REVIEW

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Pharmacological Treatment of Hallucinogen Persisting Perception Disorder (HPPD): A Systematic Review

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Learning Objectives: After participating in this CME activity, the psychiatrist should be better able to:

- Define hallucinogen persisting perception disorder (HPPD) and describe its diagnostic criteria and subtypes.
- Evaluate pharmacological and nonpharmacological interventions, including evidence-based and supportive approaches.

Abstract: Hallucinogen persisting perception disorder (HPPD) is characterized by perceptual phenomena that either linger after substance-use cessation or recur as reperceptions or flashbacks. These symptoms may be either mild and transient or long-lasting and severely burdening. Since evidence for pharmacological treatment of HPPD is unclear, we seek to provide treatment advice based on a systematic review of existing medication studies. Our search yielded 31 studies with 87 participants treated for HPPD with different types of medication. Three observational studies reported substantial symptom reduction for regimens with clonidine, clonazepam, and levetiracetam. The other 28 studies, which consist of case reports and small case series, found largely similar results for benzodiazepines, antiepileptics, antidepressants, and alpha agonists. Of those who received these pharmacological treatments, 28% showed full recovery and 61% partial recovery within a year. When HPPD was triggered by lysergic acid diethylamide, benzodiazepines were ineffective. Notably, several studies described HPPD symptom aggravation upon treatment with the antipsychotic agent risperidone. Although not statistically significant, our analysis suggests that HPPD can be treated to good effect with the aforementioned groups of medicines. On the basis of our findings, we provide a list of practice-based treatment methods and make suggestions for further research. In particular, epidemiological studies are needed to investigate the natural course of HPPD. Likewise, randomized controlled pharmacological studies are necessary to evaluate the efficacy of medications in different, well-defined HPPD subgroups.

Keywords: addiction, Alice in Wonderland syndrome, flashback, metamorphopsia, pharmacotherapy

INTRODUCTION

Given the widespread use of psychoactive substances worldwide, remarkably little is known about the long-term effects of hallucinogens and related substances, let alone about their treatment. Among the disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders, 5*th *Edition, Text Revision* (*DSM-5-TR*), hallucinogen persisting perception disorder (HPPD)—previously referred to as post-hallucinogen perception disorder and flashback syndrome—is one of the lesser-known diagnostic categories.[1] HPPD involves the continuation or recurrence of perceptual phenomena as experienced during an episode of substance use. It presents in the form of reperceptions or flashbacks. (For *DSM-5* diagnostic criteria, see Text Box 1.) Its onset can be immediate, resulting in a never-ending trip, or several days, weeks, or even years after the intoxication phase.[2] Arguably, the most notorious cause of HPPD is lysergic acid diethylamide (LSD), although the condition can also arise from substances such as mescaline, psilocybin, ibogaine, ayahuasca, ketamine, 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), cannabis, and even alcohol.[3–5] According to the *DSM-5-TR* operational definition, symptoms are identical to those

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Text Box 1.

***DSM-5* Diagnostic Criteria for HPPD[1]**

Diagnostic Criteria	292.89 (F16.983)
A.	Following cessation of hallucinogen use, reexperiencing one or more perceptual symptoms experienced while intoxicated (e.g., geometric hallucinations, false perceptions of movement in peripheral visual fields, flashes of color, intensified colors, moving object image trails, 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.	Symptoms are not attributable to other medical conditions (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better explained by another medical condition (e.g., delirium, major cognitive disorder, schizophrenia) or hypnopompic hallucinations.

experienced during the original intoxication phase.[1] In clinical practice, however, variations are also reported.[6,7] In fact, the symptoms experienced in the HPPD context are extremely varied. Perhaps best known are hyperesthesia, halos, metamorphopsias (sensory distortions), visual snow, positive afterimages, pareidolias (visual illusions), visual hallucinations, and derealization. Three quarters of these phenomena fall in the group of sensory distortions characteristic of Alice in Wonderland syndrome (named after the peculiar changes experienced by Alice in the eponymous classic children's book), which is why HPPD is also known as the substance-induced variant of this syndrome.[7–9]

Demarcation from Other Disorders

It is important to distinguish HPPD from schizophrenia spectrum disorders (which can be triggered, sustained, or aggravated by substance use, but demonstrate a different symptom profile often admixed with delusions, disorganization, catatonic symptoms, negative symptoms, and a greater emphasis on verbal auditory hallucinations); posttraumatic flashbacks (in which recurring imagery is usually panoramic, does not necessarily take the form of percepts, and is definitionally linked to previous trauma); reperceptive hallucinations (in which previously experienced scenes are reperceived in the form of hallucinations); phenomena such as palinopsia and palinacousis (in which experienced phenomena are repeatedly reperceived immediately following the original percept); and the game transfer phenomenon (in which prolonged exposure to computer/online games causes repeated aftereffects).[10] These distinctions are not only conceptually relevant; practically, their differences in severity and underlying pathology have ensuing implications for treatment. Notably, the current version of the *International Classification of Diseases* does not recognize HPPD as a diagnostic category. The concept of hallucinogen-induced psychotic disorder perhaps comes closest, but the operational definitions of these two categories are markedly different.[11]

