

LSD-Like Panic From Risperidone in Post-LSD Visual Disorder

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Risperidone, a novel antipsychotic agent, is an antagonist of postsynaptic serotonin-2 and dopamine D2 receptors. In certain individuals, the hallucinogenic drug lysergic acid diethylamide (LSD) is associated with apparently lifelong continuous visual disturbances, characterized in DSM-IV as hallucinogen-persisting perception disorder (HPPD). Because the hallucinogenic mechanism of LSD is known to act in part at postsynaptic serotonin-2 receptors, it is noteworthy that three HPPD patients treated with risperidone reported an exacerbation of LSD-like panic and visual symptoms. We conclude that HPPD may be a relative contraindication for the use of risperidone. (J Clin Psychopharmacol 1996;16:238-241)

RISPERIDONE IS A NOVEL antipsychotic agent with demonstrated safety and efficacy in the treatment of the hallucinations and delusions of schizophrenia.¹⁻⁴ It is a highly potent antagonist of both postsynaptic serotonin-2 (5-HT₂) and dopamine D2 receptors.⁵ In comparison to haloperidol, risperidone has been reported to have antidyskinetic effects and fewer extrapyramidal side effects,⁴ making it an important addition to the psychopharmacopeia. Commonly reported side effects include agitation, anxiety, insomnia, extrapyramidal symptoms, headache, and nausea.^{3,4,6}

Hallucinogen persisting perception disorder (HPPD) is a chronic, continuous, and possibly permanent disorder of the visual apparatus after the use of lysergic acid diethylamide (LSD). The empirical basis of this disorder is drawn from reports of persisting visual, somatic, and affective complaints after the use of hallucinogenic drugs.⁷⁻¹⁸ First described in 1954,⁷ early reports described patients with symptoms occurring weeks to months after use.^{8,9} Reports subsequently reported symptoms lasting from 1 to 5 years.^{10,11,17}

In 1969, Horowitz first introduced the term "flashback" into the literature. Since then, two controlled studies have described the demographics, associated drug abuse histories, symptom presentation, precipitants, comorbid disorders, and outcomes in 183 patients.^{17,19} HPPD is characterized by a variety of visual disturbances including afterimagery, flashes of light, geometric pseudohallucinations, and the persistent trailing of imagery after a stimulus leaves the visual field. For many patients, symptoms are present throughout the day or are instantly inducible. Associated features include an LSD-like dysphoria, panic attacks, and depressive disorder. HPPD is associated with abnormal tests of visual function, suggesting disinhibition in the processing of visual information.^{16,18} There is no known effective treatment, although benzodiazepines have been reported in a clinical survey to partially reduce symptoms when compared to neuroleptics. The disorder has recently been reviewed.²⁰

Because 5-HT₂ receptor antagonists are effective in treating the hallucinations of schizophrenia, their use in the treatment of HPPD is attractive, especially because the primary loci of action of LSD's hallucinatory effect in the nervous system are 5-HT₂ receptors as a partial agonist.²¹ Contrary to expectations, we found risperidone resulted in adverse reactions in HPPD patients. Accordingly, we now report the following three cases.

Case Reports

Case 1

A young woman first used LSD at age 14. Her father was alcoholic. Her total life dose was 35 trips, the last of which was at age 17. From the age of 18, she described occasional episodes in which she felt as if she were tripping, lasting under 1 minute. At 20, episodes of derealization appeared, and the perception of movement in the walls of rooms as if they were breathing. The next year she suffered the acute onset of an LSD-like euphoria and visual distortions, which then subsided but never thoroughly resolved. The daily distur-

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tions included trails of objects, particles in air, and round objects with her eyes closed. At 26, she was prescribed 2 mg of risperidone, which she increased to 3 mg the next day. On the 4th day, she described the acute onset of a wave of panic while watching TV. She felt an intense LSD-like euphoria. Her breathing became more intense. She feared she was "going crazy" and losing her hold on reality. The risperidone was discontinued after 7 days. The high level of LSD-euphoria and panic lasted 3 weeks.

Case 2

A 22-year-old college student used LSD twice between the ages of 15 and 18. His family history was positive for LSD flashbacks in a brother. The patient himself developed the continuous visual symptoms of afterimages, trailing of stimuli, and orange and blue haloes around objects at the age of 20. On giving informed consent, he was started on an open-label trial of risperidone at 1 mg at bedtime, which was increased over a 7-week period to 6 mg at bedtime. All HPPD symptoms were scored on a 0 to 7 (none to worst ever) Likert scale and summed at each dosage change (Fig. 1, bottom). In the 8th week,

the patient developed an acute anxiety attack with agitation, chest pain, shortness of breath, and fear of a heart attack. The attack lasted 6 hours. The next 2 days were associated with an intensification of visual afterimagery and haloes around objects, which returned to baseline 10 days after discontinuing the medication.

