

Isr J Psychiatry Relat Sci Vol 39 No. 2 (2002) 100-103

LSD-Induced Hallucinogen Persisting Perception Disorder with Depressive Features Treated with Reboxetine: Case Report

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Abstract: We would like to present the case of a patient who had a prior history of cannabis, ecstasy (MDMA) and LSD abuse and who developed both Hallucinogen Persisting Perception Disorder (HPPD) and a major depressive episode. Following two unsuccessful SSRIs trials, reboxetine was prescribed. During a six-month follow-up period on reboxetine 6 mg./day, no exacerbation of the visual disturbance or recurrence of the depressive features were reported. Reboxetine may have an α_2 adrenoreceptor modulating effect on both noradrenaline and serotonin release, thus reboxetine's α_2 adrenoreceptor modulating effect on noradrenaline release may affect sympathetic activity and be involved in the recovery process.

Introduction

A well described side effect associated with the use of synthetic hallucinogens, such as lysergic acid diethylamide-LSD and LSD-like substances, is the recurrence of some of the perceptual disturbances which previously appeared during intoxication, in the absence of recent use (1, 2). These phenomena are accompanied by full insight and can be short-term or long-term (3). DSM-IV describes this condition as Hallucinogen Persisting Perception Disorder (HPPD) and stresses that the re-experiencing of one or more perceptual symptoms after stopping hallucinogen use causes significant distress or impairment in social, occupational or other important areas of functioning (4).

There is some evidence regarding the role of the serotonergic system in the development of HPPD. The acute effects of LSD

appear to be mediated through 5-HT₂ post-synaptic partial agonist activity (5). HPPD may resemble the prior intoxication, implying that a mechanism related to the original one may be involved. The hypothesized participation of the serotonergic system in the genesis of HPPD led to the administration of SSRIs. Some patients reported improvement of HPPD after treatment with these agents (6).

Co-morbid depressive disorders may be present in subjects abusing LSD (7) and also in patients suffering from HPPD (8). Therefore, it may be expected that SSRIs could be of some benefit in the treatment of patients suffering from HPPD with depressive features.

We report the case of a patient presenting both HPPD and a major depressive episode who was unsuccessfully treated with SSRIs

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but reported a marked improvement in both HPPD and depressive symptoms after treatment with the potent and selective noradrenaline reuptake inhibitor reboxetine.

Case Report

A. was a 26-year-old, single, employed male. He had 12 years of schooling and had completed his compulsory military service. He had a previous history of cannabis use that started at the age of 21. He occasionally ingested ecstasy (MDMA) and LSD at trance parties. There was no other previous significant medical or psychiatric history. He experienced good trips, which were followed by short, pleasant, visual recurrences. The visual disturbances consisted of stationary changing color points which suddenly appeared and disappeared when looking at white walls and illusions of movement when looking at still objects like a pen, a glass or an armchair. They lasted fractions of a second, were accompanied by full insight and were under his control. He described these perceptual disturbances as pleasant, benign and welcome. At the age of 25 the perceptual disturbances began lasting longer than expected, and he felt that he was losing control.

He suspended all the "chemicals," e.g., LSD and MDMA, and discontinued the use of all substances of abuse besides cannabis. Two months later he suddenly experienced the appearance of a new sort of perceptual disturbance that he had not experienced in the past: a single, black luminescent moving pinpoint, which entered his visual field. He associated the appearance of "the point," as he called it, with cannabis use (9) and consequently stopped using cannabis. The point was present almost every day for periods of time that lasted between fractions of seconds to minutes, several times a day. The point almost always appeared after looking at a moving or stationary object that contained the color white, such as a white wall, a white

page of a notebook or a piece of white toilet paper. Moving objects such as a candle flame, the smoke of incense or a moving car seemed to leave trails or have shadows.

These perceptual disturbances fulfilled DSM-IV criteria for HPPD. The occurrences caused significant distress and impairment in social and occupational functioning. He was unable to work more than a few hours a day. He avoided going out because he was unable to foresee when the intruding point would appear. He felt handicapped and disabled.

Depressive features rapidly followed the onset of HPPD. He presented complaints of depressed mood most of the day, diminished interest in everyday activities, poor appetite, fatigue, low energy, poor concentration, indecisiveness, insomnia and feelings of hopelessness and helplessness. He fulfilled DSM-IV criteria for major depressive episode (4).

Prior to admission the patient had received fluoxetine up to 20 mg./day for approximately two months, with no amelioration of the HPPD or the accompanying depressive features, but with side effects such as nausea, agitation, nervousness and insomnia.

On admission routine medical laboratory tests were performed. They were all in the normal range. Ophthalmological and neurological evaluations were also unremarkable.

He received paroxetine 20 mg./day, and complained of tiredness and dizziness, and more intense and more frequent episodes of HPPD, so that it was stopped.

