Clonazepam treatment of lysergic acid diethylamide-induced hallucinogen persisting perception disorder with anxiety features

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An unique and intriguing 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. Benzodiazepines are one of the recommended agents for the treatment of HPPD but it is unclear which of them may be more helpful. The goal of our investigation was to assess the efficacy of clonazepam in the treatment of LSD-induced HPPD. Sixteen patients fulfilled entrance criteria. All complained of HPPD with anxiety features for at least 3 months and were drug free at least 3 months. They received clonazepam 2 mg/day for 2 months. Follow-up was continued for 6 months. They were weekly evaluated during the 2 months of clonazepam administration and monthly during the follow-up period using the Clinical Global Impression Scale, a Self-report Scale and Hamilton Anxiety Rating Scale. Patients reported a significant relief and the presence of only mild symptomatology during the clonazepam administration. This improvement was clearly sustained and persisted during a 6-month follow-up period. This study suggests that high potency benzodiazepines like clonazepam, which has serotonergic properties, may be more effective than low-potency benzodiazepines in the treatment of some patients with LSD-induced HPPD. *Int Clin Psychopharmacol* 18:101–105

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Introduction

Hallucinogens comprise a group of naturally occurring and synthetic agents that produce a state of intoxication, sometimes called 'trip', associated with changes in thought, mood and perception. These mind-altering effects are produced with a clear level of consciousness, full wakefulness, alertness and absence of confusion.

A unique and intriguing 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. Common recurrent visual disturbances attributed to this complex syndrome are geometric hallucinations, false perception of movement in the peripheral visual fields, flashes of colors, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia and micropsia (DSM-IV-TR, 2000).

At least two subtypes of this syndrome have been reported (Lerner *et al.*, 2000). The first is a transient, recurrent, spontaneous, reversible and generally visual benign experience. Experienced LSD users generally look at these recurrences as a 'free trip', an aspect of the psychedelic dimension, and do not seek psychiatric assistance after experiencing this kind of episodes. The second is hallucinogen persisting perception disorder (HPPD). This is long-term, spontaneous, intermittent or continuous, pervasive and either slowly reversible or irreversible. This phenomenon is entirely different from the benign 'flashback'. 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 (DSM-IV-TR, 2000). HPPD often occurs in individuals with no prior psychopathology, and may be extremely debilitating. Hallucinogen users are usually aware of these severe, intruding and disabling consequences of LSD consumption and generally actively seek psychiatric

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help (Lerner *et al.*, 2000). HPPD seems to be part of a large spectrum of non-psychopathological and psychopathological experiences reported by hallucinogen users.

While the mechanisms underlying these phenomena are unknown, several theories have been proposed. The acute effects of LSD seem to be mediated through a 5-HT_2 postsynaptic partial agonist activity (Sander-Bush *et al.*, 1988; Marek and Aghajanian, 1996) and the enhancement of glutamatergic transmission (Aghajanian and Marek, 2000). 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 (Young, 1997). An LSD-generated intense current (Garrat *et al.*, 1993) 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 (Abraham and Aldridge, 1993). Reverse tolerance or LSD sensitization originating after LSD exposure may also explain the continuation of the imagery after the stimulus has been removed (Stahl, 1996; Phillips, 1997). There may be a familial and genetic basis as well (Abraham, 1983; Abraham and Mamen, 1996).

Benzodiadepines are one of the recommended agents for the treatment of HPPD (Abraham, 1983; Abraham, 2000) but it is still unclear which of them may be more helpful (Lerner *et al.*, 2001). Slow recognition (Abraham *et al.*, 1996) or misdiagnosis of HPPD may lead to the prescription of unhelpful medications. A tendency to prescribe low potency benzodiazepines (Lerner *et al.*, 2001), such as oxazepam and lorazepam, has been observed, despite the fact that there is some evidence regarding the effectiveness of high potency benzodiazepines in the treatment of this syndrome (Abraham, 2000; Lerner *et al.*, 2001).