Typology

Two types of HPPD, introduced in or shortly before 2014, are described in the literature.[12,13] Type 1 is characterized by reperceptions or flashbacks that arise weeks to months after the intoxication phase and have a duration of seconds to minutes. It is associated with all kinds of psychotropic drugs. According to the literature, these phenomena are well tolerated, experienced as neutral or even pleasant, do not lead to functional impairment, and tend to be self-limiting.[3–5] Therefore, Type 1 is also called the benign type or flashback type of HPPD in which those who experience it do not meet an important *DSM* HPPD criterion—social and/or occupational dysfunction.[1,14] Type 2 is conceptualized as a more severe form associated with LSD and several other specific hallucinogens. It is characterized by constant reperceptions, notably in the visual sphere, that are not well tolerated, often persist for years, and tend to yield comorbid symptoms such as derealization, depersonalization, anxiety, and depression.[3] As a rule, Type-2 symptoms have substantial effects on daily functioning. There is controversy surrounding this typology, particularly that it involves a sliding scale on severity dimension. Often, Type 1 is referenced simply as a light version of Type 2 that does not satisfy *DSM-5* criteria, similar to how many forms of unhappiness do not meet criteria for major depressive disorder. Type 1 and Type 2 HPPD, however, could also represent two different disease entities with different symptoms and underlying causal mechanisms. What is relevant is that people with (either type of) HPPD who suffer from comorbid anxiety or depressive disorder tend to have less favorable prognoses.[7] Halpern and colleagues[12] confirm such prognoses in the largest prospective case series on HPPD to date. Moreover, the authors suggest that such disorders, when preexistent, may also trigger HPPD symptoms when people start using hallucinogens.

Epidemiology and Neurobiology

Studies indicate that 60% of those diagnosed with HPPD recognize the symptoms as similar to previous episodes of substance use/intoxication. In other words, 40% of people diagnosed with HPPD report different symptoms from their acute experiences, but they nonetheless associate them with prior substance use. Although large-scale empirical studies are lacking, it is estimated that substance use elicits Type 1 HPPD in about 1/20 users and Type 2 in about 1/50,000 users.[5] Given the relative lack of familiarity with HPPD among users and health professionals, these numbers are likely quite low.

The exact cause of HPPD is unclear. The name suggests that hallucinogens are the exclusive cause, but the definition and scope of the term hallucinogen is ambiguous; moreover, the *DSM-5-TR* and other diagnostic manuals do not provide a full overview of substances belonging to this group.[1,15] Since cannabis and alcohol are mentioned as possible HPPD triggers, it may be sound to acknowledge general substance use, without any further specification, as a potential etiological factor. Regarding the disorder's pathophysiology, the literature suggests that substance use may induce a loss of serotonin or 5-HT receptors, which may in turn affect the normal

processing of (especially) visual stimuli. In addition, there are indications that GABA-ergic neurons are affected in HPPD, compromising the normal filtering of unnecessary stimuli.[3] Moreover, EEG studies show electrophysiological aberrations in the visual cortex suggestive of visual seizures.[3,4]

Diagnosis and Treatment

In clinical practice, HPPD is usually diagnosed in accordance with *DSM-5* criteria. As noted, such criteria may not require strict application; similar symptoms, rather than exact reperceptions, may also fulfil the A criterion.[10] There is a fair degree of consensus that HPPD involves a chronic or recurring perception disorder following substance use, conjuring associations with intoxication. Treatment is not always necessary, especially when symptoms are fleeting and do not cause much suffering.[4] Psychoeducation and reassurance may suffice in such cases. There are no evidence-based guidelines for treating longer-lasting and intrusive or burdening symptoms, although the literature does offer several experimental and practice-based interventions. Nonpharmacological treatment largely involves substance use abstinence and learning to cope with the disorder's potential limitations.[3–5] Such approaches may involve practical advice (e.g., wearing tinted glasses and adjusting the color of computer/mobile phone/tablet displays), psychoeducation, general lifestyle advice (including food, sleep, and exercise), and cognitive behavioral therapy. Some studies also claim positive results from eye movement desensitization and reprocessing, a therapeutic technique originally developed for people with trauma-induced flashbacks.[4] Pharmacological interventions are all experimental and practice-based. Case reports and small-scale pharmacological studies show promising results with antipsychotics, antidepressants, antiepileptics, and benzodiazepines. The efficacy of these medications, however, remains unclear.[3–5] Thus, we present a systematic review designed to chart HPPD pharmacological treatment outcomes and apply the results to practice-based treatment advice.

METHODS

We carried out a systematic search in Medline, Embase, PsycInfo, and Google Scholar for relevant reports on pharmacological HPPD treatments diagnosed in accordance with *DSM-IV* or *DSM-5* criteria. Included papers could be published until November 13, 2024. We used the search terms "hallucinogen persisting perception disorder," "hallucinogen persistent perception disorder," "post-hallucinogen perception disorder," "medication," "pharmacotherapy," and "effectivity/effectiveness/efficacy." Papers written in English and Dutch were included, and we complemented digital searches with backward searches. Articles were excluded if they contained no original reports on the pharmacological treatment of HPPD. From all studies, we extracted the following data: year of publication, number of participants, sex and age of those treated, type of illicit substance used, comorbid diagnosis (if present), type of intervention, results, and follow-up duration. We did not consider statistical analysis informative given the relatively small number of publications.