Following two unsuccessful SSRI trials, reboxetine was prescribed. It was started at the low dose of 2 mg./day. The second week it was increased to 4 mg./day. The subject reported slight constipation and dry mouth. In the third week he reported less sadness and "feeling more energetic." He also noted that the point became less intrusive and that it appeared less frequently. The secondary

perceptual disturbances which usually followed the appearance of the point also seemed to appear less vividly and frequently. After one month of treatment, reboxetine was increased to 6 mg./day in the fifth week and then to 8 mg./day in the sixth. The 8 mg./day dose was accompanied by slight urinary retention and insomnia, which were dose related and resolved after return to the previous 6 mg./day dose. The subject continued to show a clinical improvement. The point did not disappear entirely, but lost its intrusive and bothersome character. It appeared solely for fractions of a second and only under stressful situations. The secondary perturbing visual disturbances which regularly followed the appearance of the point vanished entirely. The HPPD amelioration was followed by an improvement of the depressive features. During a six-month follow-up period on reboxetine 6 mg./day, no exacerbation of the visual disturbance or recurrence of the depressive features were reported.

Discussion

Different theories have been postulated to explain the return of perceptual disturbances (1, 3, 6). Accordingly, there are numerous pharmacological agents which have been reported as helpful in the treatment of the symptoms of HPPD (1, 3, 10, 11). The fact that distinctly different agents lead to some amelioration of HPPD may indicate the possible presence of HPPD subtypes which respond to these different compounds.

The identification of concurrent substance-related disorders is important for accurate psychiatric diagnosis and in the development of a treatment program (12). It is of clinical value to elucidate the sequence of symptom occurrence, as the establishment of primary and secondary disorders may frequently influence treatment.

The patient described had a history of cannabis, MDMA and LSD use. He pre-

sented LSD related visual disturbances triggered by cannabis use (9) that fulfilled criteria of HPPD (primary disorder). HPPD was consequently followed by depressive features (secondary disorder) (8).

The explanation for the observed improvement of both HPPD and the subsequent depressive disorder after reboxetine treatment remains unclear, some speculations may be made.

LSD-related HPPD could be associated with excessive sympathetic nervous activity that may be alleviated by clonidine (3). Reboxetine may have an α_2 adrenoreceptor modulating effect on both noradrenaline and serotonin release (13,14). Thus, reboxetine's α_2 adrenoreceptor modulating effect on noradrenaline release and sympathetic activity may be involved in the recovery process.

In addition, improvement of HPPD after administration of SSRIs has been reported and attributed to the down regulation of 5-HT₂ receptors, which supports the serotonergic mechanism of HPPD (6). Although reboxetine is a noradrenaline selective reuptake inhibitor, it may also affect the reuptake of serotonin resembling the effects of SSRIs. The final common pathway for all antidepressants appears to be mediated through the enhancement of 5-HT neurotransmission (15).

It should be emphasized that improvement of an underlying depression may have led to a subsequent improvement in the HPPD. Conclusions from this case report should be taken with appropriate caution.

References

1. Abraham HD, Aldridge AM, Gogia P. The psychopharmacology of hallucinogens. *Neuropsychopharmacology* 1996;14:285-298.
2. Hoffmann A. LSD: My problem child. New York: McGraw-Hill, 1980.

3. Lerner AG, Gelkopf M, Oyffe I, Finkel B, Katz S, Sigal M, Weizman A. LSD-induced hallucinogen persisting perception disorder (HPPD) treatment with clonidine: An open pilot study. *Int Clin Psychopharmacol* 2000; 18:35-37.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington DC: American Psychiatric Association, 1994.
5. Sander-Bush E, Burris KD, Knoth K. Lysergic acid diethylamide and 2,5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. *J Pharmacol Exp Ther* 1988;246:924-928.
6. Young CR. Sertraline treatment of hallucinogen persisting perception disorder. *J Clin Psychiatry* 1997; pp. 58:85.
7. Abraham HD, Fava M. Order of onset of substance abuse and depression in a sample of depressed outpatients. *Comprehensive Psychiatry* 1999;40:44-50.
8. Abraham HD. Substance-related disorders: Hallucinogen-related disorders. In: Kaplan HI, Sadock BJ, editors. *Comprehensive textbook of psychiatry*. 7th ed. Philadelphia: Lippincott Williams & Wilkins, 2000.
9. MacFadden W, Woody GE. Substance-related disorders: Cannabis-related disorders. In: Kaplan & Sadock's *Comprehensive Textbook of Psychiatry*. 7th ed. Philadelphia: Lippincott, Williams & Wilkins, 2000.
10. Lerner AG, Finkel B, Oyffe I, Merenzon I, Sigal M. Clonidine treatment of hallucinogen persisting perception disorder. *Am J Psychiatry* 1998;155:1460.
11. Lerner AG, Oyffe I, Isaacs G, Sigal M. Naltrexone treatment of hallucinogen persisting perception disorder. *Am J Psychiatry* 1997;154:437.
12. Miller NS. *The principles and practice of addictions in psychiatry*. Philadelphia: W.B. Saunders Company, 1997.
13. Mongeau R, Blier P, de Montigny C. The serotonergic and noradrenergic system of the hippocampus: their interactions and the effects of antidepressant treatments. *Brain Research Reviews* 1997;23:145-195.
14. Lucca A, Serreti A, Smeraldi E. Effects of reboxetine augmentation in SSRI resistant patients. *Hum Psychopharmacol Clin Exp* 2000;15:143-145.
15. Delgado PL, Moreno FA. Role of noradrenaline in depression. *J Clin Psychiatry* 2000;61: 5-12.