New Onset LSD Flashback Syndrome Triggered by the Initiation of SSRIs

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ABSTRACT

During the 1960s, lysergic acid diethylamide (LSD) emerged as a widely popular drug, used by a substantial portion of the adolescent and young adult population. Since Major Depressive Disorder is a common disorder, clinicians will increasingly encounter patients who used LSD in the far distant past and now require treatment with antidepressant agents. We describe such a case in the following report of a patient who experienced a troubling array of unusual side effects, which we postulate to be a new onset LSD flashback syndrome triggered by selective serotonin reuptake inhibitors (SSRIs).

CASE REPORT

A 47-year-old single white male with a long history of mood disorder and alcohol dependence, recently diagnosed with bipolar disorder by his internist, presented to our outpatient clinic seeking a second opinion. The patient reported 2 years of worsening depression and severe panic attacks. He stated that his mood was worse in the mornings and reported feelings of guilt and worthlessness, as well as initial insomnia. During a typical panic attack, which often lasted an entire day, he experienced heart palpitations, disorientation, hyperventilation, nausea, diarrhea, and stomach pain. The patient also described feelings of being "better off dead" but denied any current suicidal plan. He did not endorse any current or previous manic symptomatology.

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The patient reported active alcohol abuse at the time he was diagnosed with bipolar disorder. At the time of presentation to our clinic, he had been sober for 5 months, following an alcohol detoxification and rehabilitation program.

He had a long history of alcohol and substance abuse, beginning during adolescence and had used marijuana and lysergic acid diethylamide (LSD) frequently during high school. On average, he used one tab of LSD two to three times per week during that period. His experiences on LSD were not pleasurable, and he reported "freaking out" and having bad trips. He reported similar experiences with marijuana, and by his freshman year of college, the patient was using alcohol almost exclusively. His last experience with LSD was in college, 25 years prior to the current presentation. Once he had taken LSD, he experienced the world in a different way, often feeling claustrophobic or "a sensory overload." He reported no history of flashbacks prior to 1999.

The patient was first treated for depression and anxiety in 1999 by an internist, who prescribed paroxetine. After taking one tablet of an unspecified dose of paroxetine, he began "tripping," an experience less intense than previous trips on LSD, but still characterized by visual hallucinations of vibrant colors. This experience was an "awful bad trip." He continued to take the paroxetine as prescribed for a few days, but this reaction persisted and he stopped the medication. Subsequently, treatment with the combination of sertraline and buspirone did not result in the same "tripping" reaction, but he did not feel like himself and experienced visual disturbances, leading him to stop this treatment after a few months. He was then treated with citalopram and buspirone, which resulted in a reaction similar to that with the sertraline and buspirone combination. He was compliant with the regimen for 6 months.

A few years later, after the events of September 11, 2001, the patient took an unspecified dose of buspirone and "flipped out," feeling that he wasn't himself. In 2002, he began treatment with bupropion to help

him stop smoking and went "maniacal," experiencing palpitations, facial flushing, a terrible temper, and visual hallucinations of vivid colors, "like a trip." In summarizing his experiences with psychotropic medications, the patient reported that the paroxetine reaction was "extreme," while the other reactions were "severe." His experiences with these psychotropic medications led his internist to diagnose bipolar disorder.

DISCUSSION

Interactions of LSD with the Selective Serotonin Reuptake Inhibitors

To the best of our knowledge, this is the first case report of a patient who experienced an LSD flashback syndrome with selective serotonin reuptake inhibitor (SSRI) treatment after a very long 25-year period of abstinence from LSD use.

Although data about the interactions between SSRIs and LSD are limited, there are some reports describing this phenomenon. Bonson et al, in a study of 32 volunteer subjects who were currently using LSD and receiving chronic SSRI therapy, found that chronic SSRI administration attenuates the subjective hallucinogenic effects of LSD (1). Of the 32 subjects in this study who received SSRI treatment for at least 3 weeks, 28 individuals reported decreased responses to LSD while on the antidepressant therapy. One month after discontinuation of the SSRI, the responses to LSD of some subjects returned to normal, suggesting that the alterations in neurotransmitter systems caused by chronic SSRI treatment mediated the reduced response to LSD (1). These investigators and others have suggested that SSRI treatment does not generally have the hallucinogenic effects of LSD because SSRIs elevate serotonin (5-HT) and thus indirectly act at all subtypes of 5-HT receptors, while LSD specifically targets 5HT-2A receptors (1,2).

Interestingly, one subject in the Bonson et al study reported an increased response to LSD when taking it concurrently with fluoxetine. In contrast to the other subjects, this patient had initiated the SSRI treatment much more recently, only 1 week prior to the intensified hallucinatory experience.

Markel et al describe two patients who experienced LSD flashbacks shortly after initiation of treatment with SSRIs (3). The two cases involved teenagers who were only recently abstinent from LSD, beginning SSRI treatment within 1 year of the last LSD use. These patients described long-lasting flashbacks immediately following the initiation of SSRI therapy, consisting of visual disturbances, vivid colors, and feelings of being disconnected from reality.