RESULTS

Our systematic search yielded 100 articles purportedly describing pharmacological interventions for HPPD. Of these, we excluded 73 that did not fulfill our

Table 1.

Pharmacological Treatment of HPPD: Observational Studies

Reference	N	Mean Age (Years)	Gender	Illicit Substances Used	Comorbidity	Medication Prescribed	Duration	Outcome
Lerner et al. (2000)[16]	8	23	Unknown	Polysubstance	Unknown	Clonidine 0.025 mg three times daily	Two months	CGI:5,25(SD=0,46) →2,5(SD=0,55) SRS: 4→2
Lerner et al. (2003)[17]	16	21	11 males, 5 females	Cannabis, MDMA, LSD	Anxiety (all participants)	Clonazepam 2 mg daily	Eight weeks, with six months follow-up	T=0; t=8 weeks; t=6 months: CGI: 5,36→2,5 (p<0,001)→2,1 (p<0,008) SRS: 4,57→2,0 (p<0,001)→2,3(p<0,04) HARS: 20,7→10,6 (p<0,001)→10,21(NS)
Casa & Bosio (2005)[18]	27	22	21 males, 6 females	Unknown	Unknown	Levetiracetam 1500 mg daily	One year	25.9% full recovery after 15 days 74.1% free from flashbacks after 1 year

Abbreviations: CGI = Clinical Global Impressions Scale, HARS = Hamilton Anxiety Rating Scale, SRS = self-report scale, NS = nonsignificant.

Table 2.
Pharmacological Treatment of HPPD: Case Descriptions and Case Series

Reference	Age (Years)	Gender	Illicit Substances Used	Comorbidity	Medication Prescribed	Outcome
Abraham & Mamen (1996)[19]	18	Female	LSD	Unknown	Risperidone 3 mg daily	Aggravation
Abraham & Mamen (1996)[19]	22	Male	LSD	Unknown	Risperidone 6 mg daily	Aggravation
Abraham & Mamen (1996)[19]	40	Male	LSD	Anxiety and depression	Chlorpromazine, risperidone 1 mg twice daily	Aggravation on risperidone, partial recovery on chlorpromazine
Lerner et al. (1997)[20]	24	Male	LSD	Unknown	Benzodiazepines, antidepressants, naltrexone 50 mg daily	Partial recovery on naltrexone
Lerner et al. (1997)[20]	22	Male	LSD, MDMA	Anxiety	Benzodiazepines, naltrexone 50 mg daily	Partial recovery on naltrexone
Morehead (1997)[21]	21	Female	LSD, cannabis, polysubstance	ADHD, anxiety, dysphoria	Benzodiazepines, sertraline, risperidone 0.5 mg twice daily	Aggravation on risperidone, partial recovery on benzodiazepines
Young (1997)[22]	22	Male	LSD	Depression	Sertraline 100 mg daily	Full recovery
Lerner et al. (1998)[23]	25	Male	Benzodiazepines, MDMA, LSD, cannabis	Anxiety	Clonidine 0.025 mg three times daily	Full recovery
Aldurra & Crayton (2001)[24]	17	Male	LSD	Suicidality	Haloperidol 1 mg twice daily risperidone 2 mg daily fluoxetine 20 mg daily olanzapine 15 mg daily	Refractory on haloperidol, aggravation on risperidone, partial recovery on fluoxetine with olanzapine
Lerner et al. (2001)[25]	24	Male	Cannabis, MDMA, LSD	Unknown	Clonazepam 1 mg twice daily	Partial recovery
Lerner et al. (2001)[25]	22	Male	Cannabis	Panic attacks	Oxazepam 30 mg daily, clonazepam 0.5 mg twice daily	Full recovery on clonazepam
Lerner et al. (2003)[17]	26	Male	Cannabis, MDMA, LSD	Depression	Fluoxetine 20 mg daily, paroxetine 20 mg daily, reboxetine 8 mg daily	Full recovery on reboxetine
Gaillard & Borruat (2003)[26]	41	Male	LSD, alcohol	Panic attacks	Valproic acid 1500 mg daily	Full recovery
Espiard et al. (2005)[27]	18	Male	Cannabis, psilocybin	Dysphoria, social anxiety	Amisulpride 100 mg daily, olanzapine 5 mg daily, sertraline 150 mg daily, risperidone	Full recovery on sertraline and risperidone

(Continued)

