS. He did not report the presence of visual disturbances during NCS consumption. He also smoked tobacco on a daily basis. He fulfilled DSM-IV-TR full criteria for cannabis and nicotine dependence (3). He denied using other legal or illegal substances including alcohol, LSD or other natural-occurring or synthetic hallucinogens. During the year prior to his psychiatric evaluation he consumed only SCS ("Nice Guy" and "Spice") on a daily basis mainly during night hours, without consuming additional substances apart from tobacco. He reported visual disturbances when smoking SCS, which were perceived as "amusingly entertaining" and occurred when staring at stationary and moving objects.

Staring at stationary objects was associated to **halos**, **visual snow**, **positive afterimages** and **dimensional distortion**. Staring at moving objects was associated to **illusions of movement**, **black moving spots with open and closed eyes** (moving speckles and dots in the peripheral field) and **trailing phenomena**.

On one occasion, while under the influence of SCS, Mr. B suffered from a severe panic attack. The panic attack was interpreted by the patient as a heart attack which was ruled

out after an ER examination. Diazepam was prescribed and psychiatric consultation was recommended. The following day Mr. B suffered from an additional panic attack, which was accompanied by visual imagery similar to that experimented during SCS use. Since then, Mr. B suffered from recurrent visual recurrences which were experienced along with anxiety features. These daily episodes usually lasted between fractions of seconds to a few minutes.

On psychiatric evaluation Mr. B accurately recognized SCS as the precipitator of his condition (5-8). He reported that the panic attack was so distressing that SCS ingestion was immediately ceased. Disturbances were sufficiently severe to cause significant distress, anxiety and impairment in social and occupational functioning. He fulfilled DSM-IV-TR full criteria of HPPD (3). As in the case of R described above, all examinations revealed no abnormalities

Uncomplicated outpatient SCS withdrawal was described as mild and treated with low doses of clonazepam, in a regimen described in the previous case. Mild anxiety features and sleep disturbances accompanied the withdrawal process. The patient was reluctant to be treated with "chemical drugs" (i.e., medications) and only accepted to take medication for a period of one month. He preferred to cope with his condition without medications, psychotherapy or counseling.

Mr. B's episodes of HPPD gradually became more benign and less distressing. His condition dramatically started to improve. After clonazepam suspension he continued to communicate a clear improvement in the frequency of perceptual disturbances. During the following three months symptoms disappeared almost completely. At the end of six months an almost total absence of visual disturbances was reported. Despite the profound reported improvement, he continued to suffer from benign non-distressing perceptual disturbances characterized by **black moving spots** in his visual fields.

DISCUSSION

Though HPPD has been well-described and reviewed in the literature following use of various hallucinogenic substances (9), little is known about these phenomena following use of new "designer drugs." Above we described two cases of HPPD following SCS use.

While the exact subjacent mechanism of SCS associated perceptual disturbances is largely unknown, there is some knowledge indicating similarities with those proposed mechanisms associated with the use of LSD (6) and NCS (1).

Serotonin neurotransmission seems to be involved in the origin of both acute and persisting LSD (6) and NCS induced perceptual disturbances (1). The acute short-term effects of LSD seem to be mediated through a 5-HT_{2A} postsynaptic partial agonist activity (10) which may alter and modify how individuals experience their senses and perceptions. Similarly, the acute short-term effects of cannabis appear to be related to serotonergic systems (1). Although the main acute pharmacological effects of cannabis are mediated through cannabinoid receptors (1), it is known that cannabis might severely impair serotonergic neurotransmission (11, 12). This disruption appears be responsible for most of the cannabis effects on cognition and perception (13, 14) and could be linked to the capability of cannabis to produce perceptual aberrations (15, 16) including visual disturbances (1).

Chronic long-term effects of LSD, namely Flashback-Type or HPPD I and HPPD-Type or HPPD II (5-8) may partially or entirely recapitulate the primary hallucinogenic intoxication, presupposing that a mechanism similar to the original one may be implicated.

The cardinal mechanism believed to underlie this condition appears to be a vulnerably or predisposition of LSD consumers continue to centrally process visual imagery after the visualization has been totally eradicated from the visual field (17). Persistence of visual disturbances associated to permanent disinhibtion of visual processors could be triggered by an LSD-engendered intense excessive current (18) or NCS-engendered similar mechanism (1) which might lead and contribute to the destruction or dysfunction of cortical serotonergic inhibitory inter-neurons with GABA-nergic outputs (19). Irreversible destruction or reversible dysfunction may hypothetically be responsible for the distinct types of benign short-term transient or pervasive long-term permanent recurring visual disturbances (1, 5-8).

High potency cannabis (20) affecting serotonergic neurotransmission (13, 14), could similarly recapitulate and induce the recurrence of benign short-term transient (1) or pervasive long-term permanent visual disturbances in subjects. The anandamidergic system also seems to be implicated, affecting and impairing areas of visual information processing (21, 22). The function of the endogenous cannabinoid system as well as the CNS on central visual processing is not entirely known and understood and requires further investigation and clarification.

NCS have led to the development of SCS. SCS have been synthesized and produced for biomedical research purposes because they may become promising medications. They constitute a new class of synthetic "designer" cannabinoid-like substances that bind, activate and exert their effects through cannabinoid receptors which indirectly may alter serotonin transmission and modulate anxiety. Chronic activation of CB2 receptors may result in an upregulation of $5HT2_A$ receptor density and function (20, 21). These substances, including their chemical structure, have been extensively reviewed (23). Cannabinoid receptors are part of the intricate endocannabinoid system which is not entirely and clearly understood (23). These substances might show higher potency and affinity for cannabinoid receptors (24) and might exhibit long half-lives and active metabolites (25). Therefore, it is plausible and logical to speculate that synthetic cannabis, as observed in natural cannabis (1), might affect serotonin neurotransmission (20, 21) leading to the emergence of HPPD through a mechanism similar to those described as being responsible of the genesis of LSD and NCS visual disturbances (1, 5-8).

In both described cases, there was previous use of NCS without associated visual disturbances, followed by initiation and continuous use of SCS. In both cases a panic attack-like "bad trip" accompanied by visual disturbances led to complete and total suspension of any substance consumption. Furthermore, patients continue to suffer from HPPD-Type visual disturbances (HPPD II) (5-8) following discontinuation of SCS. Though significant clinical improvement was noted following treatment with clonazepam, both patients continued to suffer from benign focal visual disturbances (trailing phenomenon and black moving spots) which were not associated with significant anxiety.

We propose that in light of the increasing use of SCS, clinical psychiatrists should be aware of these perceptual side effects.

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