Hallucinogen Persistent Perception Disorder Induced by New Psychoactive Substituted Phenethylamines; A Review with Illustrative Case

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Abstract: Hallucinogen Persistent Perception Disorder (HPPD) is considered an "uncommon" disorder described in association with use of hallucinogens such as LSD, mescaline and psilocybin. Despite multiple mentions of persistence of visual disturbances reported by users on online forums, clinicians may not be aware of this complication. There have been few descriptions of HPPD in association with use of new psychoactive substances (such as 2C-E). Increasing use of these designer stimulants places greater numbers at risk for psychiatric morbidities including HPPD. Here we report the first documented case of HPPD due to high dose 2C-E and blunting of symptoms with addition of lamotrigine.

Keywords: Stimulants, hallucinogen, psychoactive, phenylethylamines.

INTRODUCTION

Hallucinogens are a group of substances that include both naturally occurring and synthetic agents. During intoxication hallucinogens induce a reversible and transient state characterized by a variety of perceptual disturbances including visual illusions and hallucinations. A rare phenomenon termed hallucinogen persistent perception disorder (HPPD) has been observed in users of hallucinogens Reports have been, most commonly associated with use of LSD. This diagnostic category has been included as a DSM diagnosis since DSM IV. There is a corresponding ICD-10 code for this diagnosis (Hallucinogen Use, unspecified with hallucinogen persisting perception disorder). The incidence of this disorder is uncertain. An online survey suggests that 0.12-4.1% of users may develop HPPD [1]. It is characterized by partial recurrence or persistence of visual disturbances previously experienced during intoxication following drug-free periods of varying lengths ranging from days to years. Such experiences have similarities to acute LSD intoxication and take the form of various geometrical shapes, peripheral visual field flickers, flashes of colors, halos and palinopsia (trailing phenomena). Unlike true psychosis, users are able to recognize these as hallucinatory experiences. Little is known about the long-term natural history of this disorder [2]. Symptoms are recurrent and may be precipitated by stress, change in ambient light or use of alcohol, and cannabis. Precipitation after use of risperidone has also been reported to precipitate such phenomena [3-6]. Case reports of LSD [7, 8], MDMA [9] and psilocybin [10] have been extensively described. Rarely cases have been reported that are attributed to newer psychoactive substances.

Phenylethylamines are a class of substances with documented psychoactive stimulant effects that include amphetamines, methamphetamines and MDMA. When manipulated chemically in research laboratories they produce ring-substituted compounds that result in enhanced effects and novel psychoactive properties. Since first synthesized and popularized in the 1970s by the biochemist Alexander Shulgin, prevalence of use of these substances have varied over time. Recently, there has been a somewhat dramatic increase in the availability and use of these designer substances. The United Nations Office on Drugs and Crime (UNODC) on new psychoactive substances have reported the use of increasing numbers of such compounds.

Despite some identified phenylethylamines having been included as schedule-I substances, the number of reports made to UNDOC has quadrupled in recent years with approximately 20% attributed to phenylethylamines [11].

One such molecule is 4-ethyl-2,5-dimethoxy-phenethylamine (2C-E or "Europa") [12]. Ingested in pill form or powder as suggested by the drug information website, Erowid, a 10-20mg dose produces a rapid onset of perceptual changes with duration of effect from three hours to 24 hours [3, 13]. A dose-effect relationship is described by users with reports of changes with increasing dosages in the nature, duration and intensity of effects. Erowid users have reported normal thought processes without impaired judgment while experiencing visual and auditory perceptual disturbance giving, a property valued by some who use this agent. Some perceptual disturbances are described as distortions in perception of time, distortion of sounds described as echoing, or shifting of pitch. Auditory hallucinations perceived as scraping or popping sounds are commonly experienced.

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Visual disturbances are similar to those associated with mescaline and LSD use. However more geometrically complex and more intense appreciation of color effects of hallucinations are commonly reported. These agents do not appear to induce euphoria.

CASE REPORT

This 24 year-old computer technician presented to psychiatric evaluation reporting recreational use in the recent past of 2C-E‟s obtained through online means from an overseas supplier. He described using 10-15mg pills daily while taking 2-3 days off to "replace the serotonin". Occasionally he would use 20-30mg resulting in a more intensified and longer-lasting experience. After a month of use, he experimented with a 50mg dose. He described, as a result, "tripping for 20 hours straight". Following this episode he began to experience a persistent, low threshold, visual perceptual disturbances in the form of flickering "visual snow", blurring of small patterns and occasional halo effects as well as perception of motion in periphery of his visual fields. No closed-eye disturbances were noted. This had been ongoing for approximately two years after the use reported at the time of presentation to psychiatric care despite relative abstinence from stimulant or hallucinogen use. He reported that a one time subsequent use exacerbated and prolonged the duration of the psychoactive effect.

