Persistent Palinopsia Following Ingestion of Lysergic Acid Diethylamide (LSD)

Aki Kawasaki, MD, Valerie Purvin, MD

Objective: To identify a distinctive chronic visual complication of lysergic acid diethylamide (LSD) use.

Design: Description of the clinical findings in three patients with this disorder.

Setting: A neuro-ophthalmology referral center.

Results: All three patients experienced prolonged afterimages (palinopsia) during LSD intoxication and have continued to be symptomatic up to 3 years after they ceased to ingest the drug. Results of neuro-ophthalmologic and neurologic examinations and neuroimaging and electrophysiologic studies were normal.

Conclusions: We have described three patients in whom persistent palinopsia developed following ingestion of LSD. Clinicians should inquire about past LSD use in all patients who initially have seemingly spontaneous, isolated palinopsia. Recognition of this distinctive clinical syndrome associated with LSD use might avoid unnecessary anxiety and excessive diagnostic tests for patients with this disorder.

(Arch Ophthalmol. 1996;114:47-50)

LYSERGIC ACID diethylamide (LSD) is an illicit substance that induces an altered state of perception, mood, and thought without clouding of consciousness. Hallucinations and illusions that are produced by acute LSD intoxication are predominantly visual and include image distortion, color intensification, geometric hallucinations, and a false perception of movement.[1,2] The spontaneous recurrence of the LSD-induced experience following discontinuation of drug use is known as hallucinogen persisting perception disorder (HPPD).[3] The well-known "flashback" represents a spontaneous and transitory HPPD experience, but HPPD can also manifest as a long-term, constant alteration of perception.

Palinopsia is the visual perseveration of a recently seen object and can occur with acute ingestion of LSD. We describe three young patients who experienced palinopsia during acute LSD intoxication; later, they described a recurrence and persistence of palinopsia despite drug abstinence. Recognition of this distinctive clinical syndrome associated with LSD use might avoid unnecessary anxiety and excessive diagnostic tests for patients with this disorder.

From the Midwest Eye Institute, Methodist Hospital of Indiana and the Departments of Ophthalmology and Neurology, Indiana University Medical Center, Indianapolis.
The authors have no proprietary interests in any of the products named in the manuscript.

REPORT OF CASES

CASE 1

A 21-year-old woman, who was a college student, had a history of occasional LSD intake that resulted in "mild trips" of a dreamlike state, visual hallucinations, and palinopsia. She denied any prior flashbacks or prolonged visual disturbances. Four months after her last ingestion of LSD, she underwent a routine extraction of impacted wisdom teeth. The following anesthetic agents were used to perform this extraction: fentanyl citrate, methohexital (Brevital) sodium, midazolam hydrochloride (Versed) and local lidocaine hydrochloride, bupivacaine hydrochloride (Marcaine), and dexamethasone sodium phosphate (Decadron). As her drowsiness cleared, she noted visual perseveration of recently viewed objects that had similarly occurred with her previous LSD-induced experience.

The palinopic images appeared in the complementary color, were more vivid in bright illumination, and lasted up to 20 seconds. Despite no further LSD abuse in the next 3 years, her palinopsia has been continuously present since then. Findings from her neuro-ophthalmologic and

neurologic examinations were normal. Cranial magnetic resonance imaging scans, a visual evoked response, an electroencephalogram, and an electroretinogram were normal.

CASE 2

A 17-year-old boy began to experience abnormal persistence of images 2 months after an LSD trip. This seemed to have been precipitated by a prolonged hot bath and was continuous thereafter. Images persisted up to 1 minute, were more prominent with high-contrast images, and were typically of a complementary color to the original. Sometimes, he saw colors that were not there; at other times, he saw "flickering lights" or geometric shapes. There was no alteration of consciousness at these times.

Medical and ocular histories were noncontributory. Results of a complete neuro-ophthalmologic and neurologic examination were normal, as were an electroretinogram and magnetic resonance imaging scan.

CASE 3

A healthy 15-year-old boy had once used cocaine and opiate several years ago, but he first tried LSD in 1992.

During the next year, he abused LSD exclusively and frequently. In 1993, he noted palinopsia that was precipitated by moving objects. The palinopic image appeared as a series of ghost images that trailed behind the original moving object for a few seconds. This occurred with any object that was viewed in motion. The persistency of palinopsia during his LSD-free intervals prompted discontinuance of LSD; yet, the palinopsia remained constant and unchanged at 6-month follow-up. Results of his neuro-ophthalmologic and neurologic examinations were normal.

