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Flashbacks and HPPD: A Clinical-oriented Concise Review

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ABSTRACT

A unique characteristic of LSD, LSD-like and substances with hallucinogenic properties is the recurrence of some or all the hallucinogenic symptoms which had appeared during the intoxication after the immediate effects of the substance had worn off. This recurring syndrome, mainly visual, is not clearly understood. The terms Flashback and Hallucinogen Persisting Perception Disorder (HPPD) have been used interchangeably in the professional literature. We have observed at least two different recurrent syndromes, the first Flashback Type we refer to as HPPD I, a generally short-term, non-distressing, benign and reversible state accompanied by a pleasant affect. In contrast, the second HPPD Type we refer to as HPPD II, a generally long-term, distressing, pervasive, either slowly reversible or irreversible, non-benign state accompanied by an unpleasant affect. HPPD I and II appear to be part of a broad spectrum of non-psychopathological and psychopathological states reported by hallucinogen users. HPPD I and II may be clinically characterized by prodromal symptoms, onset, content of visual imagery, precipitators, frequency, duration and intensity of perceptual recurrences, severity, course, differential diagnosis, accompanying mood and affect, insight and remission. Pharmacological therapy with or without preceding or following co-occurring psychiatric disorders have been shown to ameliorate this syndrome. A large variety of medications may be utilized to alleviate this condition, but with differential results suggesting several subtypes. The purpose of this manuscript is to provide a clinical-oriented, comprehensive and concise review to treating psychiatrists.

INTRODUCTION

Hallucinogens encompass a group of naturally occurring and synthetic substances (1) which may trigger a transient and generally reversible state of intoxication characterized by perceptual disturbances primarily visual in nature, often referred to as "trips" (2, 3). A unique characteristic of LSD (lysergic acid diethylamide) and LSD-like substances is the total or partial recurrence of perceptual disturbances which appeared during previous intoxication and reappeared in the absence of voluntarily or involuntarily recent use (1-3). This syndrome is still poorly understood (2, 3). LSD is the prototype of synthetic hallucinogenic substances and it is probably the most investigated hallucinogen associated with the etiology of this condition. Other substances that have been associated with the development of this condition include: psilocybin (Magic Mushrooms or Shrooms) (4), mescaline (San Pedro and Peyote Hallucinogenic Cacti) (5), cannabis (6), 5-MeO-DiPT (Synthetic Hallucinogen) (7), Ecstasy (MDMA) (8), Phencyclidine (PCP) (9, 10), dextromethorphan (11) and ketamine (12). Datura, salvia divinorum, ayahuasca, ibogaine, synthetic cannabis and inhalants also appeared to be implicated (13). Recurrent visual disturbances attributed to this syndrome are geometric hallucinations, false perception of movement in the peripheral visual fields, flashes of colors, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia and micropsia (9). A variety of distinct visual disturbances that are reminiscent of those generated by the previous use of substances have been widely reported and described by patients.

ETIOLOGY

LSD's acute effects seem to emerge through a 5-HT_2 post-synaptic partial agonist activity (14). Recurrent imagery

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may partially or totally look like the previously experienced "trip," indicating that a mechanism similar to the original intoxication may be implicated. The basic mechanism underlying this syndrome appears to affect vulnerable LSD users who develop chronic disinhibition of visual processors and consequent dysfunction in CNS function (3,15-17). This disinhibition might be associated with an LSD-generated intense current (18) that led to the destruction or dysfunction of cortical serotonergic inhibitory interneurons with GABA-nergic outputs mechanisms which are involved with sensory filtering process of unnecessary stimuli in certain brain areas (16, 18). Investigations of HPPD patients with qEEG mapping indicate that the disorder is represented by disinhibition in the cerebral cortex (15). Thus, an unsuccessful defective sensory gating mechanism may be involved in the pathogenesis of this syndrome (19), facilitating the continuation of the central process of visual imagery after the image has been removed from the visual field (20). It has also been postulated that reverse tolerance or sensitization that had originated after LSD exposure may explain the flashbacks after the stimulus has been removed (21). There may also be a familial and genetic basis as well (2). These processes might play a role in benign transient or pervasive persistence of the visual imagery and associated features (22, 23). HPPD is still poorly understood due to great variability of recurrent perceptual disturbances and different subtypes associated with various psychotropic substances, and may suggest that multiple mechanisms are involved in the etiology (22, 23).