Table 2.
Continued

Reference	Age (Years)	Gender	Illicit Substances Used	Comorbidity	Medication Prescribed	Outcome
Hermle et al. (2012)[28]	33	Female	LSD, cannabis, MDMA, psilocybin, ketamine	Depressive disorder, anxiety disorder	Sertraline 200 mg daily, citalopram 30 mg daily, fluoxetine 20 mg daily, risperidone 1 mg daily, lamotrigine 200 mg daily	Partial recovery on lamotrigine
Hanck & Schellekens (2013)[29]	23	Male	MDMA	Anxiety, depression	Citalopram 20 mg daily	Partial recovery
Hermle et al. (2013)[30]	17	Male	LSD, alcohol, cannabis	Anxiety	Lamotrigine 200 mg daily, clonidine 0.025 mg twice daily	Partial recovery
Sullivan (2013)[31]	21	Male	Cannabis, alcohol, ayahuasca	Depression	Clonidine carbidopa/levodopa	Partial recovery
Lerner et al. (2014)[32]	26	Male	Cannabis, synthetic cannabis	Panic attacks	Clonazepam 1 mg twice daily	Partial recovery
Lerner et al. (2014)[32]	24	Male	Cannabis, synthetic cannabis	Panic attacks	Diazepam, clonazepam 1 mg twice daily	Partial recovery
Neven & Blom (2014)[33]	39	Male	LSD, amphetamine, cocaine, cannabis	ADHD, borderline personality disorder, depressive disorder	Flupentixol, quetiapine, clozapine with either valproic acid or lamotrigine, trazodone, fluvoxamine, benzodiazepines	Treatment refractory
Subr amanian & Doran (2014)[34]	38	Female	LSD, cannabis, cocaine, MDMA	Panic attacks	Alprazolam, risperidone 0.5 mg daily	Partial recovery on risperidone
Brodrick & Mitchell (2016)[35]	30	Male	LSD, phencyclidine, cocaine	Depression, bipolar disorder	Citalopram 40 mg daily, lamotrigine 50 mg daily, mirtazapine 15 mg daily	Treatment refractory
Stanciu & Penders (2016)[36]	24	Male	2C-E	Bipolar II disorder	Benzodiazepines, SSRIs, antipsychotics, lamotrigine	Partial recovery on benzodiazepines and lamotrigine
Coppola & Mondola (2017)[37]	18	Male	Cannabis	None	Clonazepam 6 mg daily, JWH-122 (cannabidiol-1 receptor agonist)	Partial recovery

(Continued)

Table 2.
Continued

Reference	Age (Years)	Gender	Illicit Substances Used	Comorbidity	Medication Prescribed	Outcome
Anderson et al. (2018)[38]	27	Female	MDMA, amphetamine, cannabis	Epilepsy, schizophrenia, depression, anxiety	Risperidone, lamotrigine 100 mg daily	Full recovery on lamotrigine
Skryabin et al. (2018)[39]	27	Male	MDMA, alcohol	Anxiety, depression	Amitriptyline 25 mg daily, tofisopam 150 mg daily with lamotrigine 200 mg daily and sertraline 50 mg daily	Refractory on amitriptyline, partial recovery on tofisopam, lamotrigine, and sertraline
Skryabin et al. (2018)[39]	31	Male	Alcohol, cannabis, LSD	Depression	Tofisopam 150 mg daily with lamotrigine 200 mg daily and sertraline 100 mg daily	Partial recovery
Kurtom et al. (2019)[40]	21	Male	LSD, cannabis	None	Clonazepam 1 mg daily	Full recovery
Rymowicz & Tsuang (2021)[41]	20	Male	Dextromethorphan	Unknown	Antipsychotics, lamotrigine with clonazepam	Partial recovery on lamotrigine and clonazepam
Ford et al. (2022)[5]	33	Male	LSD	Unknown	SSRIs, SNRIs	Partial recovery
Ford et al. (2022)[5]	25	Male	Psilocybin, synthetic cannabis	Unknown	Benzodiazepines	Full recovery
Ford et al. (2022)[5]	34	Male	MDMA, LSD, cannabis, cocaine, psilocybin	Unknown	Lamotrigine, lorazepam, clonazepam, escitalopram	Partial recovery
Ayyub et al. (2023)[42]	28	Male	LSD, cannabis	ADD, anxiety, bipolar disorder, depression, PTSD, schizophrenia/schizoaffective disorder	Lamotrigine 50 mg daily	Partial recovery
Christensen et al. (2023)[43]	37	Male	LSD, cannabis, cocaine, methamphetamine, alcohol	PTSD, depression, suicidality	Clonazepam 0.5 mg three times daily, ziprasidone 40 mg twice daily, bupropion 300 mg daily, clonazepam 0.5 mg twice daily, naltrexone 50 mg daily with lamotrigine 200 mg twice daily	Partial recovery on naltrexone and lamotrigine, full recovery on clonazepam
Ryan & Kulkarni (2023)[44]	22	Male	Ketamine, MDMA, laughing gas	Depressive disorder	Antidepressants, clonidine, lamotrigine, lurasidone, clonazepam, onabotulinumtoxinA	Partial recovery on TCA, clonazepam, and onabotulinumtoxinA

Abbreviations: ADD = attention deficit disorder, ADHD = attention-deficit/hyperactivity disorder, PTSD = posttraumatic stress disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

