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## Flashback and Hallucinogen Persisting Perception Disorder: Clinical Aspects and Pharmacological Treatment Approach

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**Abstract:** One unique characteristic of lysergic acid diethylamide (LSD) and LSD-like substances is the recurrence of some of the symptoms which appeared during the intoxication after the immediate effect of the hallucinogen has worn off. This recurring syndrome, mainly visual, has not been clearly understood, appreciated or distinguished from other clinical entities by clinicians. The terms Flashback and Hallucinogen Persisting Perception Disorder (HPPD) are used interchangeably in the professional literature. Flashback is a usually short-term, non-distressing, spontaneous, recurrent, reversible and benign condition accompanied by a pleasant affect. In contrast, HPPD is a generally long-term, distressing, spontaneous, recurrent, pervasive, either slowly reversible or irreversible, non-benign condition accompanied by an unpleasant dysphoric affect. Flashback and HPPD appear to be part of a vast and broad spectrum of non-psychopathological and psychopathological states reported by hallucinogen users. Pharmacological agents such as clonidine, perphenazine and clonazepam have been shown to ameliorate this syndrome in some of the individuals seeking treatment.

### Introduction

Hallucinogens comprise a group of naturally occurring and synthetic agents that produce a state of intoxication, sometimes called "trip," associated with changes in thought, mood and perception. These mind-altering effects are produced with a clear level of consciousness, full wakefulness, alertness and absence of confusion. The prototype of the hallucinogen group is lysergic acid diethylamide (LSD) (1).

One unique characteristic of LSD and LSD-like substances is the recurrence of some of the symptoms which appear during

the intoxication after the immediate effect of the hallucinogen has worn off (2).

The original trip or intoxication may be experienced as "good" or "bad." In the same way, the phenomenon frequently referred to as flashback recapitulates the prior "trip" or intoxication that may also be "good" or "bad," reflecting the primary experience. A previous "good" trip, however, does not always ensure a "good" recurrence.

These recurring phenomena may be characterized by prodromal symptoms, presentation onset, content, frequency, duration and intensity of the recurrences, accompanying affect and insight.

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## Etiology

While the precise mechanisms underlying these phenomena are unknown, several theories have been proposed.

The acute effects of LSD seem to be mediated through a 5-HT<sub>2</sub> postsynaptic partial agonist activity (3) whereby this syndrome may resemble the previous experience, implying that a mechanism related to the original one may be involved. The basic mechanism underlying this syndrome appears to be that vulnerable LSD users continue the central process of visual imagery after the image has been removed from the visual field (4). An LSD-generated intense current (5) may provoke the destruction or dysfunction of cortical serotonergic inhibitory interneurons with GABA-ergic outputs and lead to the persistence of the visual imagery due to chronic disinhibition of visual processors (6).

Reverse tolerance that had originated after LSD exposure may also explain the continuation of the imagery after the stimulus has been removed (7). There may be a familial and genetic basis as well (8, 9).

## From Flashback to Hallucinogen Persisting Perception Disorder

Sandison et al. first described LSD recurrences following therapeutic use of the substance in 1954 (10). Cooper reported adverse reactions lasting more than 24 hours (11) and Elkes et al. suggested the possibility of LSD having prolonged adverse effects (12). Eisner and Cohen observed the spontaneous appearance of LSD-like phenomena at varying periods following treatment (13). Patients taking LSD medication welcomed these spontaneous returns of imagery or free trips as "relaxing and beneficial."

Rosenthal described *persistent hallucinosis*, a chronic hallucinatory state with spontaneous perceptual recurrences similar to those experienced during an LSD

trip (14). Robbins et al. reported similar adverse effects lasting as long as one year after substance use (15). Abraham reported individuals who experienced recurrences five years following the use of hallucinogens (9).

Horowitz seems to be the one who introduced the term *flashback*. He described spontaneous return of perceptual distortions, increased susceptibility to spontaneous imagery and recurrent unbidden images after LSD use (16). He observed that the most frequent and clearest content of the flashbacks appears to involve the visual sensory system, but they were also reported to be expressed by other sensory modalities such as taste, smell, touch, kinesthetic, vestibular changes and auditory images. He also mentioned there being occurrences of distortions of time sense, self image and reality sense.