CLINICAL SYNDROMES

Nomenclature used to describe this multi-faceted phenomenon can be confusing and requires clarification (23). Primarily, two subtypes of substance-use associated recurrent perceptual disturbances have been described, including benign Flashback Type or "free trips" (22-24) referred to as **HPPD I**, and non-benign HPPD Type (22-24) referred to as **HPPD II**. One additional subtype is the return of visual disturbances accompanied by newly generated visual imagery which was not experienced during the original "trip." Distinct substances may lead to similar but not identical subtypes of visual recurrences, and may vary greatly for different substances.

FLASHBACK TYPE OR HPPD I

It is a generally transient, recurrent, trigger-precipitated or spontaneous, reversible and visually benign experience (22-24). It is typically a condition in which the re-experiencing of one or more perceptual symptoms may not produce significant distress or impairment in individual, familial, social, occupational or other important areas of functioning. Experienced LSD users view and relate to these re-occurrences as a "free trip," an innocuous and trivial aspect of the broad psychedelic dimension, and do not generally seek psychiatric assistance after experiencing these perceptual episodes. Certain individuals may experience the reiterative recurrence of the same single flashback, or a variety of them (22-24).

HALLUCINOGEN PERSISTING PERCEPTION DISORDER TYPE OR HPPD II

It is a typically chronic, recurrent, trigger-precipitated or spontaneous, slowly reversible or irreversible and highly distressing visually pervasive experience (22-24). It is a radically different condition in which the re-experiencing of one or more perceptual symptoms may produce significant distress or impairment in individual, familial, social, occupational or other important areas of functioning. Users are certainly aware of these severe, intruding and disabling consequences of substance consumption and generally actively seek psychiatric help (22-24). Individuals suffering from **HPPD II** regularly stop the ingestion of these substances including cannabis derivatives, synthetic cannabis and alcohol. **HPPD II** appears to be an under-reported, misdiagnosed or under-diagnosed disruptive side effect (22-24). Additional factors that may contribute to this lack of accurate reports and diagnoses may include patient guilt, relatively ineffective treatments and poor awareness of the disorder in the medical community. **HPPD II** may be more common and frequent than generally considered.

The principal difference between these two conditions rests on the patient's perception of impairment and disability. **HPPD I** is perceived as a benign pleasant state whereas **HPPD II** is perceived as a severe, unpleasant state. **HPPD I** is typically perceived as a short-term benign condition although it may be long-term in duration. **HPPD II** is generally a more severe, unpleasant long-term condition. The individual's subjective experience determines the seriousness of **HPPD I** and **HPPD II**, and widely varies from one person to another (22-25).

HPPD I and **HPPD II** may be clinically characterized by prodromal symptoms, onset, content of visual imagery, precipitators, frequency, duration and intensity of perceptual recurrences, severity, course, differential diagnosis, accompanying mood and affect, insight and remission (23).

PRODROMAL SYMPTOMS

HPPD I onset may be preceded by prodromal symptoms which could encompass typical "auras," slight and surprising feelings of self-detachment, depersonalization, derealization and a mild sense of strangeness or disconnection (23). **HPPD II** onset could also include bursting "auras," feelings of self-detachment, a grave sense of imminent, irreversible and uncontrollable changes, sharp depersonalization-derealization and a severe sense of strangeness (23). Prodromal symptoms are more frequently reported in **HPPD II** (23).