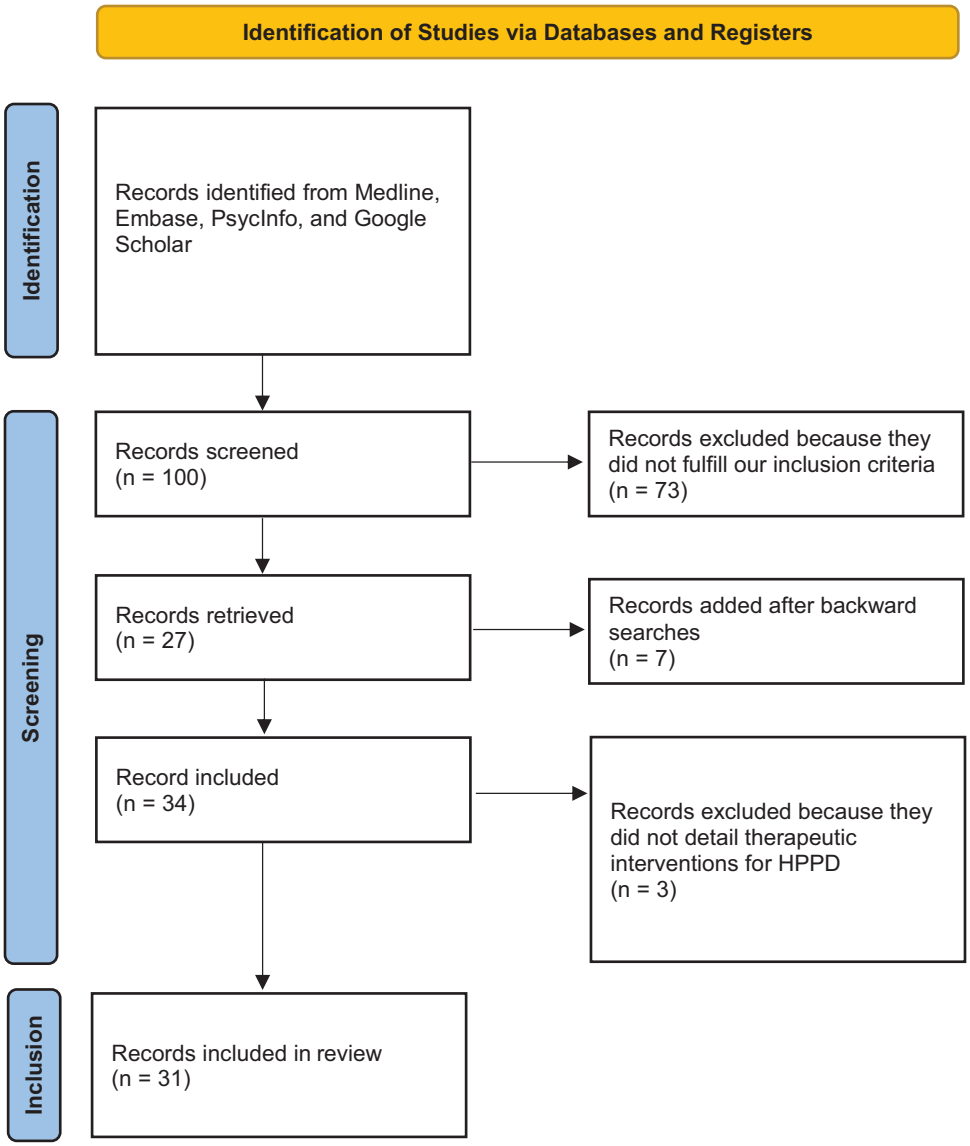

Figure 1. PRISMA flow diagram.[45]

inclusion criteria. Cross-referencing yielded 7 more studies. Following full examination of the remaining 34 articles, another 3 were excluded because they did not discuss HPPD or lacked a description of pharmacological interventions. Thus, we arrived at a total number of 31 articles for review, describing 87 unique individuals. 51 participants were involved in observational studies (Table 1) and 36 in case series and case reports (Table 2). Figure 1 depicts a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Observational Studies

We found three relevant observational studies (Table 1). The first, by Lerner and colleagues,[16] reports on eight people meeting *DSM-IV* HPPD criteria who had refrained from substance use for three months. They were all given three doses of 0.025 mg clonidine a day. The effects were evaluated weekly via the Clinical Global Impressions (CGI) Scale,[46] a clinician-rated tool with scores from 1–7 to assess illness severity. Additionally, participants filled out a self-report assessment with scores 1–5 ranging from "no symptoms" to "severe symptoms." Two people dropped out during the study. On average, the remaining six showed reduction in clinician-rated CGI scores from 5.25 to 2.5 within two months, and reduction in participant-rated scores from 4 to 2. The duration of follow-up was not given. The authors concluded that clonidine may help reduce HPPD severity.