COMMENT

Palinopsia has traditionally been associated with large destructive lesions (eg, infarction, tumor, trauma, and arteriovenous malformation) of the nondominant parietooccipital cortex.[4-6] In such cases, the patients have manifested other signs of cortical dysfunction (eg, homonymous hemianopia, hemiparesis, hemisensory deficit, or mental status change), and cranial neuroimaging has usually revealed the responsible structural lesion. Less commonly, results of radiologic studies have been normal, and the cause of palinopsia was attributed to seizure discharge, migraine, anoxia, or toxic-metabolic encephalopathy.[5,7-10]

Palinopsia also has been previously reported as a side effect of medication. Hughes and Lessell[11] described three patients who experienced palinopsia while they were taking trazodone hydrochloride (Desyrel). Findings from neurologic examinations, visual fields, and radiologic studies were normal, and the symptom resolved when the medication was discontinued. In contrast, Purvin[12] described three patients whose palinopsia was induced by clomiphene citrate (Clomid), and was persistent even after discontinuation of the medication. To our knowledge, clomiphene citrate is the only prescription drug that has been associated with the irreversible toxic side effect of palinopsia.

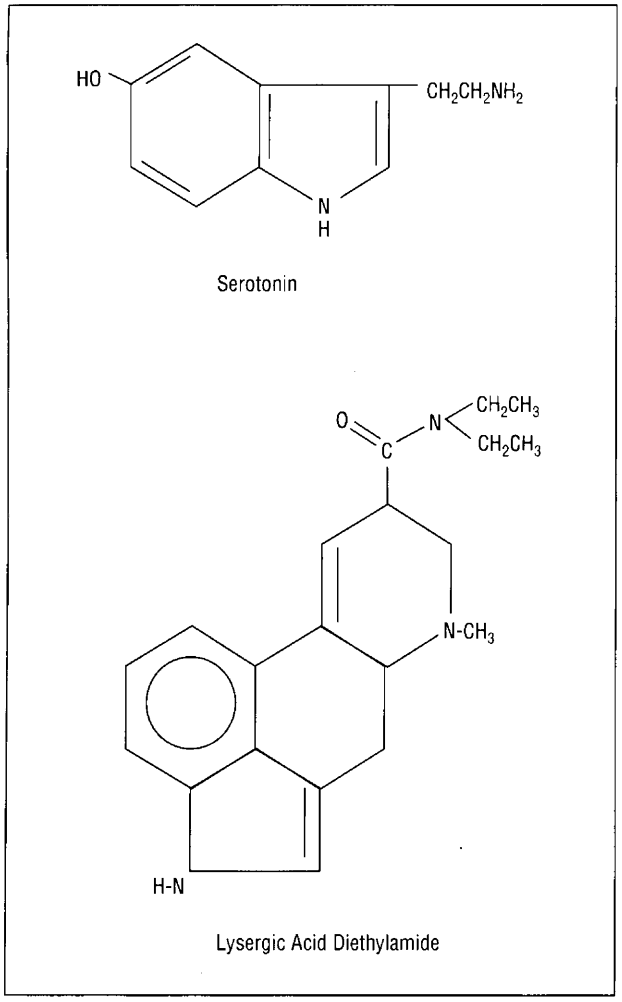
Diagnostic Criteria for 292.89 HPPD (Flashbacks)*

Criterion	Description
A	The reexperiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (eg, geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia)
B	The symptoms in criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C	The symptoms are not due to a general medical condition (eg, anatomic lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder (eg, delirium, dementia, schizophrenia) or hypnopompic hallucinations

**Data from the American Psychiatric Association, Washington, DC.[3] HPPD indicates hallucinogen persisting perception disorder.*

Illicit hallucinogenic drugs, also called psychedelic and psychotomimetic agents, appear in both natural and synthetic forms. The best known of the natural hallucinogens are psilocybin (mushrooms) and mescaline (peyote cactus), and the most widely abused synthetic hallucinogen is LSD. Mescaline and LSD have been reported to cause palinopsia routinely during the intoxicated state. Among practiced LSD users, the particular type of palinopsia that occurs only for moving objects has been simply dubbed the "trailing" phenomenon.[13,14] This visual perseveration is characterized by a series of discrete, discontinuous stationary images that trail behind the actual moving stimulus object, and it is often likened to a stroboscopic photograph with multiple exposures.