ONSET

HPPD I may slowly commence whereas **HPPD II** might abruptly erupt. Episodes of **HPPD I** and **II** may spontaneously emerge or be precipitated by identified triggers. Episodes may be continuous, intermittent or suddenly paroxysmal. Duration of episodes may range from one long-lasting experience, e.g., "to be stuck," to multiple episodes lasting from almost imperceptible fractions of seconds to longer periods of time. Duration between episodes may be shorter for **HPPD I** than **HPPD II**. Episodes may immediately or gradually disappear (23).

HPPD I and **II** onsets may be preceded by already pre-existing mental disorders such as anxiety, mood, somatoform, sleep and dissociative disorders or severe mental illnesses like schizophrenia, but may also contribute to the development of these disorders acting as a trigger (23).

HPPD I onset may occur unaccompanied by any prominent additional psychiatric disorder appearing to be a sole, unique and independent condition. The clear clinical association between **HPPD I** and **HPPD II** with preceding or subsequent psychiatric disorders should be clinically approached, pharmacologically medicated and comprehensively treated as genuine co-occurring psychiatric disorders.

CONTENT OF VISUAL IMAGERY

Contents vary widely, only a few of which have been described in DSM-IV-TR (9). Some of the visual disturbances may include ***floaters*** (a spot or spots that appear to drift in front of the eye), ***visualizations*** of dots, mottles or specks when entering a darkened room, ***fractals*** (self-similarity perception or small parts seen having the same and identical shape as the whole), ***repetition*** of still or moving patterns, ***sharpness*** of color contrasts, ***pareidolia*** (an image within an image), ***superimposition*** of geometric patterns (6), ***distorted*** perception of distance (objects seen slightly closer or more distant) (6), ***monochromatic vision*** (the visual perception of different colors as one color with different tonalities) (23), intense ***fragmentation*** of still or moving objects, ***recurrent synesthesia*** (stimulation of one sensory pathway leads to automatic, involuntary reactions or experiences in a second sensory pathway) (26), ***geometric phosphenes*** (non-specific luminous perceptions that occur when the eyes are closed and may originate from entopic stimuli arising from within the eye itself) and ***imagistic phosphenes*** (unbidden formed images without geometric patterns generated on closing an eye and pressing it with a finger), ***acquired dyslexia*** and ***aeropsia or visual snow*** (virtually seeing particles of air) (2).

PRECIPITATORS

A number of triggers of **HPPD I** and **II** have been reported. Some reported triggers are: entering a dark environment, intention and sexual intercourse (2); exercise and exposure to noise (23); pregnancy, delivery and post-partum depression (23); photophobia, police car flashing lights, neon lights, monotonous activities and tobacco smoking (23), use of phenothiazines (2) and risperidone (25), as well as ECT treatment in patients with a past history of LSD use (27). Additional precipitators include smoking cannabis products including synthetic cannabis or by listening to acid or trance music when participating in parties (6, 23). Patients may be generally able to accurately point out the specific substance or specific trigger responsible for the syndrome from among the many substances they had consumed or triggers to which they have been previously exposed (23).

FREQUENCY, DURATION AND INTENSITY OF PERCEPTUAL RECURRENCES

After **HPPD I** onset, episodes tend to occur with less frequency, duration and intensity. Past substance users may voluntarily elicit visual imagery with or without known precipitators (2, 23).

After **HPPD II** onset, episodes tend to occur more in frequency, duration and intensity. Individuals might feel a partial or complete lose of control, where the condition may trigger or be accompanied by severe mental illness. A sense of helplessness, advancing general impairment, increasing limitation, functioning incapability, deterioration, debilitation, treatment resistance and slow or partial remission might convert **HPPD II** into a serious and severe mental disorder.

SEVERITY

Patients with **HPPD I** usually relate to their condition as a mild, benign and transitory hallucinogenic experience. Patients presenting with **HPPD II** typically relate to their condition as being moderately or severely disturbing.