The second observational study, carried out by the same group, describes 16 individuals with HPPD diagnosed in accordance with *DSM-IV* criteria.[16,47] Participants had all been taking multiple substances, such as MDMA, cannabis, and LSD; all held the latter agent responsible for their HPPD symptoms. Prior to study onset, all participants had been treated with benzodiazepines, which was either

insufficiently effective or generated too many side effects. In the study, they were subsequently treated with a daily dose of 2 mg clonazepam. Medication response was evaluated via the clinician-rated CGI and the Hamilton Anxiety Rating Scale (HARS),[48] as well as a participant-rated scale. During the two-month treatment period, 2 participants dropped out, while the remaining 14 showed significant improvement on all three scales. By the end of the six-month follow-up period, CGI and self-report scores again showed significant symptom reduction. HARS scores, however, did not, prompting the authors to conclude that clonazepam may be effective for HPPD treatment. The third observational study,[18] published as a poster abstract, reports on 27 people with HPPD who had been treated with 1,500 mg of levetiracetam every day for a year. During this period, flashback frequency was assessed. Fifteen days into the regimen, 26% of participants remained free from flashbacks. This percentage increased to 74% at 12-month follow-up, with only 11% reporting no improvement. Since there was no attrition and levetiracetam was well-tolerated, the authors concluded (conservatively) that levetiracetam may be effective for HPPD treatment.

Case Series and Case Descriptions

The 28-case series/case reports described a total of 36 people diagnosed with HPPD. Of these, five were female (14%) with a mean age of 26 years (Table 2). In this group, 23 had been using LSD (64%), 20 cannabis (56%), 11 MDMA (31%), 5 cocaine (14%), 3 psilocybin (8%), 2 ketamine (6%), 1 ayahuasca (3%), 1 4-ethyl-2, 5-dimethoxy-β-phenethylamine (2C-E) (3%), and 1 dextromethorphan (3%). Note that a substantial number of participants used multiple substances. The participants were treated with medicines from seven different groups, including: (1) antipsychotics (risperidone, chlorpromazine, haloperidol, flupentixol, ziprasidone, lurasidone, olanzapine, quetiapine, amisulpride, or clozapine); (2) benzodiazepines (lorazepam, clonazepam, oxazepam, diazepam, or tofisopam); (3) antidepressants (sertraline, fluoxetine, paroxetine, reboxetine, citalopram, escitalopram, trazodone, mirtazapine, bupropion, or amitriptyline); (4) an opioid antagonist (naltrexone); (5) an alpha-2-adrenergic agonist (clonidine); (6) antiepileptics (valproic acid or lamotrigine), and an (7) antiparkinson agent (levodopa). Of the 36 people described, 10 (28%) showed full recovery and 22 (61%) partial recovery. Two participants (6%) reported no effects from their medications and 2 others (6%) reported symptom aggravation. Those who recovered fully used benzodiazepines (clonazepam, n=3), an antiepileptic (valproic acid or lamotrigine, n=2), an antidepressant (sertraline or reboxetine, n=2), clonidine (n=1), or the antipsychotic risperidone (n=1). It is noteworthy, however, that five other papers reported symptom aggravation with risperidone. Partial improvement was obtained with benzodiazepines (n=6 for clonazepam, n=2 for tofisopam, n=1 for diazepam, n=1 for lorazepam), antiepileptics (n=9 for lamotrigine), antipsychotics (chlorpromazine, olanzapine, risperidone), antidepressants (fluoxetine, citalopram, escitalopram, sertraline), an opioid antagonist (n=3 for naltrexone), and an alpha-2-adrenergic agonist (clonidine). In some cases, a combination of medicines were prescribed, rendering it impossible to tell which was effective. And in certain situations, the primary aim of administering these medications was to treat comorbid conditions such as anxiety or depression.

DISCUSSION

Our analysis revealed that a variety of pharmacological agents were beneficial for treating HPPD, but statistically significant results could not be obtained due to the small number of participants, lack of randomized placebo-controlled trials, and breadth of medicines prescribed. That said, the potentially effective agents described in the three observational studies fell into the benzodiazepine, antiepileptic, and alpha agonist groups. In the smaller studies, benzodiazepines, antiepileptics, and antidepressants were most effective; the large majority of individual medicines from these groups promote (either partial or full) recovery. The reasons for choosing a particular pharmacological agent were largely unclear in the studies. Even when the choice of a certain agent seemed inspired by a comorbid condition, this rationale was rarely made explicit. Although, this course seems wise given our findings that people with HPPD and a comorbid anxiety or mood disorder tend to have worse outcomes, prompting our recommendation to simultaneously treat any comorbid condition.[7]

Comparison with Previous Reviews

Our findings partially align with prior reviews. Based on their case series, as well as 24 previously published articles, Ford and colleagues[5] found that full HPPD recovery was only obtained with benzodiazepines and partial recovery with antiepileptics in combination with benzodiazepines. Another review by Doyle and colleagues[4] assessed 16 published articles. They noted partial success with an array of pharmacological agents, including benzodiazepines, alpha-2-adrenergic agonists, antidepressants, second-generation antipsychotics, antiepileptics, and opioid antagonists.[4] An earlier review by Martinotti and colleagues[3] was also based on 16 articles. The authors mentioned efficacy for an even wider range of pharmacological agents and recommended combining several different medications to treat HPPD and any underlying or new comorbid disorders. In an even earlier study based on 15 publications, Orsolini and colleagues[2] offered a nuanced analysis of different pharmacological agents used in clinical practice for HPPD treatment. They formulated hypotheses on possible working mechanisms, without, however, providing a clear answer as to which compounds may be superior in specific circumstances.