Palinopsia (and the trailing variant) as a long-standing and potentially irreversible toxic consequence of LSD use is hardly mentioned in the neurologic or ophthalmologic literature. Levi and Miller[15] described six patients with a variety of visual illusions that were associated with previous use of various illicit drugs. One of three patients who had previously used LSD (in addition to other drugs) had chronic palinopsia.[15] However, palinopsia, as well as other chronic visual disturbances from LSD, has been well detailed in the psychiatric literature.[1-3,13,14,16-23] One possible reason for this discrepancy may be differences in descriptive terminology. Psychiatrists do not use the term *palinopsia*; instead, they refer to this symptom as "afterimagery" or "visual flashbacks." Another factor may be the relative lack of exposure among general neurologists and ophthalmologists to the long-term care of substance abusers. Finally, these patients may be reluctant to seek out non–mental health professionals with regard to symptoms that are related to illegal drugs.



The molecular structures of serotonin (top) and lysergic acid diethylamide (bottom).

According to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[3] palinopsia following hallucinogen use is one symptom of a broader category called HPPD. The specific criteria for this disorder are listed in the **Table**.

Abraham[2] reviewed this phenomenon in 123 LSD users; he characterized and ranked the 16 most commonly reported visual symptoms of HPPD that were, in order, geometric pseudohallucinations, perceptions in the peripheral field, flashes of color, intensified colors, trailing phenomenon, imagistic pseudohallucinations, positive afterimages, halos around objects, macropsia, micropsia, geometric phosphenes, imagistic phosphenes, pareidolia (image within image), color confusions, negative afterimages, and difficulty with reading. The users of LSD often had more than one visual symptom. The mean (±SD) number of the type of visual flashback (HPPD) was 4.8±3.0 per subject. Although HPPD can follow a single LSD exposure, the data of Abraham[2] suggested a peak incidence that occurred at 15 LSD exposures with a second smaller peak at 40 to 50 LSD exposures. No linear dose-response relationship was noted. The visual perceptual disorder persisted in half of the sample during 5 years.

Common precipitating factors of HPPD are emergence into a dark environment (16%), intentional induction (14%), and marijuana use (14%). Medications that may precipitate or exacerbate post-LSD visual symptoms include phenothiazines, amphetamines, antiparkinsonian drugs, cold remedies, and serotonin reuptake inhibitor antidepressants.[1,2,24] Medications that are believed to alleviate symptoms are benzodiazepines (in eight [89%] of nine cases), and there has been a single case report of barbiturate and alcohol as well.

In addition to the subjective accounts of affected individuals, findings from electrophysiologic studies support the notion that LSD may cause permanent alterations of the visual pathways. Abraham and Wolf[25] found decreased dark adaptation and depressed critical flicker fusion in subjects with a history of LSD use in comparison with that in a matched control group. A specific form of impaired color discrimination also has been described in LSD users.[26] Individuals who were previously exposed to LSD had difficulty in identifying the color of a circular target that was surrounded by a circle of a different color when compared with the ability of control subjects to perform this task. Abraham[26] hypothesized a defective inhibition of visual information that caused increased "visual noise" in these individuals such that the persistent signal from the background interfered with recognition of the target. In addition, sensory evoked potentials were found to be abnormal in 76.5% of a group of subjects with persistent post-LSD hallucinosis vs only 7.1% of 14 control subjects who were also drug abusers but did not experience hallucinations.[27]

The pathophysiologic mechanism of HPPD is not fully understood. Lysergic acid diethylamide most closely resembles serotonin (5-hydroxytryptamine or 5-HT) in molecular configuration (**Figure**). There are multiple classes of 5-HT receptors that are widely distributed in peripheral tissues and in the central nervous system. In general, serotoninergic action in the central nervous system is inhibitory and serves to modulate rather than mediate specific functions. The affinity of LSD at postsynaptic $5\text{-}HT_2$ receptors in cell populations that have been found in the locus caeruleus and cerebral cortex has been implicated in the pathogenesis of perceptual alterations.[28] One recent theory proposes that LSD binds and destroys small serotonin-responsive cortical interneurons that have an inhibitory output, usually γ-aminobutyric acid–mediated. The visual predominance of LSD-related hallucinations may stem from the high density of serotonin receptors in the primary somatosensory cortex, and the HPPD phenomenon may be related to a failure of the normal inhibitory messages on an activated visual circuit.[27,29]

Approximately one fourth to one third of LSD users will experience some form of HPPD.[17,23,30] Approximately 5% of high school seniors have tried LSD at least once, and the popularity of this hallucinogen continues to rise.[31] We have described three patients in whom persistent palinopsia developed following ingestion of LSD. Clinicians should inquire about past LSD use in all patients who have seemingly spontaneous, isolated palinopsia. If prior LSD use is acknowledged, and similar

palinopsia has been noted while the person is under active LSD influence, a diagnosis of HPPD is confirmed, and no further investigations are warranted.

