# Clinical and laboratory observations

## LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents

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**Two adolescents with a long history of abuse of lysergic acid diethylamide (LSD) and symptoms consistent with major depressive disorder, on initiation of antidepressant therapy with selective serotonin reuptake inhibitor agents, had the new onset or worsening of LSD flashback syndrome. The similarity in neuroreceptor physiology for both LSD and serotonin suggests that the LSD flashback syndrome may be induced by these drugs in patients with a history of LSD abuse. (J PEDIATR 1994;125:817-9)**

The resurgence of abuse of psychedelic drugs such as lysergic acid diethylamide has been reported among adolescents and college students in the United States.[1] Predictors of drug abuse trends suggest that the abuse of these substances among teenagers will increase.[2] One of the major untoward effects that results from the chronic use of these drugs, particularly LSD, are "flashback" or recurrent hallucinatory episodes that are not due to the presence of the drug in the brain and may occur months to years after cessation of use.[3-5] Concurrently the recognition of major depressive disorders among adolescents, particularly those with a history of illicit substance or alcohol abuse, has increased.[6, 7] Consequently, it seems highly likely that physicians who routinely treat adolescents will come in contact with teenagers who have a major depressive disorder and a history of chronic or occasional LSD use.

Supported in part by a National Research Service Award (Dr. Markel), National Institutes of Health, National Center for Human Genome Research (grant No. 5 F32 HG00037-02).

Submitted for publication Oct. 19, 1994; accepted June 7, 1994.

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We report two such teenagers who had either worsening or a new onset of an LSD flashback syndrome on initiation of antidepressant therapy with selective serotonin reuptake inhibitor agents (sertraline hydrochloride [Zoloft] and paroxetine hydrochloride [Paxil].

### CASE REPORTS

**Patient 1.** An 18-year-old female adolescent was seen at the University of Michigan Adolescent Clinic with a complaint of feeling sad and anxious. She reported worsening symptoms of insomnia, lack of interest in usually enjoyable activities, decreased appetite, decreased libido, and daily crying spells during the preceding month. She also complained of "panic attacks," including episodes of hyperventilation, palpitations, sweating, and feelings of fear. When asked what she most frightened her, she replied, "Having another LSD flashback." Further inquiry revealed that the patient

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| LSD | Lysergic acid diethylamide |
| SSRI | Selective serotonin reuptake inhibitor |
| 5-HT | 5-Hydroxytryptamine |

had a long history of illicit drug and alcohol abuse, including smoking one half to one pack of cigarettes per day, smoking 8 gm of marijuana per week for the past 6 years, and a 4-year history of weekly LSD "trips" with her boyfriend.

The patient's last use of LSD was 10 months before her first clinic visit. She had used LSD synthesized in "home laboratories." The first of four LSD flashbacks occurred after the use of LSD was stopped. She also reported having abstained from cigarettes and

marijuana during the preceding 9 months because they seemed to cause symptoms of increased heart and respiratory rates and feelings of paranoia, which made her "panic attacks" even more severe. The flashbacks lasted about 1 to 2 hours and were described as being extremely unpleasant. The patient felt as if she were suddenly in a "cartoon." Colors were described as vivid and "unreal," and people who were present during these episodes were transformed into "monsters."

The medical history was noncontributory in regard to any other major medical, psychiatric, or surgical problem. The patient's family history included drug and alcohol abuse by both parents and her older brother. Her mother had been treated for depression with tricyclic antidepressants. Added stressors included a recent move to a new town, a disruptive family situation in which the patient had no family member on whom she could rely, and school failure. Finally, a close friend, with whom she had used LSD, became "strung out on LSD" and had been admitted to a psychiatric hospital for treatment of acute schizophrenia. The patient's major concern was the development of an irretractable flashback syndrome and hospitalization like her friend. Her physical examination findings were normal.

In light of the depressive symptoms and those of either a panic disorder or, possibly, an organic, marijuana-induced anxiety disorder, sertraline, 50 mg daily, was prescribed and the patient was instructed to abstain completely from illicit drugs, alcohol, and tobacco. Two days later, however, she returned to the clinic in an agitated state, complaining of the "worst flashback of my life," which lasted more than 15 hours. Because of her refusal to take another dose of sertraline, her antidepressant was changed to a similar but structurally different selective serotonin reuptake inhibitor, paroxetine hydrochloride. Two days later she reported a similar flashback experience that began approximately 1 hour after taking the antidepressant and lasted a full day. The SSRIs were discontinued and the flashbacks ceased. A trial of psychotherapy for the patient's depression was initiated. She has not complained of flashback episodes since discontinuing the SSRI agents for the past 6 months, she continues to abstain from illicit drugs, and her depression appears to have resolved.