Schick and Smith described flashbacks of three categories: perceptual, somatic and emotional (17). Perceptual flashbacks, principally the visual ones, are the most frequent and commonplace, although any sensory modality may be affected. Somatic flashbacks may consist of feelings of body changes and depersonalization and emotional flashbacks may be recurrences of distressing emotions originally associated with past LSD "trips."

Abraham suggested that some LSD users may have a sustained or irreversible impairment in color discrimination (18). He recognized a number of visual disturbances compatible with LSD induced flashback syndrome: acquired color confusion, difficulty reading, flashes of color, geometric hallucinations, geometric and imagistic phosphenes (bright images seen with eyes closed), halos around objects, illusions of movement in the peripheral field, intensified colors, macropsia, micropsia, negative and positive afterimages, pareidolias (an image within an image), and trailing phenomena (moving objects seen as a series of discrete

and discontinuous images) (9). He also reported a number of precipitants of the flashback phenomena, such as emergence into a dark environment, intention, exercise, fatigue, noise, sexual intercourse, phenothiazines and substance related disorders.

We have interviewed subjects who reported occurrences during pregnancy, delivery and post-partum depression and others who reported triggers such as police car flashing lights and neon lights, monotonous activities and tobacco smoking.

Of special interest is the triggering of recurrences by listening to acid or trance music when participating in "full moon" and rave parties. Subjects usually take hallucinogens or *entactogens* (19, 20), e.g., MDMA (Ecstasy), before and during the party. On some occasions, however, they consume no substances and just rely on the imagery and recurrence of feelings that will be elicited during the rave. Interestingly, flashbacks have also been reported after the use of MDMA (21).

Other frequently abused hallucinogenic substances of plant origin, for example, psilocybin (magic mushrooms) and mescaline (peyote cacti) surprisingly have not been mentioned in the professional literature as capable of producing the return of imagery.

The flashback phenomenon is not accurately delineated in DSM-III (22); it is described as Posthallucination Perception Disorder in DSM-III-R (23) and it has been replaced by Hallucination Persisting Perception Disorder (HPPD) in DSM-IV (24).

The terms flashback and HPPD are used interchangeably. Anderson and O'Malley were the first to suggest that the term flashback seems to be inadequate (25), but this well known and popular nomenclature is still used by both professionals and laymen and is generally regarded as a pleasurable "free trip" that is benign in nature (26). DSM-IV more accurately describes HPPD and emphasizes that it is a distressing entity.

The updated use of terminology apparently reflects the fact that there is probably a broad range of pathological and non-pathological states that are grouped together and may play an interactive role in the clinical and non-clinical descriptions provided by hallucinogen users. This intriguing and complex post-hallucinogen recurrent syndrome appears to encompass at least two clearly recognizable and delineated subtypes (26). The following descriptions have been taken from clinical practice, by psychiatric interview and from a small sample size of eight patients. They are representative and not exhaustive.

### Flashback-type

This is a generally short-term, non-distressing, recurrent, spontaneous, reversible and benign condition. The accompanying affect is pleasant. Users do not generally report the presence of prodromal symptoms. The onset of flashback may first start with a frequency of few times a day. The experience may last from a fraction of second up to minutes. Its intensity is not appreciated as disturbing or painful.

Flashback content usually includes visionary elements, although auditory, tactile, olfactory, gustatory, somatic and kinesthetic may be present. Subjects may report seeing animated images, e.g., flying winged animals and fairies, still formed images, e.g., precious stones, gold and silver jewels or formless moving images, e.g., kaleidoscopic figures, flashes of lights and fireworks.

Synesthesia flashbacks as in "seeing a sound, hearing a color and smelling through the hair" are not uncommon. Monochromatic flashback experience is the vision of a landscape in various tones of the same color.

These recurrences may be perceived as meaningful, beatific, spiritual, mind-boggling, revealing, mystical soul flights, out-of-body experiences or complex ecstatic

states, and are basically non-pathological in nature. In essence, these experiences resemble the "state of mind" of the previous hallucinogen intoxication.

Flashbacks usually occur spontaneously, but certain subjects are able to voluntarily elicit and stop them. Flashback presentation onset is usually not accurately recalled and individuals also may be unable to remember the substance responsible for it. After presentation onset, flashbacks usually decrease in frequency, duration, intensity and rapidly wear off. Full insight, reality testing and judgment are maintained during the experience. The accompanying affect usually disappears along with the recurrence. Experienced hallucinogen users generally look upon a flashback as a "free trip," an aspect of the psychedelic dimension, and do not seek psychiatric assistance after experiencing such an episode. Certain individuals may experience the recurrence of the same single flashback while other perhaps more suggestible subjects may have a variety of them.