Accepted for publication June 26, 1995.

Reprint requests to Midwest Eye Institute, 201 Pennsylvania Pkwy, Indianapolis, IN 46280-1381 (Dr Kawasaki).

REFERENCES

1. Abraham HD, Aldridge AM. Adverse consequences of lysergic acid diethylamide. *Addiction.* 1993;88:1327-1334.
2. Abraham HD. Visual phenomenology of the LSD flashback. *Arch Gen Psychiatry.* 1983;40:884-889.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association; 1994.
4. Michel EM, Troost BT. Palinopsia: cerebral localization with computed tomography. *Neurology.* 1980;30:887-889.
5. Bender MB, Feldman M, Sobin AJ. Palinopsia. *Brain.* 1968;91:321-328.
6. Kinsbourne M, Warrington E. A study of visual perseveration. *J Neurol Neurosurg Psychiatry.* 1963;26:468-475.
7. Swash M. Visual perseveration in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry.* 1979;42:569-571.
8. Klee A, Willanger R. Disturbances of visual perception in migraine. *Acta Neurol Scand.* 1966;42:400-414.
9. Adler A. Disintegration and restoration of optic recognition in visual agnosia. *Arch Neurol Psychiatry.* 1944;51:243-259.
10. Johnson SF, Loge RV. Palinopsia due to nonketotic hyperglycemia. *West J Med.* 1988;148:331-332.
11. Hughes MS, Lessell S. Trazodone-induced palinopsia. *Arch Ophthalmol.* 1990; 108:399-400.
12. Purvin VA. Visual disturbance secondary to clomiphene citrate. *Arch Ophthalmol.* 1995;113:482-484.
13. Anderson WH, O'Malley JE. Trifluoperazine for the 'trailing' phenomenon. *JAMA.* 1972;220:1244-1245.
14. Asher H. 'Trailing' phenomenon—a long-lasting LSD side effect. *Am J Psychiatry.* 1971;127:1233-1234.
15. Levi L, Miller NR. Visual illusions associated with drug abuse. *J Clin Neuro Ophthalmol.* 1990;10:103-110.
16. Rosenthal SH. Persistent hallucinosis following repeated administration of hallucinogenic drugs. *Am J Psychiatry.* 1964;121:238-244.
17. Horowitz MJ. Flashbacks: recurrent intrusive images after the use of LSD. *Am J Psychiatry.* 1969;565-569.
18. Sandison RA, Spencer AM, Whitelaw JD. The therapeutic value of lysergic and diethylamide in mental illness. *J Ment Sci.* 1954;100:491-502.
19. Eisner BG, Cohen S. Psychotherapy with lysergic acid diethylamide. *J Nerv Ment Dis.* 1958;127:528-539.
20. Cooper HA. Hallucinogenic drugs. *Lancet.* 1955;268:1078-1079.
21. Elkes C, Elkes J, Mayer-Gross W. Hallucinogenic drugs. *Lancet.* 1955;267: 719.
22. Kaminer Y, Hrecznyj B. Lysergic acid diethylamide–induced chronic visual disturbances in an adolescent. *J Nerv Ment Dis.* 1991;179:173-174.
23. Robbins E, Frosch WA, Stern M. Further observations on untoward reactions to LSD. *Am J Psychiatry.* 1967;124:393-395.
24. Markel H, Lee A, Holmes RD, Domino EF. LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *J Pediatr.* 1994;125:817-819.
25. Abraham HD, Wolf E. Visual function in past users of LSD: psychophysical findings. *J Abnorm Psychol.* 1988;97:443-447.
26. Abraham HD. A chronic impairment of colour vision in users of LSD. *Br J Psychiatry.* 1982;140:518-520.
27. Abraham HD. Visual hallucinations in macular degeneration. *Am J Psychiatry.* 1993;150:1758.
28. Aghajanian GK. Serotonin and the action of LSD in the brain. *Psychiatr Ann.* 1994;24:137-141.
29. Wilson MA, Molliver ME. Serotonin innervation patterns in primate cerebral cortex: specific local ablations. *Soc Neurosci Abstr. 1986;12:427.*
30. Hollister L. Drug-induced psychoses and schizophrenic reactions: a critical comparison. *Ann N Y Acad Sci.* 1962;96:80-92.
31. Gold MS, Schuchard K, Gleaton T. LSD use among US high school students. *JAMA.* 1994;271:426-427.