Case 3

A 40-year-old married builder had used LSD six to eight times at the age of 18. His last use of the drug left him with a "disintegrating" feeling in which his "body felt alien to his mind." This sense of depersonalization has persisted to the present. A week after his last trip, he spontaneously began to reexperience thoughts and imagery of his LSD use, including dots on a blank wall, intensification of lights, and trails of his hand when he moved one across his visual field. For 2 years, he withdrew in a state of anxiety and depression. Low-dose chlorpromazine was beneficial. At 40, he gave informed consent and was treated with risperidone in an open trial for continuing visual disturbances. HPPD was scored as in case 2 (Fig. 1, top). At a dosage of 1 mg/day for 1 month, he reported mild improvement in dereal-

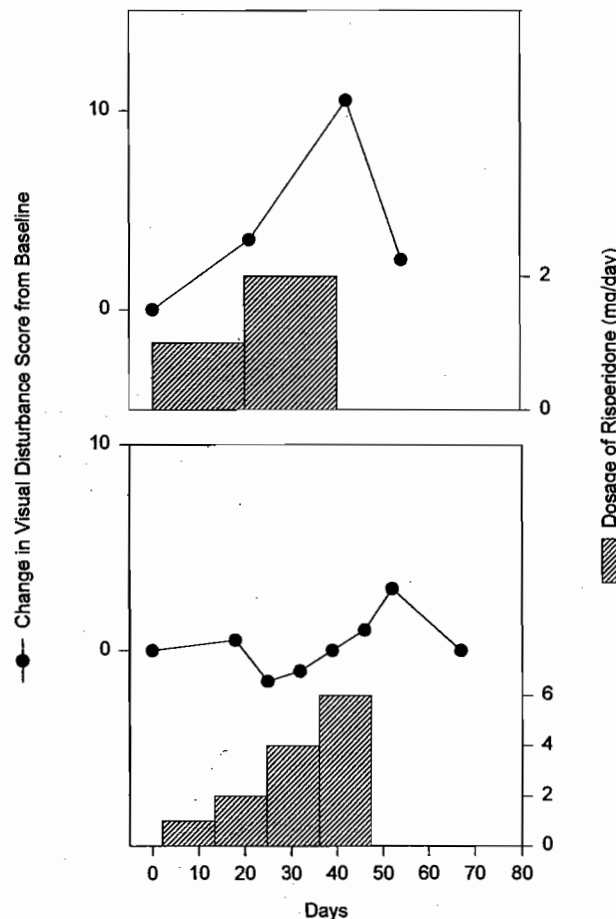


FIG. 1. LSD-like visual disorder as a function of risperidone. Case 2, bottom; case 3, top.

ization. The day the dosage was increased to 1 mg twice a day, he suffered the abrupt onset of daily panic attacks and an intense emotional level of excitement similar to his LSD use. Objects appeared alien to him. "A tree did not look like a tree." Three days later the symptoms began to subside. One month later he reported increased panic attacks and a depressed mood linked to enhanced patterns he continued to see in wood.

Discussion

Common to each of these cases were the prior use of LSD, the development of HPPD, the attempt to treat HPPD with risperidone, the abrupt onset of panic attacks, and an intensification of the HPPD visual symptoms. Symptoms tended to return to their baseline levels when the medicine was discontinued. Although these case reports suggest a causal relationship between the serotonin antagonist and the onset of panic and intensified HPPD, they do not represent double-blind placebo-controlled assessment of the effects of risperidone on HPPD. On the other hand, attention is drawn to the possibility that risperidone in HPPD may induce panic and an LSD-like mood and intensify the visual symptoms of HPPD.

Other explanations are possible. In controlled clinical trials, risperidone has been found to be associated with anxiety, panic, agitation, and akathisia as side effects. It is not likely these patients were exhibiting uncomplicated akathisia. Owens⁶ reviewed extrapyramidal side effects associated with risperidone in three large international drug trials^{3,4} and reported the incidence of akathisia to be equal to that seen in placebo-treated subjects and less than that seen in haloperidol subjects. On the other hand, we have seen a fourth HPPD patient given risperidone for hallucinations who developed brief panicky feelings with only a mild worsening of visual pseudohallucinations and transient akathisia at 6 mg/day.