Interactions of LSD with the Serotonergic Receptor System

Since the discovery of the hallucinogenic properties of LSD in 1943, investigators have worked to elucidate the mechanisms by which the drug exerts its effects. In the 1950s, the serotonin (5-HT) hypothesis of the action of hallucinogenic drugs suggested that LSD worked as a 5-HT antagonist in the central nervous system and later suggested that LSD could also mimic the actions of 5-HT (2).

Research in the 1970s and 1980s expanded upon the 5-HT hypothesis, describing various subtypes of serotonin receptors. For several hallucinogenic drugs, including LSD, there was no correlation between their affinity at the 5-HT1A receptors and their hallucinogenic activity. There was, however, a high correlation between hallucinogenic properties and the affinity of these drugs at 5-HT2 receptors (2).

The long-term effects of LSD on the central nervous system remain unclear. Nevertheless, there is a documented phenomenon of Hallucinogen Persisting Perception Disorder (HPPD), in which individuals have "flashbacks" years after cessation of LSD use. The research regarding HPPD has been limited, due in part to varying definitions of the term "flashbacks" (4). One proposed etiology of this disorder is that LSD causes a destruction of inhibitory interneurons that are serotonergic at the soma and GABAergic at the terminals (5,6). This hypothesis is supported by the partial responsiveness of HPPD to treatment with GABA agonists such as benzodiazepines. Another suggested etiology is that hallucinogen exposure may combine with other biological co-factors, such as cannabis or alcohol, to dysregulate genes linked to visual cue processing (4). This hypothesis is supported by data showing that LSD alters the genetic expression of neuroreceptors thought to be involved in the pathophysiology of psychotic disorders such as schizophrenia (4,7).

Postulated Mechanisms for LSD Flashbacks Following Initiation of SSRIs

There are several possible explanations for these flashback responses to acute SSRI therapy in patients who are concomitan tly abusing LSD. First, these individuals' reports could reflect the somatic, hallucinatory, and sympathomimetic sensations that patients sometimes report following initiation of SSRI treatment in the absence of LSD. It is possible that individuals who use or have used hallucinogenic drugs are more sensitive than non-users to these SSRI side effects (1). An alternative explanation is that initial SSRI therapy potentiates the effects of LSD, since acute fluoxetine administration has been shown to increase

the LSD-induced suppression of serotonin raphe neuron firing (8). This suppression normally results in a disinhibition of target neurons in the visual and limbic systems, accounting for the changes in mood and altered visual perception associated with LSD. Increased inhibition of raphe firing by co-administration of an SSRI with LSD could therefore result in enhanced hallucinogenic effects of LSD due to disinhibition of visual and limbic system neurons. Thus, the aforementioned individual in the Bonson et al study may have had an increased response to LSD during initial fluoxetine therapy due to a potentiation based on the similar initial effects of both drugs (1).

Our patient differs from those described in the Bonson et al study in that he had not used LSD in many years, whereas the volunteer subjects were using LSD while receiving SSRI treatment. Also, in contrast to our patient, the two patients in the Markel et al case report used LSD only 10 to 11 months prior to the initiation of SSRI therapy (3).

There are several possible explanations for our patient's reaction to the initiation of SSRI therapy. One is that his previous exposure to LSD resulted in the destruction of inhibitory serotonergic interneurons. Perhaps these interneurons have an inhibitory effect on 5HT2 receptors in LSD-naïve patients, blunting potential hallucinogenic effects mediated by these receptors. In our patient, this inhibition may have been absent, so that the sudden increase in 5HT produced by initial SSRI therapy would lead to hallucinogenic experiences.

Another explanation is that our patient's serotonin receptors remained in a state of permanent up-regulation following his previous LSD use. As a result, an acute surge of synaptic serotonin, as can be seen with the initiation of SSRI treatment, would result in a highly enhanced sertotonin signal (9), which might lead to hallucinogenic effects.

Our patient might have been experiencing the commonly reported sympathomimetic side effects of initial treatment with serotonergic antidepressants and identified these effects as similar to his past LSD experiences. It has been suggested that flashbacks represent increased awareness of normal visual phenomena, or normal memory of emotionally distressing experiences induced by LSD in the past (4). It is possible that our patient was more attuned to unusual visual or somatic sensations due to his past experiences with LSD.

Several factors could affect our formulation of this case. First, our patient admitted to having used other substances in the past, such as marijuana and alcohol, and it is likely that he was using alcohol while receiving SSRI therapy. These substances may have contributed to his hallucinatory experiences. As mentioned previously, hallucinogen exposure may combine with cannabis or alcohol to dysregulate genes linked to visual cue processing, thus leading to flashbacks (4). Additionally, both SSRIs and LSD act on a variety of neurotransmitter systems, in addition to the serotonergic system. Thus, alterations in other neurotransmitter levels may have affected our patient as well. His account of his experiences was also retrospective; perhaps his memories of the visual and somatic sensations were more extreme than the actual experiences themselves. As is so often the case, it is likely that a number of phenomena were at play simultaneously, resulting in an integrated, complicated, and often confusing clinical picture.

With these limitations in mind, one disturbing implication of this case is that exposure to LSD, and perhaps other hallucinogens that share its pharmacology, may permanently alter key neuronal systems that produce a vulnerability to flashbacks, even years after the cessation of the drug.

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