**Patient 2.** A 17-year-old male adolescent had a 7-year history of polydrug abuse, including daily to weekly LSD use, daily consumption of marijuana, and occasional use of ethyl alcohol; his drug of choice was LSD. Subsequent to being arrested for purveying illegal substances, detention in a home for juvenile delinquents, and mandatory daily participation in Narcotics Anonymous, he had successfully abstained from all drugs of abuse for the previous 11 months. His medical history was noncontributory, but a psychiatric history revealed that shortly after his arrest he had a major depressive disorder and was given paroxetine, 20 mg/day, with excellent results. The social history included a disruptive family situation, truancy from school, and trouble with the police. There was a strong family history of drug and alcohol abuse. His mother was a recovering alcoholic and his father a chronic abuser of marijuana, LSD, and alcohol. His father had been treated with SSRI agents (both fluoxetine and paroxetine) for depression and reported new onset of a flashback syndrome.

Physical examination findings were noncontributory. The patient, on further questioning about his medication, described daily flashback episodes 2 weeks after beginning paroxetine. He described the episodes as "almost nonstop" and consisting primarily of visual disturbances of color and texture, particularly when he focused on a moving object. He denied flashbacks that were disturbing or frightening. He also denied having had such episodes before beginning antidepressant therapy. When asked why he had not mentioned these episodes before our examination, he replied that (1) no one had asked, (2) they were not unduly distressful, and (3) he had enjoyed the "free trip", or flashback experience.

## DISCUSSION

The potential association of LSD flashback syndrome and the initiation of treatment for depression with SSRI agents has both clinical and pharmacologic significance. As with other neurotransmitters, serotonin (5-hydroxytryptamine) evokes cellular responses by acting on discrete receptors.[8] At least six types of 5-HT receptors have been characterized (5-$HT_1$, 5-$HT_2$, and 5-$HT_3$ with further subdivision of the 5-$HT_1$ receptor into three types, 5-$HT_{1A}$, 5-$HT_{1B}$, and 5-$HT_{1C}$).[9] It has been proposed that depression is the result of a functional deficit in central nervous system serotonin levels, but the exact mechanism remains unclear.[10]

Lysergic acid diethylamide has been recognized as an agent that increases serotonin levels in the brain.[11, 12] Recent radioreceptor binding assay studies have shown that LSD has specific binding affinities for the 5-$HT_1$ and 5-$HT_2$ receptors in rat and mouse brain.[13] Further, pharmacologic studies of the effects of serotonin and LSD in rodents have shown that LSD mimics 5-HT in producing inhibition at both presynaptic and postsynaptic sites. For example, LSD strongly inhibits serotonergic neuron firing by binding to presynaptic autoreceptors on the soma or dendrites. This finding, called the "presynaptic hypothesis," explains LSD-induced hallucinations as a disinhibition of forebrain neurons receiving serotonergic input.[14]

Other investigations of the mechanism action of LSD, however, indicate a different, postsynaptic agonistic effect on 5-$HT_2$ receptors. Thus another possible mechanism that might explain the relationship of LSD abuse, treatment with SSRI agents, and the exacerbation of the flashback syndrome would be increased stimulation of 5-$HT_1$ and 5-$HT_2$ receptor sites, resulting from the blockade of serotonin reuptake and an increased concentration of serotonin in the central nervous system, yielding LSD-like flashbacks.[15]

Various other factors have been associated with the appearance of LSD flashbacks, including the concurrent use of marijuana,[16] psychosocial stress, decreased sensory input, emergence into a dark environment, fatigue, fever, and extreme relaxation.[3] The abuse of other hallucinogens might also be a trigger for the "flashback" phenomenon. Both of our patients reported a long history of marijuana abuse but denied its use during the previous 9 months. Patient 1 was experiencing stress.

Great care is mandatory in eliciting a complete substance abuse history in patients with depression, especially when one is treating adolescents. It would also be prudent to warn patients with a history of LSD use, for whom SSRI agents seem the most logical choice of treatment, that flashback or hallucinatory episodes are possible and to approach such

psychopharmacotherapy with caution. Chlorpromazine has been recommended for the amelioration of flashbacks, but this drug is probably not useful for adolescents because of its side effects. Antidepressants that would treat the depression but not act through a 5-HT mechanism, such as the selective noradrenergic uptake inhibitors (e.g., desipramine) might be considered. Although further prospective observations and, if possible, actual challenge tests under controlled situations are warranted, we suggest that LSD flashback syndrome may be induced or potentiated by SSRIs in patients with a history of LSD use.

We are indebted to Dr. David Rosen, of the University of Michigan Department of Pediatrics, and to the anonymous reviewers of this manuscript.

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# Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs

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**Children with rheumatic disease (N = 250) were examined for shallow facial scars similar to those described in drug-induced pseudoporphyria. Users of a nonsteroidal antiinflammatory drug were 2.4 times as likely as nonusers to have four or more facial scars; this relative risk was increased to 6.0 in users of naproxen. (J PEDIATR 1994;125:819-22)**

Submitted for publication April 4, 1994; accepted June 28, 1994.

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Pseudoporphyria-like lesions have been described in adults and children treated with naproxen.[1-8] These lesions usually occur in connection with sun exposure, begin with blistering, and heal with shallow scars. We had not observed such lesions in our patients and suspected that the reason is that our geographic area provides only limited sun exposure.