COURSE

The syndrome's course can be related to both "good" or "bad" trips of the previous intoxication. When the hallucinogenic experience stops, a latent period may precede the onset of the return of the visual imagery. This latent period may last from hours or days up to years and re-emerge as either **HPPD I** or **II** with or without any recognized trigger.

If the individual's primary hallucinogenic intoxication continues beyond the subjectively expected time the effects should last (23), this experience is generally accompanied by anxiety (GAD-like or Panic Disorder-like) or depressive features and a threatening feeling of loss of control (22, 23). This clinical status might predict the onset of **HPPD II**. **HPPD I** has a generally short-term, reversible and benign course, conversely **HPPD II** has a generally long-term, irreversible or slowly reversible and pervasive course.

DIFFERENTIAL DIAGNOSIS

It is essential to rule out any organic diseases (9). A comprehensive physical and laboratory examination is mandatory. A complete ophthalmological and neurological evaluation should be conducted. EEG, CT and MRI are on occasion also recommended (23).

ACCOMPANYING MOOD AND AFFECT

Following **HPPD I** onset, accompanying mood and affect may be pleasant. Occasionally visual imagery appearing at inappropriate settings may elicit negative mood and affect and disturb functioning (23).

HPPD II onset is usually associated with negative mood and affect. Anxiety and depressive features may frequently augment during every new episode. Anxiety might transform into panic attack. Anticipatory anxiety may precede every future additional visual imagery episode and avoidant behavior may entirely limit normal functioning. It may resemble a panic disorder (23).

INSIGHT

Following **HPPD I** and **II** onset, full insight, reality testing and judgment are maintained before, during and after new episodes. Individuals reporting continuous, persisting and unremitting visual imagery episodes might show reality testing and judgment partially and transiently impaired (23).

REMISSION

Pharmacologically treated or untreated **HPPD I**, in the absence of additional aggravating precipitators like ongoing substance use, tends to gradually fade away and disappear (22-24). **HPPD I** rarely transforms into **HPPD II**.

Pharmacologically treated **HPPD II**, despite administered treatment, tends sometimes to be chronic in nature. Inexplicably, sometimes disturbing **HPPD II** may slowly transform into innocuous **HPPD I** (22-24). **HPPD I** and **II** appear to be part of an abundant large spectrum of non-psychopathological and psychopathological experiences reported by users (23).

PHARMACOLOGICAL TREATMENT

Stemming from the still unclear pathogenesis, the numerous substances associated with the genesis of this condition, the myriad of reported perceptual-visual disturbances, the various HPPD subtypes and the preceding or following co-occurring psychiatric disorders, distinct medications have been used toward different targets with different outcomes. No single or multiple medications seem to be completely effective but some of them may lead to clinical improvement (23). Subjects who experience **HPPD I** do not usually seek pharmacological treatment. Those who actively do so generally present with **HPPD II**.

The professional literature on the effectiveness of pharmacological treatment is debatable and mainly rests on open label studies and case studies. There is an ample non-professional reported information based on individual substance experimentation. The absence of double blind investigations stems from methodological problems in controlling random variables when designing controlled research (23). Clinical studies can be difficult to carry out. The academic literature regarding this condition, although limited, has been comprehensively reviewed (5).

Pharmacological agents have been used targeting visual disturbances, anxiety, depression and paroxysmal visual seizures-like episodes (23). Some mechanisms of action can be hypothetically explained whereas others might remain obscure and difficult to explicate. Visual disturbances without co-occurring psychiatric disorders may require pharmacological treatment generally based on one starting medication. Visual disturbances with preceding or following co-occurring psychiatric disorders may require treatment generally based on a polypharmacy approach. Challenging patients are those presenting with **HPPD I** and **II** who are already receiving concomitant medication for co-occurring psychiatry disorders.