The purpose of this study was to evaluate the benefit of clonazepam in the treatment of LSD-induced HPPD with anxiety features.

Methods

Sixteen patients who fulfilled DSM-IV diagnostic criteria of HPPD were enrolled (American Psychiatric Association, 2000). All the subjects reported anxiety features. Eleven were male and five were female. They were unmarried, had 12 years of schooling, were of middle class social status and their average age was 21.125 years (SD = 2.500, range = 17–24). All subjects had a reasonable level of functioning, despite the impairment produced by HPPD. All the individuals had a history of polysubstance use disorder, including cannabis, MDMA and LSD abuse. All the subjects identified LSD as the trigger of their visual disturbances. They complained of HPPD for at least 3 months, and were drug free for at least 3 months, as assessed by random weekly urine drug screening tests.

All the patients previously underwent therapeutic trials with short-acting, low potency benzodiazepines. Some of them received other pharmacological agents. These medications were suspended due to side-effects or lack of improvement. Patients were referred or applied themselves for treatment.

The proposal of a fixed dose of clonazepam 2 mg/day over 2 months rested on a previous report (Lerner *et al.*, 2001) and the concomitant comorbid anxiety. After their informed consent was obtained, we started the patients on a regimen of 0.25 mg of clonazepam b.i.d on the first day, which was flexible and individually raised up to 2 mg b.i.d. at the end of the first week, in order to avoid side-effects. Then, the sample received clonazepam 2 mg/day until completion at 2 months. After the completion of this phase, clonazepam was gradually discontinued, 0.5 mg weekly, over 1 month, to prevent rebound-relapse symptoms. Follow-up started with clonazepam discontinuation and continued for 6 months.

The individuals were evaluated by the principal author using the Clinical Global Impression Scale (CGI) (Guy, 1976) which is a likert-type intensity scale (1–7, normal to extremely ill) assessing severity of mental symptoms and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). We also used a Self-Report Scale (SRS), which inquires on the severity of HPPD (1–5, normal to severe). We have successfully used the SRS in previous studies to measure the severity of HPPD distress-related symptoms (Lerner *et al.*, 2000, 2001).

The assessment using CGI, SRS and HAM-A was effected weekly for 8 weeks during the trial, and monthly during the 6-month follow-up period.

Results

Two patients dropped out of treatment before the end of the 2-month investigation and were consequently removed from the sample. Results comparing baseline to 8 weeks into treatment and 8 weeks into treatment to follow-up after 6 months on the CGI, SRS and HAM-A are presented in Table 1.

A more in-depth look at the HAM-A showed only the anxious mood, tension, insomnia and intellectual items to have been reduced significantly. The other items could not be reduced because of a floor effect. The low baseline rating of these items is in accordance with the description

Table 1 Assessment of changes on Clinical Global Impression Scale (CGI), Self-Report Scale (SRS) and Hamilton Anxiety Rating Scale (HAM-A), comparing baseline versus 8 weeks into treatment and 8 weeks into treatment versus follow-up after 6 months

P	*t*	Follow-up, $n = 14$ (mean ± SD)	*P*	*t*	8 weeks, $n = 14$ (mean ± SD)	Baseline, $n = 14$ (mean ± SD)	Tests
< 0.008	3.2	2.1 ± 0.62	< 0.001	16.3	2.5 ± 0.52	5.36 ± 0.63	CGI
< 0.04	2.3	1.70 ± 0.47	< 0.001	18.7	2.0 ± 0.0	4.57 ± 0.52	SRS
NS	1.1	10.21 ± 1.07	< 0.001	32.5	10.6 ± 1.01	20.7 ± 1.20	HAM-A

of HPPD, with associated anxious features suggesting the presence of only specific accompanying anxiety-related complaints in this syndrome. All scores were reduced significantly after the 8-week procedure. During the follow-up period, an additional improvement in symptomatology was found, as observed on the CGI and the SRS, but not on the HAM-A average. Very mild symptomatology persisted at the end of the pharmacological trial, during the clonazepam discontinuation and free-clonazepam follow-up period. These results indicate a significant improvement due to clonazepam administration.

