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## **LSD-Induced Hallucinogen Persisting Perception Disorder Treated with Clonazepam: Two Case Reports**

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*Abstract:* Benzodiazepines are recommended for the treatment of Hallucinogen Persisting Perception Disorder (HPPD), although it is unclear which may be more helpful. Two out-patients with LSD-induced HPPD were successfully treated with clonazepam. They had not responded to low potency benzodiazepines or low doses of classic antipsychotics. After clonazepam discontinuation they reported a marked improvement and only mild symptomatology which persisted during a six month follow-up period. High potency benzodiazepines like clonazepam, which has serotonergic properties, may be superior to low-potency benzodiazepines in the treatment of some patients with LSD-induced HPPD.

### **Introduction**

An unique characteristic of lysergic acid diethylamide (LSD) and LSD-like substances is the recurrence of some of the symptoms which appear during the intoxication, in the absence of recent intake of hallucinogens. Hallucinogen persisting perception disorder (HPPD) is a condition in which the re-experiencing of one or more perceptual symptoms causes significant distress or impairment in social, occupational or other important areas of functioning and may be extremely debilitating (1). Hallucinogen users are usually aware of these consequences of LSD consumption and seek psychiatric help (2).

HPPD appears to be part of a spectrum of non-psychopathological and psychopathological states reported by hallucinogen users. While the precise mechanisms underlying these phenomena are unknown, several theories have been proposed.

The acute effects of LSD seem to be mediated through a 5-HT<sub>2</sub> postsynaptic partial agonist activity (3) whereby the syndrome may resemble the previous experience, implying that a mechanism related to the original one may be involved. The basic mechanism underlying this syndrome appears to be that vulnerable LSD users continue the central process of visual imagery after the image has been removed from the visual field (4). An LSD-generated intense current (5) may provoke the destruction or dysfunction of cortical serotonergic inhibitory interneurons with GABA-ergic outputs and lead to the persistence of the visual imagery due to chronic disinhibition of visual processors (6). Reverse tolerance that had originated after LSD exposure may also explain the continuation of the imagery after the stimulus has been removed (7). There may also be a familial and genetic basis (6, 8, 9).

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Benzodiazepines are one of the recommended agents for the treatment of HPPD, but it is unclear which of them may be more helpful. We report the cases of two out-patients who were previously unsuccessfully treated with small doses of classic antipsychotics and low-potency short-acting benzodiazepines. They remarkably improved after clonazepam administration.

### Case 1

A 24-year-old male student, with a three years previous history of cannabis, ecstasy (MDMA) and LSD abuse, discontinued substance use four months ago after being "scratched and bruised" by the last LSD blotter. He described his experience as a "chemical hit" that provoked a horror trip phenomenon accompanied by intolerable anxiety. Twenty-four hours after the last LSD intake he experienced prodromal symptoms such as photophobia and feelings of detachment and disconnection. Subsequently he reported being bothered by visual disturbances of flashes of colors that "blinded" him, body image distortion, derealization, positive and negative afterimages and trailing phenomena (moving objects seen as a series of discrete and discontinuous images). These episodes usually lasted between a fraction of a second and a few minutes.

He was almost unable to attend lessons, concentrate, study and sit exams. He became isolated, only maintaining contact with a few friends who "forced" him to go out, as he preferred to remain at home.

The perceptual disturbances were severe enough to cause significant distress, anxiety and impairment in social and occupational functioning. He fulfilled DSM-IV diagnostic criteria of HPPD. There was no neurological or psychiatric history.

He was medicated with zuclopenthixol 10 mg/day for a few days which was

suspended due to anticholinergic side effects. Then he received lorazepam up to 3 mg/day for one month without any improvement.

After admission we started a regimen of 0.25 mg of clonazepam twice a day for the first week which was increased to 0.50 mg twice a day for the second week. He did not report improvement so clonazepam was raised to 1 mg twice a day the third week. After two weeks of treatment at this dose he reported considerable improvement in the frequency of perceptual disturbances and the accompanying anxiety. During the following two months symptoms disappeared almost completely. Then clonazepam was gradually discontinued over the following month.