BENZODIAZEPINES

Benzodiazepines appear effective in alleviating but not eradicating this condition (1), and effectiveness may be related to activity at cortical serotonergic inhibitory inter-

neurons with GABA-nergic outputs (1, 3). Oxazepam (5-10 mg/day) and Lorazepam (0.5-1 mg/day) at low doses have shown little efficacy (28), Clorazepate (5-10 mg/day) seems to be helpful in some cases (13), Alprazolam 0.25-0.75 mg/day) has been used with some success (29) and Clonazepam (0.5-1.5 mg/day) appears to be the most effective (22, 28). It is suggested that Clonazepam may have effects on serotonergic systems enhancing transmission (30), and leading to improvement in patients (28). Benzodiazepines appear to play a central role as a suggested primary treatment for a large number of patients, but their abuse potential might be inconvenient and bothersome for some subjects with a past history of substance use (2, 22, 23, 28). A carefully monitored prescription of Clonazepam or Alprazolam can help avoid this (23, 29).

SYMPATHOLYTIC CENTRALLY ACTING α_2 PRESYNAPTIC ADRENERGIC AGONISTS

Clonidine is an optional treatment for individuals with a past history of substance-related disorders due to its low profile of abuse and dependence. Improvement has been observed in some patients (24). Effectiveness may be based on the evidence that clonidine may increase plasma GABA levels in humans (31) having a benzodiazepine-like effect. Clonidine may also reduce locus ceruleus activity and decrease adrenergic activity (32), reduction which can be effective in the treatment of PTSD (33). Then, as in PTSD-related flashbacks, some visual disturbances could be associated with excessive sympathetic nervous activity that may be alleviated by Clonidine (24). It is recommended to start treatment with small doses of Clonidine (0.050–0.075 mg/day) which is well tolerated, has minimal side effects and no abuse potential (24). Lofexidine, another sympatholytic centrally acting α_2 presynaptic adrenergic agonist similar to Clonidine, also appears to be effective in some cases (13).

SEROTONIN DOPAMINE RECEPTOR ANTAGONISTS

Risperidone was considered a reasonable treatment for visual disturbances due to its proven efficiency in the treatment of hallucinations in schizophrenia. LSD appears to act mainly as a partial agonist at postsynaptic serotonin receptors, thus Risperidone which is a highly potent antagonist of both postsynaptic 5-HT_2 and D_2 receptors was expected to be useful. In contrast to this conjecture, Risperidone at recommended (34) and low doses (35) aggravated visual disturbances and related anxiety. This worsening was later imputed to a Risperidone alpha 2 presynaptic antagonism and noradrenaline release (36). In addition, Risperidone was associated with the re-experiencing of visual disturbances in some patients suffering from schizophrenia with a past history of LSD use (25).

Some patients have found low dosages of atypical antipsychotics to be beneficial, for instance: Olanzapine (5–7.5 mg/day), Quetiapine (up to 25–75 mg/day) and Amisulpride (300–600 mg /day) (13). Low doses of Aripiprazole and Asenapine seem to be effective in some cases (13).

DOPAMINE RECEPTOR ANTAGONISTS

Haloperidol (37) and Trifluoperazine (38) have been previously reported to be helpful in treatment. Currently, these agents are largely not prescribed and are no longer recommended. There are only a few agents in this family which are still used, including Perphenazine in small doses (4-8 mg/day) (23, 29) and Zuclopenthixol (2-10 mg/day) (23). These treatments at low doses are well tolerated and may be an effective treatment among the dopamine receptor antagonists. These patients appear to be more sensitive to dopamine receptor agonists even at low doses, requiring monitoring of extra-pyramidal side effects.