Discussion

HPPD may be characterized by an identifiable trigger, prodromal symptoms, presentation onset, content of perceptual disturbances, frequency, duration and intensity of the recurrences, insight, accompanying affect and course (Abraham, 2000; Lerner *et al.*, 2002a). Generally, HPPD may present with anxious or depressive features, its severity may be mild, moderate and severe and its course may be benign or pervasive. Patients may notice the presence of a subtle perceptual incident or a full-blown syndrome. Visual disturbances, the commonest perceptual recurrent symptoms, may range from a mildly distressing, isolated occurrence up to severely distressing, multiple changing different occurrences. In certain subjects, HPPD tends to remit spontaneously or improve without pharmacological treatment. Others may develop a chronic relapsing syndrome. They learn to 'live' with HPPD, despite some sort of disabilities. It is still unclear whether HPPD is an infrequent rare condition, or whether it is an under or misdiagnosed disorder. Interestingly, HPPD appears to be a syndrome encompassing several diagnostic subtypes that may respond to different medications.

The complexity and diversity of HPPD undoubtedly make it a very complicated syndrome to study. The literature on the efficacy of pharmacological agents is controversial and is mainly based on open label studies, case series and case reports. The lack of double-blind studies stems from the serious difficulties in controlling and randomizing variables when planning and designing clinical investigations.

The generally recognized target symptoms in the treatment of HPPD are visual disturbances, anxiety and depressive features. There is no recognized effective pharmacological treatment capable of totally removing HPPD-related symptoms. Medications may only reduce the severity of HPPD or its associated complaints.

Clonidine may be an available treatment for patients reporting LSD-induced HPPD. It was hypothesized that the hyperarousal, traumatic nightmares and flashbacks which characterize post-traumatic stress disorder (PTSD) are related to long-term potentiation of locus ceruleus pathways to the hippocampus and amygdala (van der Kolk *et al.*, 1985). Pharmacological agents which can dampen the hyperarousal associated to PTSD may show a palliative if not a curative role (Friedman, 1988). Clonidine suppresses locus ceruleus activity and reduces adrenergic activity (Davidson, 1992). Therefore, it appears to be helpful in the treatment of some patients suffering from PTSD-associated flashbacks (Kolb *et al.*, 1984) and LSD-induced HPPD (Lerner *et al.*, 1998).

There is some evidence that dopamine receptor antagonists, such as haloperidol (Moskowitz, 1971), trifluoperazine (Anderson and O'Malley, 1972) and perphenazine (Miller, 1997) may be helpful. Unfortunately, the frequent appearance of side-effects in naive patients usually undermines patient compliance and patients tend to stop medication.

Risperidone, a serotonin dopamine receptor antagonist, was considered as a plausible treatment for HPPD, because LSD appears to act mainly as a partial agonist at postsynaptic serotonin receptors. In contradiction to this assumption, risperidone at recommended (Abraham and Mamen, 1996) and low doses (Morehead, 1997) exacerbated HPPD and the associated anxiety. This exacerbation was later attributed to a α_2 presynaptic antagonism effects of risperidone (Alcantara, 1998).

There are controversial data regarding the selective serotonin reuptake inhibitor (SSRI) sertraline which has been reported to worsen (Markel *et al.*, 1994) and oppositely to improve HPPD (Young, 1997). Amelioration of HPPD after chronic administration of SSRIs was attributed to the down regulation of 5-HT_2 receptors, adding further evidence to support the serotonergic mechanism of HPPD (Young, 1997). Reboxetine, a noradrenaline selective reuptake inhibitor, also appears

to be helpful in the treatment of some subjects complaining of HPPD with depressive features (Lerner *et al.*, 2002b). Reboxetine may have an α_2 adrenoreceptor modulating effect on both noradrenaline and serotonin release (Lucca *et al.*, 2000). Reboxetine may also affect the reuptake of serotonin and lead to down regulation of 5-HT_2 receptors resembling the improvement of HPPD after administration of SSRIs (Young, 1997; Lerner *et al.*, 2002b).