He was evaluated using the Clinical Global Impression scale (CGI), a Likert-type scale (1-7, normal to extremely ill) assessing severity of mental symptoms (10). A self-report scale (SRS) inquiring on the severity of symptoms (1-5, normal to severe) was also administered (2). His improvement was assessed every week the first month and every two weeks until the completion of clonazepam discontinuation. He was evaluated every month during a six month follow-up period. Despite the reported improvement, the trailing phenomena persisted over the follow-up period.

### Case 2

The patient was a 22-year-old male student with a two year history of cannabis abuse. He stopped substance use two months ago after experiencing a horror trip phenomenon accompanied by panic attacks. The "bad trip" occurred after his first LSD consumption and he attributed it to the intake of a "chemical" blotter. He reported trails of images of moving objects, body image distortion, derealization and spontaneous imagery of faces. These lasted fractions of

seconds and were severe enough to cause distress, anxiety and impairment in social and occupational functioning. He fulfilled DSM-IV diagnostic criteria of HPPD. There was no neurological or psychiatric history. He had been treated with perphenazine 8 mg for one week and stopped it due to blurred vision. He then received oxazepam up to 30 mg a day for three weeks with no significant improvement and marked drowsiness and daytime sedation.

After admission we started 0.25 mg of clonazepam twice a day the first week which was raised to 0.50 mg twice a day the second week. He reported a gradual improvement in the frequency of perceptual disturbances and anxiety. Over the next two months symptoms disappeared almost completely and thus tapering was started. Clonazepam was gradually reduced over a month. His improvement was assessed using CGI and SRS every week the first month and fortnightly until the completion of clonazepam discontinuation. The evaluation continued every month during a six month follow-up period. He has remained symptom free, except for the trailing phenomenon, over the follow-up period.

## Discussion

The literature on the efficacy of pharmacological agents is controversial and mainly supported by small open studies, case series and case reports. Several pharmacological approaches have been used in the treatment of HPPD. Benzodiazepines, haloperidol, trifluoperazine, perphenazine, phenytoin, naltrexone, sertraline, carbamazepine, valproic acid and clonidine have been shown to be helpful (2, 4, 8, 11, 12).

HPPD appears to be a syndrome which encompasses several diagnostic subtypes that may respond to different medications. What remain unanswered are the nature and characteristics of these subtypes and the

pharmacological approaches to their treatments. It is accepted that benzodiazepines are the treatment of choice for the majority of the patients suffering from this disorder (2). They seem to be useful in some patients (8, 11) and may alleviate but not eradicate this clinical entity (13). Their effectiveness may be related to benzodiazepine activity at cortical serotonergic inhibitory interneurons with GABA-ergic outputs (6, 13).

Nevertheless, among the range of benzodiazepines, it is unclear which may be more helpful in the management of HPPD, as they vary in characteristics such as half-life, potency and side effect profile. Alprazolam has been reported as a possible treatment (11) and we have observed clinical improvement with clonazepam (2). Which benzodiazepine is preferred, at what dose and for how long are questions raised by clinicians when facing a patient presenting HPPD. The abuse potential of alprazolam might be troublesome in individuals with previous or concomitant substance-related disorders. Clonazepam has been successfully used for the treatment of alprazolam dependence (14).

The presented cases showed a sustained improvement during clonazepam treatment which persisted over a six month follow-up after discontinuation. A maximum dose of 2 mg/day followed by a slow discontinuation were needed in order to manage this condition, although the trailing phenomenon remained over a six month follow-up period. The decision to prescribe clonazepam instead of clonidine (2) rested on the observation that patients who did not benefit from former benzodiazepine treatment will be expected not to benefit from clonidine. It is suggested that clonazepam may have effects on serotonergic systems and that it may enhance serotonergic transmission (15). The specific serotonergic properties of clonazepam may play a role in the improvement in our patients. Among the

benzodiazepines, clonazepam seems to have a low abuse potential profile even in long-term treatments (16). Nevertheless, patients with a history of substance related disorders should be rationally prescribed and closely monitored (17). Conclusions from these two case reports should be taken with caution. Extraneous factors such as a highly trained and motivated staff, psychotherapy and the expectations raised by a new treatment modality may also account for the reported improvement. Controlled studies would be desirable.

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