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LSD-induced hallucinogen persisting perception disorder treatment with clonidine: an open pilot study

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A pilot open study was conducted in order to evaluate the efficacy of clonidine in the treatment of LSD-induced hallucinogen persisting perception disorder (HPPD). Eight patients fulfilled entrance criteria. All complained of HPPD for at least 3 months and were drug free at least 3 months. They received fixed low doses of clonidine, 0.025 mg, three times a day for 2 months. They were evaluated by the Clinical Global Impression Scale (CGI) and a self-report scale on the severity of symptoms (graded 0–5). Patients scored an average of 5.25 (SD = 0.46) on the CGI and 4 on the self-report scale at baseline, indicating marked psychopathology. One patient dropped out at week 3 and a second patient dropped out at week 5. Of the six patients remaining at the end of 2 months, the average CGI score was 2.5 (SD = 0.55) and the self-report scale score was 2, indicating mild symptomatology. LSD-related flashbacks associated with excessive sympathetic nervous activity may be alleviated with clonidine in some patients.

Keywords: clonidine, flashback, lysergic acid diethylamide

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. At least two subtypes of this syndrome have been delineated.

The first type is the 'flashback'. This is a transient, recurrent, spontaneous, reversible and generally benign experience. Experienced LSD users generally look at a flashback. as a 'free trip', an aspect of the psychedelic dimension, and do not seek psychiatric assistance after experiencing this kind of episode.

The second type is the 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 'flashback' type. 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, 1994). 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 help.

The mechanisms underlying these phenomena are unknown, although different theories have been proposed (Abraham, 1983; Abraham and Aldrige, 1993; Abraham and Mamen, 1996; Stahl, 1996).

We previously reported the improvement observed in some patients who presented with HPPD and were

treated with clonidine (Lerner *et al.*, 1998)). We subsequently conducted a preliminary open study in order to further evaluate the benefit of clonidine in the treatment of LSD-induced HPPD.

METHODS

Eight patients who fulfilled DSM-IV diagnostic criteria of HPPD were enrolled. They were unmarrried, had completed their compulsory army service, had 12 years of schooling, were of middle class had an average age of 23.25 years (SD = 2.49, range 21–26 years). All subjects had a history of polysubstance use disorder, including benzodiazepines abuse, complained of HPPD for at least 3 months, and were drug free for at least 3 months, as witnessed by random weekly urine drug screen tests. After their written informed consent was obtained, they received low fixed doses of clonidine, 0.025 mg, three times a day for 2 months. They were evaluated weekly by a the principal author using the Clinical Global Impression scale (CGI). The CGI is a likert-type scale (1–7, normal to extremely ill) assessing severity of mental symptoms (Guy, 1976). Furthermore, a self-report scale inquiring on the severity of symptoms (1–5, normal to severe) was also administered.

RESULTS

Patients scored an average of 5.25 (SD = 0.46) on the CGI and 4 on the self-report scale at baseline, indicating marked psychopathology. One patient dropped out at week 3 and a second patient dropped out at week 5. Of the six patients remaining at the end of 2 months, the average CGI score was 2.5 (SD = 0.55) and the self-report scale score was 2 for all patients, indicating very mild symptomatology.

DISCUSSION

Distinct pharmacological approaches have been used in the treatment of HPPD. The literature concerning the efficacy of pharmacological agents is controversial and mainly based on case reports. The usual target symptoms for HPPD treatment are visual hallucinations and anxiety.

Serotonin–dopamine receptor antagonists, such as risperidone, at recommended (Abraham and Mamen, 1996) and low doses (Morehead, 1997) appear to exacerbate HPPD and the associated anxiety. Despite the evidence that support the efficacy of dopamine receptor antagonists such as haloperidol (Moskowitz, 1971), trifluoperazine (Anderson and O'Malley, 1972) and small doses of perphenazine (Miller, 1997), it is widely accepted by psychiatrists that neuroleptics are not suitable for HPPD. Selective serotonin reuptake inhibitors also appear to worsen symptoms of HPPD (Markel *et al.*, 1994).

In contrast, long-acting opioid receptor antagonists like naltrexone may be helpful in specific cases of LSD-induced HPPD (Lerner *et al.*, 1997). Benzodiazepines appear to be useful in some patients who suffer from this condition (Abraham, 1983). Alprazolam has been found helpful (Miller, 1997) and we used clonazepam with success in a small number of patients. They appear to be the treatment of choice for the majority of patients, but their abuse potential might be troublesome in individuals with substance-related disorders, especially those with benzodiazepines abuse (Lerner *et al.*, 1998)

Clonidine appeared to be helpful in at least six out of eight patients of our study. Various suggested mechanisms may partially explain these clinical observations. There is some evidence that clonidine stimulates a central release of γ-aminobutyric acid (GABA) in animals (Pittaluga and Raiter, 1988) and increases plasma GABA levels in humans (Kemph *et al.*, 1993). Thus, clonidine may have a benzodiazepine-like effect.

In addition, it was proposed that the flashbacks characterizing post-traumatic stress disorder (PTSD) are related to long-term potentiation of the locus ceruleus pathways to the hippocampus and amygdala (Van der Kolk, 1985). Agents that can reduce central noradrenergic function and attenuate the hyperarousal associated to PTSD should have a palliative if not a curative role (Friedman, 1988). Clonidine reduces locus ceruleus activity and decreases adrenergic activity (Davidson, 1992) and therefore appears to be helpful in the treatment of PTSD (Kolb, 1984). We think that, similar to PTSD related flashbacks, LSD-related HPPD could be associated with excessive sympathetic nervous activity that may be alleviated by clonidine.

Clonidine at low doses is well tolerated, has minimal side-effects, has no abuse potential and may improve HPPD. We suggest, from our preliminary data, that clonidine should be taken into consideration as a medication for the treatment of LSD-induced HPPD, especially for patients who have a history of benzodiazepine abuse.

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