An interesting combination of fluoxetine and olanzapine was also been reported to be effective, although the favourable reported response to this combination remains unclear (Aldurra and Crayton, 2001).

Long-acting receptor antagonists, such as naltrexone, have been reported to be ineffective (Abraham, 2001) and controversially helpful in specific cases of LSD-induced HPPD (Lerner *et al.*, 1997). The underlying mechanism of the efficacy of naltrexone could be that HPPD may be so distressing as to represent painful stimuli, which has been shown to provoke a greater release of endorphins (Lerner *et al.*, 1997).

There is some evidence that anticonvulsive agents such as phenytoin, carbamazepine and valproic acid (Thurlow and Girvin, 1971; Abraham, 2000) may ameliorate this psychopathology, which may be interpreted as a 'visual seizure' (Thurlow and Girvin, 1971). Such an approach may help to explain the efficacy of benzodiazepines. Benzodiazepines seem to be the treatment of choice for the majority of patients (Abraham, 1983). They may improve, but not totally remove, this condition (Abraham *et al.*, 1996). Among the wide range of available benzodiazepines, it is still unclear which of them may be more effective (Lerner *et al.*, 2001).

In our study, clonazepam proved to be helpful and well tolerated. Patients reported a significant relief in their visual disturbances and accompanying anxiety features, and this was maintained over the follow-up period. Compared to a previous study, in which we evaluated the efficacy of clonidine in the treatment of HPPD, we found a similar reduction of more than 50% on the CGI and on the SRS after 2 months of treatment (Lerner *et al.*, 2000). It should be stressed that it is unlikely that all of the sample undergoing clonazepam treatment achieved a natural and spontaneous remission. Slow clonazepam discontinuation probably contributed to the good results. The amelioration, although partial, was sustained. The trailing phenomenon (e.g. moving objects are seen as a series of discrete and discontinuous images as they move across the visual field) (Abraham, 1983; Sadock, 2000), was remarkably refractory. Mild temporary daytime sedation and mild psychomotor impairment were the more frequent reported side-effects.

The effectiveness of benzodiazepine may be related to benzodiazepine activity at cortical serotonergic inhibitory interneurons with GABAergic outputs (Abraham and Aldridge, 1993; Abraham *et al.*, 1996). Additional benefits regarding clonazepam may be proposed. There is a substantial amount of literature suggesting that clonazepam may affect serotonergic systems and that it may enhance serotonergic transmission (Bodkin and White, 1989; Hewlett *et al.*, 1992). This may secondarily lead to down regulation of 5-HT_2 receptors, which may contribute to the HPPD symptoms remission (Young, 1997). The specific serotonergic characteristics of clonazepam, along with its high potency, rapid rate of absorption and long lasting action, may play an important, although unclear role, in the observed improvement of the reported patients.

Among the benzodiazepines, clonazepam seems to have a low abuse potential profile, even in long-term treatment (Pollack, 1987; Schenck and Mahowald, 1996).

Patients with a previous or present history of substance-related disorders should be rationally prescribed and closely monitored (Trudeau, 1994; Lerner *et al.*, 2001). Certain patients may need short-term courses or intermittent benzodiazepines prescription. Wisely, long-term administration of benzodiazepines (Ashton, 1994) may be taken into account as an alternative option for those presenting with non-remitting, treatment-resistant, pervasive HPPD.

Despite the limitations of its methodology, our study provides more data regarding the efficacy of benzodiazepines in general, and clonazepam in particular, in the pharmacological management of HPPD.

The issues regarding duration and dose of clonazepam administration remain unanswered. It is possible that some patients may respond to lower doses and shorter periods of clonazepam treatment. Further clinical investigations are needed in this area.

According to the results of our study, high-potency long-acting benzodiazepines such as clonazepam, when wisely prescribed, are preferable to low-potency short-acting ones in the management of patients suffering from HPPD.

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