Family histories were negative for psychiatric illness other than alcoholism. Although LSD may be associated with prolonged psychoses, this was not so regarding our patients. At the time of their clinical presentation, no patient was delusional. Each patient knew the visual disturbances were "not real." No patient ever required a psychiatric hospitalization. Three of the four cases, at the time this article was first submitted, had undergone Structural Clinical Interviews for DSM-III-R with Psychotic Screens (SCID-P) before treatment with risperidone. All SCID-P data were negative for symptoms of psychosis save for the presence of the post-LSD visual disturbances. It should also be noted that the presence of persistent visual disturbances after LSD use are more precisely characterized as pseudohallucinations rather than true hallucinations.²⁰

Our three cases did not present with classical anxiety. Although Chouinard and associates⁴ reported data showing anxiety and agitation were commonly reported to be associated with risperidone, anxiety in the risperidone group did not appear to follow a monotonic dose-response curve to risperidone nor did the percentages reach statistical significance in any dosage cell compared to the base rate of anxiety (40.9%) in the placebo-treated group. We performed a meta-analysis comparing all risperidone-treated subjects ($N = 92$) with the placebo-treated controls ($N = 22$) on the variable of anxiety during treatment. Using a 2×2 contingency table, anxiety again did not exceed what would be expected randomly ($\chi^2 = 0.16, p > 0.2$).

What sets the above three cases apart from akathisia, agitation, or anxiety is the progressive exacerbation of their post-LSD hallucinations with increasing doses of risperidone, as well as the spontaneous reports from these patients of the return of an LSD-like mood state. Visual disturbances are not commonly considered diagnostic features of akathisia, generalized anxiety, or panic disorder. By comparison, each patient specifically related his or her visual disturbances to LSD-like dysphoria, commenting spontaneously they felt the experience was "like an intense acid high," "on LSD again," and marked by "an intensification of visual reflections and haloes around objects." The pseudohallucinations were stereotypical for diagnostic criteria described in the literature for HPPD,¹⁷ including DSM-IV. The time elapsed from the last LSD use and the development of symptoms of HPPD would suggest that the association between LSD and chronic visual disturbances is tenuous, save for the fact that a comparison of 60 substance abusers with HPPD and 60 substance abusers without HPPD found that LSD use was the only drug overrepresented in the HPPD group.¹⁹

The mechanism for such a response to 5-HT₂ antagonism is not known. Such visual disturbances in association with increasing doses of risperidone have not been described to date in the multicenter risperidone trials. Interestingly, a controlled study of nefazodone, another 5-HT₂ receptor antagonist, also reported that the side effect of visual trailing, a common post-LSD symptom, was overrepresented more than threefold compared to the placebo group²² (personal communication, D. Roberts, 1995). The 5-HT₂ receptor is widely distributed in the cerebral cortex.^{2,23,24} Agents operating at the 5HT₂ receptor as agonists have been shown to have hallucinogenic properties. Hallucinogenic drugs have been shown to be associated with prolonged psychoses, though not in all patients.²⁰ This raises the possibility that certain individuals are particularly vulnerable to hallucinatory and panic-inducing effects of 5-HT₂-mediated drugs. Possible sources of vulnerabil-

ity include recent covert caffeinism; cocaine, amphetamine, cannabis, or hallucinogen use; alcohol or sedative withdrawal; HIV infection of the CNS; complex partial seizures; and head trauma. Drug abuse was reduced as a likelihood by negative urine enzyme-multiplied immunoassay test drug screens on three of the four subjects. The rapid reversibility of symptoms on discontinuation of risperidone argues against any condition such as seizure disorder, CNS tumor, or stroke. The relatively young ages of these patients and the absence of hypertension argue against transient ischemic attacks. The occurrence of flashbacks in a sibling in case 2 suggests a familial, and possibly genetic, basis to the disorder.

Sheldon and Aghajanian²⁵ have recently reported that 5-HT₂ receptors are located on inhibitory interneurons in the rat pyriform cortex. In studies of LSD on 5-HT₂ nerve cell receptors, Garratt²⁶ found that in the rat facial motor nucleus, a region rich in 5-HT₂ cells, LSD resulted in generating a current greater than that by 5-HT, and with a prolonged duration. Although LSD has not been shown to act as an excitotoxin at 5-HT₂ receptors, such a mechanism in vulnerable individuals could result in the dysfunction or destruction of inhibitory interneurons, resulting in chronic disinhibition of visual processors.²⁰ The use of a drug suppressing 5-HT₂ function could then result in an intensification of visual symptoms.