A complicating factor in all of the studies, including the present one, is a lack of knowledge about the natural course of HPPD. As a consequence, it remains unclear how HPPD symptoms develop without pharmacological intervention. Additionally, none of the studies included a control group, and the case series and case reports rarely used questionnaires or other assessment tools. Due to such limitations, it is difficult to extrapolate precise information on pharmacological treatment effectiveness. Before delving further into implications for clinical practice and future research, we provide some historical context.

Historical Aspects

HPPD was introduced as a diagnostic category in the *DSM-III-R* under the name post-hallucinogen perception disorder barely 25 years after the first reports of delayed and prolonged adverse reactions to LSD use.[49–52] Such reactions had already been described in the 19th century. For example, the English physician Havelock Ellis noted symptoms in the context of mescaline use.[53,54] It may indeed be true that by chronicling the prolonged sensitization to the color blue and the lingering sense of derealization Ellis described HPPD *avant la lettre*. It was not until the 1950s, however, that the first recognizable case descriptions were published. Their appearance in high-ranking journals such as *The Lancet* and the *American Journal of Psychiatry* likely reflected the broad fascination with this enigmatic condition. At the time, serious reports of therapeutic LSD use in therapy sessions and other controlled environments were outnumbered by sensationalist texts about recreational hallucinogen use by "consciousness expanders, bohemians, college students, and artists," which often involved multiple exposures to substances of varying quality.[50–52,55] During those early years, adverse hallucinogen effects were primarily attributed to: (1) unsupervised use, (2) multiple drug exposures, and (3) premorbid personality traits.[55] As to the pathophysiology of delayed reactions, early hypotheses centered on premorbid personalities, a toxic effect on the brain, and a toxic effect on the retina.[55] The latter possibility was soon ruled out in experiments among blind people (some of whom had undergone bilateral enucleation) who experienced the same visual effects as sighted people while using LSD.[56]

By 1967, adverse hallucinogen reactions had been described in 21 scientific studies composed of 225 unique individuals.[57] Nevertheless, scientists were still unclear about the nature and origins of these reactions. In an attempt to create order, various classifications were drawn up, including categories like psychosis, mood swings, suicidality, regression to childish behavior, psychopathic behavior, and many other groupings.[51,58] In retrospect, only a fraction of these categories comply with what we now deem HPPD. For example, within the group of 225 people Smart and Bateman[57] analyzed in their 1967 review, 142 had a so-called delayed reaction, but only 11 (8%) had a "spontaneous recurrence." It was not until 1969 that the latter phenomenon was coined a flashback. The term post-hallucinogen perception disorder was not introduced until 1987. It was then changed to HPPD in 2000.[49,59–61]

Notably, the distinctions between Type 1 and Type 2 HPPD were only proposed around 2014, and with it the distinction between flashbacks (as relatively brief phenomena) and longer-lasting or permanent phenomena—what we call reperceptions.[12] Curiously, the aforementioned studies from the 1950s and 60s (including one large-scale study of some 10,000 individuals who received LSD in psychotherapeutic contexts) did not describe any long-lasting phenomena. Though it is tempting to attribute this possible omission to researchers' relative unfamiliarity with hallucinogens or to a lack of attention to chronic reperceptions, the reason is largely unknown. Additionally, until quite recently, flashbacks or reperceptions experienced in HPPD contexts were habitually designated hallucinations even though early authors singled out numerous phenomena that fit the sensory distortion description. For example, in 1955 Cooper[51] reported on people who experienced objects changing shape, their bodies appearing smaller, a subjective swelling of the hands, and unreliable time judgments. Such phenomena are now deemed characteristic of Alice in Wonderland syndrome, and a recent systematic review reported that these experiences make up 76% of HPPD symptoms.[7]

Comparison with Alice in Wonderland syndrome

In light of the substantial phenomenological overlap between HPPD and Alice in Wonderland syndrome, a comparison may teach us something about HPPD and, in particular, its treatment. Alice in Wonderland syndrome is characterized by sensory distortions, which differ conceptually, phenomenologically, and pathophysiologically from hallucinations and illusions.[8] Well-known examples of such distortions are micropsia (seeing things smaller than they are), macropsia (seeing things larger), plagiopsia (seeing vertical lines as slanted), and prosopometamorphopsia (seeing distortions exclusively in human faces). In addition to visual distortions, people with Alice in Wonderland syndrome may also experience distortions in other sensory modalities, derealization, and/or depersonalization.[9] These phenomena can be caused by conditions belonging to eight etiological categories: (1) encephalitis, (2) migraines, (3) epilepsy, (4) central nervous system lesions, (5) peripheral nervous system lesions, (6) psychiatric disorders, (7) medications, and (8) illicit substances.[8] A recent lesion-mapping study demonstrated that brain lesions in Alice in Wonderland syndrome are scattered throughout the brain, as expected with such a heterogeneous condition. 85% of these lesions, however, show increased connectivity with two brain areas that play important roles in size and bodily perception.[62] Thus, there is also coherence at the pathophysiological level, justifying use of the term syndrome. Future research is needed to establish whether something similar holds true for HPPD.