Based on previous prescription trials, he reported somewhat of an improvement when taking benzodiazepines but no change with SSRIs or antipsychotics. Work-related stress appeared to worsen the sensations. Despite lack of significant impairment in daily function he noted that, because of these disturbances of visual accommodation, his eyes would fatigue rapidly while performing demanding visual tasks on his computer. On presentation, basic laboratory workup and urine drug screen were unrevealing. The patient had a co-morbid diagnosis of Bipolar II disorder, primarily depressed episodes, These episodes failed to respond to trials of lithium, valproic acid, and quetiapine. However, when lamotrigine was initiated and slowly titrated upward he noted, within five days, a gradual amelioration of the intensity of the perceptual disturbances. Follow-up after six weeks indicated continued improvement while on lamotrigine.

DISCUSSION

HPPD is considered a rare post-hallucinogen use disorder consisting primarily of visual perceptual disturbances. A literature search returns only a handful of published cases associated with LSD, MDMA, psilocybin. However there are frequent mentions in the online drug community suggesting similarity of effect with use of some newer psychoactive substances. It is likely that this phenomenon is underrecognized by clinicians [14]. A web-based questionnaire of hallucinogen users found 61.7% experienced visual hallucinations after cessation of use. However, only 4.2% of those report it spontaneously [1]. HPPD may be an unusually severe form of a common syndrome of post-hallucinogen visual disturbances. It can occur after one time use, a high dose, or simply with chronic use. The time between drug cessation and onset of symptoms also varies. The length of time during which patients experience symptoms is varied and stress, photic changes, alcohol, cannabis and risperidone have been shown to exacerbate symptoms.

The pathophysiologic mechanism for these symptoms remains obscure. Some have suggested that use of some hallucinogenics may produce an imbalance in icentral inhibitory-excitatory activity shifting the balance towards unapposed glutaminergic pathways [9, 15]. This may provide an understanding as to why benzodiazepines result some degree of improvement [7]. To date no effective treatment exists as knowledge has been completely based on case reports. SSRIs, benzodiazepines, haloperidol, trifluoperazine, perphenazine, olanzapine, risperidone, naltrexone, clonidine, roboxetine, phenytoin, carbamazepine, valproic acid have been tried with inconclusive outcomes. Risperidone has been reported to worsen symptoms. Lamotrigine, as shown in a similar report, appeared helpful in this case. Although the exact mechanism is not understood it is postulated that it has a neuroprotective effect. Although in the previously published case lamotrigine was titrated to maximum dose of 200mg over a yearlong trial, our patient experienced progressive blunting of symptoms progressively with increasing dosage. Although the use of electroconvulsive therapy (ECT) has been shown to be efficacious in management of bath salts and methamphetamine (stimulants) induced long term persisting psychotic symptoms, it has not been explored in management of HPPD [16].

SUMMARY AND CONCLUSION

This report is the first to describe development of HPPD following use of 2C-E, a clinically underreported perceptual disorder, previously described with hallucinogen use. Although considered rare, the burden of disease can be substantial. Our secondary intention is also to highlight the gaps in evidence for possible psychiatric sequelae resulting from use of a growing number of new psychoactive substances. Due to their novelty, little is known about the properties they possess. As in a similar report by Hermle *et al*., HPPD symptoms remitted upon titration of lamotrigine to 200mg during the course of 12 months and remained in remission with dose reduction to 100mg [2]. This patient experienced blunting of peripheral flickers during beginning with addition of lamotrigine at doses of 50mg. Six weeks after treatment initiation improvement was sustained.

Given the increasing use of new psychoactive substances and the limited information on side effects, clinicians should be aware of the potential of at least one of these agents to induce HPPD symptoms either on first use, with chronic use, or with excessive dosing. Other symptoms may also be underreported due to concern over legal consequences. However these disorders are extensively elaborated within in the online community. Given the lack of documented cases and limited published data, physicians have little evidence to guide treatment. Discontinuing use of these substance and use of lamotrigine may have resulted in a gradual progressive blunting of symptoms in this patient. Clinicians should be aware of drug monitoring surveys that may make it possible for the tracking of prevalent patterns of drug use. This would prompt more targeted screening for such

substances leading to early recognition and intervention to avoid complications such as described here. Monitoring the future (MTF) studies have yet to track new psychoactive substances despite reports from UNDOC and data from overseas reports of drug seizures. The most recent National Forensic Laboratory Information System (NFLIS, program that tracks national, regional and local emerging drug patterns) survey does not include 2C-E in the drug categories surveyed. Liquid chromatography mass spectrometry in tandem (LC-MS/MS) has been shown to identify 2C-E in urine if use is suspected [17].

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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