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References

1. Leysen JE, Janssen PM, Megens AA, Schotte A. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. *J Clin Psychiatry* 1994;55:5-12.
2. Mesotten F, Suy E, Pietquin M, Burton P, Heylen S, Gelders Y. Therapeutic effect and safety of increasing doses of risperidone (R 64766) in psychotic patients. *Psychopharmacology* 1989;99:445-9.
3. Borison RL, Pathiraja AP, Diamond BI, Meibach RC. Risperidone: clinical safety and efficacy in schizophrenia. *Psychopharmacol Bull* 1992;28:213-8.
4. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, Labelle A, Beauclair L, Arnott W. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993;13:25-40.
5. Leysen JE, Janssen PM, Gommeren W, Wynants J, Pauwels PJ, Janssen PA. In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotics risperidone and ocapiperidone. *Mol Pharmacol* 1992;41:494-508.
6. Owens DG. Extrapyramidal side effects and tolerability of risperidone: a review. *J Clin Psychiatry* 1994;55:29-35.
7. Sandison RA, Spencer AM, Whitelaw JD. The therapeutic value of lysergic acid diethylamide in mental illness. *J Ment Sci* 1954;100:491-502.
8. Eisner BG, Cohen S. Psychotherapy with lysergic acid diethylamide. *J Nerv Ment Dis* 1958;127:528-39.
9. Rosenthal SH. Persistent hallucinosis following repeated administration of hallucinogenic drugs. *Am J Psychiatry* 1964;121:238-44.
10. Robbins E, Frosch WA, Stern M. Further observations on untoward reactions to LSD. *Am J Psychiatry* 1967;124:393-5.
11. Holsten F. Flashbacks: a personal follow-up. *Arch Psychiatr Nervenkr* 1976;222:293-304.
12. Horowitz MJ. Flashbacks: recurrent intrusive images after the use of LSD. *Am J Psychiatry* 1969;126:565-9.
13. Shick JFE, Smith D. Analysis of the LSD flashback. *J Psychedel Drugs* 1970;3:13-9.
14. Anderson W, O'Malley J. Trifluoperazine for the trailing phenomenon. *JAMA* 1972;220:1244-5.
15. Abraham HD. Visual disturbances in a population of LSD users. 143th Annual Meeting of the American Psychiatric Association. New Orleans, 1981.
16. Abraham HD. A chronic impairment of color vision in users of LSD. *Br J Psychiatry* 1982;140:518-20.
17. Abraham HD. Visual phenomenology of the LSD flashback. *Arch Gen Psychiatry* 1983;40:884-9.
18. Abraham HD, Wolf E. Visual function in past users of LSD: psychophysical findings. *J Abnorm Psychol* 1988;97:443-7.
19. Abraham HD, Duffy FH, Crayton J, Yeoh H. The diagnosis and treatment of chronic visual disturbances following LSD. 148th Annual Meeting of the American Psychiatric Association. Miami, 1995.
20. Abraham HD, Aldridge AM. Adverse consequences of lysergic acid diethylamide. *Addiction* 1993;88:1327-34.
21. Glennon RA, Titeler M, McKenney JD. Evidence for 5-HT₂ involvement in the mechanism of action of hallucinogenic agents. *Life Sci* 1984;35:2505-11.
22. Fontaine R, Ontiveros A, Elie R, Kensler TT, Roberts DL, Kaplita S, Ecker JA, Faludi G. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. *J Clin Psychiatry* 1994;55:234-41.
23. Pazos A, Cortés R, Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors. *Brain Res* 1985;346:231-49.
24. Morilak DA, Garlow SJ, Ciaranello RD. Immunocytochemical localization and description of neurons expressing serotonin₂ receptors in the rat brain. *Neuroscience* 1993;54:701-17.
25. Sheldon PW, Aghajanian GK. Serotonin (5-HT) induces IPSPs in pyramidal layer cells of rat pyriform cortex: evidence for the involvement of a 5-HT₂-activated interneuron. *Brain Res* 1990;506:62-9.
26. Garratt JC, Alreja M, Aghajanian GK. LSD has high efficacy relative to serotonin in enhancing the cationic current I_h: intracellular studies in rat facial motoneurons. *Synapse* 1993;13:123-34.