Depending on setting, these otherwise generally unexpected and spontaneous benign experiences might become life threatening and dangerous for the "flashbacker" and their surroundings, e.g., when they are operating machinery, driving, diving, flying and so on.

Developing flashbacks after a single exposure, the returning of the same imagery, the capacity of multiple precipitants to provoke the same imagery, a more prolonged than expected recurrence and the presence or persistence of a dysphoric affect after the flashback dissipated may actually be HPPD prodromal symptoms.

### **HPPD-type**

Although HPPD is a well-recognized and described diagnosis in DSM-IV, some clinical aspects need to be added to its description. It is a condition that is generally long-term, distressing, recurrent, spontaneous, pervasive,

either slowly reversible or irreversible and non-benign. The accompanying mood is dysphoric and unpleasant.

Prodromal symptoms which may precede HPPD presentation might be feelings of self detachment, imminent changes and disconnection. Sometimes HPPD presentation might be anticipated by previous flashback episodes.

HPPD may spontaneously and abruptly emerge as an uncontrollable outburst of a variety of formed and unformed single or multiple visual disturbances.

Patients may report being "scratched or bruised" by a specific hallucinogen. They may accurately point out and identify the specific substance responsible for the "scratch" from among many substances they had consumed. They usually attribute HPPD to a "chemical hit."

The frequency of HPPD may range from a very long-lasting single episode, e.g., "being stuck," to multiple episodes lasting fractions of seconds e.g., "a continuing visual bombardment of colors." Intensity is perceived as disturbing or painful e.g., "a hurting and blinding flash of light."

HPPD content generally includes sensory elements such as those in flashbacks. False visual perceptions and misperceptions are the most common. Individuals may report serious, severe and complex recurrent experiences.

On occasion, moving body parts or unmoving objects are seen reduced and then enlarged or to alternate in size, e.g., macropsia-micropsia syndrome.

Partial depersonalization is the misperception of arms transforming into tree branches, fingers becoming worms or the body being connected to a speaker through the umbilical cord. A patient after childbirth reported partial macropsia in both hands. She was unable to grasp a glass, to button a shirt, to perform simple tasks and function nor-

mally. She was also unable to hold and breastfeed her baby.

One specific and common report is a form of derealization syndrome: "the bubble." Patients might feel like they are inside a transparent bubble, with clear edges which may or may not be visible but from which there is no escape. The bubble may be transformed into an egg accompanied by the appropriated smell. The full bubble experience is like being in a subtle and delicate but distressing sort of cell or prison.

Total depersonalization-metamorphosis syndrome signifies a complex experience of "becoming an orange or a dolphin." A subject who felt that he was a grapefruit was terrified by the fear that he will be squeezed, converted into grapefruit juice and then drunk. He was even able to "see" himself transformed and to smell the citrus aroma.

After presentation HPPD usually tends to be a continuous, intermittent or paroxysmal process. The accompanying affect usually continues for certain periods of time after the HPPD ceases. Expectation anxiety and avoidance behavior may develop in response to HPPD.

These recurrences are perceived as debilitating, deteriorating, disintegrating and disturbing. They are experienced as overwhelming, terrifying and horror-filled phenomena that are basically pathological in nature. Full insight, reality testing and judgment are usually maintained during the experience.

In certain situations a person experiencing HPPD may behave with poor insight, e.g., trying to avoid and escape a giant attacking eagle which flew out of the subject's teshirt.

Sometimes a briefly total but dangerous lack of insight may occur: in the "window syndrome," subjects may see themselves growing wings or being transformed into angels or becoming birds able to float and fly.

Acting on this misperceptions, they may accidentally fall to their deaths.

HPPD type is clearly altogether different from the flashback type. It is a condition which may cause significant distress or impairment in social, occupational or other important areas of functioning (24). HPPD often occurs in individuals with no prior diagnosed psychopathology. Hallucinogen users are usually aware of these severe, intruding and disabling consequences of hallucinogen consumption and do actively seek psychiatric assistance.

### **Pharmacological Treatment**

Subjects who experience flashbacks usually do not seek pharmacological treatment (26). Those who actively do so generally fulfill DSM-IV criteria for HPPD.