ANTIEPILEPTIC AGENTS

Visual disturbances with paroxysmal onset have been interpreted as visual seizures, an approach which also helped to explain the efficacy of benzodiazepines and led to the use of Phenytoin (39). Pharmacological agents like Valproic Acid (200-600 mg/day), Carbamazepine (200-600 mg/day), Oxcarbamazepine (300 mg/day), Gabapentin (300-900 mg/day), Topiramate (25-100 mg/day) and Levetiracetam (250-500 mg/day) may be useful (13). Lamotrigine at different doses (25-200 mg/day) also seems to have some therapeutic usefulness (13, 40). These medications may also be helpful when visual disturbances are accompanied by mood swings and mood disorders. Effective doses can vary between patients. Experience and expertise are recommended to use these medications.

SEROTONIN SELECTIVE REUPTAKE INHIBITORS

There are controversial reports regarding SSRIs like Sertraline which has been reported to worsen (41) as well as improve (18) visual disturbances. Alleviation after long-term administration of SSRIs was attributed to the down regulation of 5-HT_2 receptors, adding further evidence to support the serotonergic mechanisms underlying this syndrome (18). Other SSRIs which have been utilized with some success are Citalopram (10-20 mg/day) (42), Paroxetine (10-20 mg/day) and Escitalopram (10-20 mg/

day) (13). NSRI like Duloxetine (30-60 mg/day) and Milnacipram (25-50 mg/day) have shown some improvement in symptomology (13). NRE like Reboxetine have also been tried with some success (43). These medications could help in treating visual disturbances with co-occurring anxiety and depressive disorders (22, 43).

LONG-ACTING OPIOID RECEPTOR ANTAGONISTS

Naltrexone may assist in specific cases. The underlying mechanism of Naltrexone's efficacy could be that visual imagery and associated features might be so distressing as to represent painful stimuli, which have been shown to provoke a greater release of endorphins (44). Naltrexone has been generally used alone or with other agents, in chronic patients with continuous unremitting visual disturbances that previously did not respond to other medications (13, 44).

CALCIUM CHANNEL BLOCKERS

These medications have been utilized in treating recurrent perceptual disturbances in patients with co-occurring anxiety and mood disorders. Despite the weak evidence of the role of calcium in the genesis of these disorders, medications affecting calcium channels may be useful in the treatment of anxiety disorders (45-48). Verapamil (180 mg/day) and Nifedipine (30-60 mg/day) have been used with success in some patients (13). These medications may be utilized alone or with other agents in subjects who previously did not respond to different remedies.

BETA BLOCKERS

There is clinical evidence for the efficacy of a β-noradrenergic receptor blockade with Propranolol in the alleviation of anxiety symptoms (49). Propanolol at low (20-60 mg/day) and high doses (240 mg/day) have been used to reduce the accompanying anxiety of visual imagery, being used alone or with other agents in chronic patients who previously did not respond to other medications remedies (13).

CATECHOL-O-METHYL TRANFERASE INHIBITIORS (COMT)

A combination of reversible COMT inhibitor Tolcapone, Carbidopa and Levodopa augmentation appear to be helpful in some HPPD subjects (19). Studies of HPPD patients with qEEG mapping showed that HPPD is represented by disinhibition (16, 50) in the cerebral cortex (15). The rationale behind this treatment is that improving sensory gating by dopaminergic enhancers may lead to inhibition of COMT that may reduce symptoms in HPPD.

DISCUSSION

In summary, the critical first step towards understanding HPPD syndromes is the establishment of accepted terminology and treatment targets. **HPPD I** is typically an independent condition without co-occurring psychiatric disorders and can be treated with one type of medication, i.e., clonidine, clonazepam or small doses of first or second generation antipsychotics. **HPPD II** as a condition is largely associated with co-occurring psychiatric disorder. If one medication is ineffective, a combination of medications may be needed according to preceding or subsequent psychopathology.

Clinical experience and comprehensive knowledge of these phenomena is vital for a successful treatment outcomes. Some symptoms may rapidly subside whereas others like "trailing phenomenon" (51) may be resistant to treatment.

Controlled studies are needed to more accurately understand these complicated substance-associated phenomena and to clinically evaluate the efficacy of different medications used in distinct subtypes for treating those affected by this syndrome (23).

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