As to treatment, there are no evidence-based guidelines for Alice in Wonderland syndrome. Although, in clinical practice positive results are often reported for pharmacological treatment of underlying disorders.[8] Thus, encephalitis can be successfully treated with antibiotics or virostatic agents, epilepsy and migraines with antiepileptics, and so on. An exception is treatment with rivastigmine or other cholinesterase inhibitors, which, in clinical practice, may prove effective even in the absence of neurocognitive disorders. This exception may be due to acetylcholine's important role in perception; these medicines help restore an imbalance in this neurotransmitter system.[8] As we've outlined, HPPD is also treated with an array of pharmacological interventions, but they are rarely aimed at the neurotransmitter systems targeted by the illicit substances used. Since the various recreational drugs that can cause HPPD affect the brain via different neurotransmitter systems, it is possible that microlesions or functional aberrations arise in different systems. Therefore, tailored treatment should be aimed at the relevant system. While this hypothesis needs empirical testing, theoretically, it could explain why the success rates of many medicines vary so widely.

Implications for Clinical Practice

Although our findings do not allow for an evidence-based treatment protocol, we conclude that the following interventions may be beneficial to people with HPPD. First, HPPD deserves greater recognition among health professionals and the general population—similar to Alice in Wonderland syndrome. Such recognition will likely lead to earlier diagnosis and treatment and improved diagnostic procedures. To facilitate the latter, we recommend taking the full spectrum of potential HPPD symptoms into account, including the numerous sensory distortions characteristic of Alice in Wonderland syndrome. When there is need for treatment with mild symptoms (brief, without comorbidity or substantial burdening), it may suffice to offer psychoeducation, reassurance, and advice to remain abstinent of the suspected symptom-inducing substance. (See Text Box 2 for a summary of proposed interventions.) In cases with substantial burden, where psychoeducation and other nonpharmacological interventions have proven ineffective, we propose pharmacological treatment of any comorbid disorders (e.g., anxiety disorders or mood disorders) in accordance with existing treatment guidelines and protocols. If this course also proves ineffective, we propose off-label use of benzodiazepines, antidepressants, antiepileptics, or alpha agonists despite the limited scientific evidence of their effectiveness for HPPD treatment. If this method is unsuccessful, it is important to taper off the prescribed medication, and switch to a pharmacological agent from one of the other groups. For those with LSD-related HPPD, as well as those with high addiction sensitivity, we urge reticence with benzodiazepine treatment given Lerner and colleagues'[17] negative findings and the fact that benzodiazepines can be highly addictive. Based on our review, we recommend an antidepressant (especially with comorbid depression) or an antiepileptic in such cases. We also believe that the efficacy of off-label cholinesterase inhibitors is worth investigating. These agents tend to generate few side effects or interactions and do not promote addiction. Finally, given case descriptions of risperidone-induced aggravation of HPPD symptoms, moderation with this medication appears prudent.

Text Box 2.

Practice-Based Advice for HPPD Treatment

- Provide psychoeducation.
- Promote substance-use abstinence.
- Give practical advice regarding use of colored glasses, background color on one's computer/mobile phone/tablet, the need to focus on engaging tasks in the outside world, and general lifestyle factors (e.g., food, sleep, exercise).
- Treat comorbid disorders, such as anxiety and mood disorders.
- Prescribe a benzodiazepine, antiepileptic, antidepressant, or alpha agonist (off-label).
- When ineffective, switch to a pharmacological agent from one of the other groups.
- Avoid benzodiazepines in cases of HPPD after LSD use.
- Avoid benzodiazepines in cases of addiction sensitivity.

Limitations

An important limitation of this study is the lack of randomized, placebo-controlled studies, the relatively small number of evaluated treatment options, the breadth of pharmacological agents prescribed, and the heterogeneity of the included studies, with sometimes considerable differences in design, diagnostic instruments and criteria, study duration, effect evaluation, and follow-up. We initially aimed to develop a practice-based treatment algorithm, but given these limitations, even ranking the efficacy of the various medicines prescribed was unattainable. Despite such restrictions, our review yielded predominantly positive effects for pharmacological HPPD treatment. In addition to indicating possible involvement of diverging neurotransmitter systems, our findings may also point to (1) a placebo effect, (2) a primary effect on any comorbid disorder(s), (3) an underappreciated effect of psychoeducation and psychosocial interventions, (4) an underappreciation of the disorder's natural course, and (5) publication bias. (Studies reporting favorable outcomes are more readily published than those documenting no or negative results.) Another important limitation is the lack of studies on the natural course of HPPD, the *sine qua non* for any effect study. Last, there is substantial phenomenological overlap between HPPD and Alice in Wonderland

syndrome, a condition associated with numerous underlying organic causes (most prominently migraine and epilepsy). The presence of this syndrome, however, was only rarely assessed in the reviewed studies.

CONCLUSION

Our systematic review leads us to conclude that a single, effective therapeutic cannot be singled out for HPPD treatment. Case studies and small case series, however, point to potentially favorable effects of benzodiazepines, antiepileptics, antidepressants, and alpha agonists. Further research is needed to chart the natural course of HPPD and assess the effects of various medication groups in the HPPD subtypes caused by substances with diverging effects on different neurotransmitter systems.

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