The literature on the efficacy of pharmacological agents is controversial and mainly based on open label studies, case series and case reports. The lack of double blind studies stems from the difficulties in controlling and randomizing variables when designing controlled studies.

Several distinct pharmacological approaches have been used and the usual target symptoms in the treatment of HPPD are visual hallucinations and anxiety (26).

Benzodiazepines appear to be helpful. They may alleviate but not eradicate this condition (27). Their effectiveness may be related to benzodiazepine activity at cortical serotonergic inhibitory interneurons with GABA-ergic outputs (6, 27). Alprazolam has been used with success (28) and we have found clonazepam useful in a small number of patients (26). Benzodiazepines seem to be the treatment of choice for the majority of patients, but their abuse potential might be troublesome in individuals with substance-related disorders (29).

Clonidine may be an effective treatment for individuals with a past history of substance related disorders. We reported the

improvement observed in some patients who participated in an open label study (26). Various mechanisms may partially explain these clinical observations. There is some evidence that clonidine increases plasma GABA levels in humans (30) and may thus have a benzodiazepine-like effect. Since clonidine also reduces locus ceruleus activity and decreases adrenergic activity (31), it may be helpful in the treatment of PTSD (32). Our opinion is that, as in PTSD-related recurrences, LSD-related HPPD could be associated with excessive sympathetic nervous activity that may be alleviated by clonidine.

Risperidone, a highly potent antagonist of both postsynaptic 5-HT<sub>2</sub> and D<sub>2</sub> receptors, with proven effectiveness in the treatment of the hallucinations of schizophrenia and safe side effect profile, was considered as being a plausible treatment for HPPD because LSD appears to act mainly as a partial agonist at postsynaptic serotonin receptors. In contradiction to this assumption, risperidone at recommended (8) and low doses (33) exacerbates HPPD and the associated anxiety. This exacerbation was later attributed to a risperidone alpha 2 presynaptic antagonism (34).

There is some evidence that dopamine receptor antagonists such as haloperidol (35) and trifluoperazine (25) may be helpful. Unfortunately the frequent appearance of side effects in naive patients usually undermines the patient's compliance, and they tend to stop medication. Small doses of perphenazine (28) are well tolerated and seem to be a reasonably effective treatment among the choice of dopamine receptor antagonists.

There is some evidence that phenytoin may ameliorate this psychopathology which may be interpreted as a visual seizure (36), an approach which may help to explain the efficacy of benzodiazepines.

There are contradictory reports regarding

selective serotonin reuptake inhibitors which both appear to worsen (37) or improve (4) HPPD. Alleviation of HPPD after chronic administration of SSRIs was attributed to the down regulation of 5-HT<sub>2</sub> receptors, adding further evidence to support the serotonergic mechanism of HPPD (4).

Long-acting opioid receptor antagonists, such as naltrexone, may be helpful in specific cases of LSD-induced HPPD. The underlying mechanism of naltrexone's efficacy could be that HPPD may be so distressing as to represent painful stimuli, which has been shown to provoke a greater release of endorphins (38).

After establishment of the diagnosis it is suggested to start treatment with small doses of clonidine (0.050-0.075 mg/day) which is well tolerated at low doses, has minimal side effects and has no abuse potential (26).

A second choice may be small doses of perphenazine (4-8 mg/day) and a third option may be the careful prescription of clonazepam (0.5-1.5 mg/day) or alprazolam (0.25-0.75 mg/day) to those subjects who do not respond to the previous medications. Treatment of patients with HPPD and benzodiazepine abuse may become a serious challenge. A previous history of other substance related disorders may require that the clinician closely monitor the benzodiazepine administration due to its potential abuse. Some amelioration is usually reported after treatment initiation probably due to placebo effect. Sustained improvement is generally achieved after several months of medication. Some symptoms, e.g., "trailing phenomenon," might be frustratingly resistant.

It should be kept in mind that HPPD may precede, precipitate, perpetuate or exacerbate a concomitant psychiatric disorder. HPPD may be an associated psychiatric disorder which coexists with another Axis I disorder. According to our clinical experience the Axis I disorders most commonly

associated with HPPD are major depressive disorder, dysthymic disorder, bipolar I and II disorders, panic disorder and schizophrenia. After the difficult task of dual diagnosing, a comprehensive pharmacological treatment approach should be mapped out.

Controlled studies are needed to more accurately understand this syndrome and to clinically evaluate the efficacy of different medications used for treating it.

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