

REVIEW

Adverse consequences of lysergic acid diethylamide

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Abstract

The continued endemic use of hallucinogenic drugs, and of LSD in particular, raises concern regarding their short and long term adverse consequences. The epidemiology of LSD abuse is reviewed suggesting an increase in LSD use among the young as the prevalence rates for other substances continues to fall. Evidence supports the association of LSD use with panic reactions, prolonged schizoaffective psychoses and post-hallucinogen perceptual disorder, the latter being present continually for as long as 5 years. Evidence does not support claims of genetic disorders arising from hallucinogens. In light of the foregoing, current data confirm earlier findings of long lasting psychopathology arising in vulnerable individuals from the use of LSD. A hypothetical long term molecular mechanism of adverse effects is proposed.

Introduction

This review addresses clinical and neuropharmacological reports on lysergic acid diethylamide (LSD). First discovered by Hofmann in 1943, it was Condrau who first noted the drug's ability to alter perceptions and mood in the presence of an unaltered sensorium, in distinction to other agents such as heavy metals, bromine, cardiac glycosides, and anticholinergics, each of which may cause hallucinations, but usually in the context of a toxic delirium.¹

While epidemiological surveys report a decline in use of the majority of classes of abusable substances in recent years, major hallucinogenic drugs, predominantly LSD, have maintained a

steady, somewhat increasing trend in the past decade. In 1990 7.6% of the total US population had used a hallucinogenic drug at some time in their lives,² 5.5% of a US household population age 12 and over reported LSD use, about 3% have used mescaline, psilocybin or PCP and 1% peyote.³ Epidemiological evidence supports the clinical perception that hallucinogen users tend to be the disaffected, Caucasian, male offspring of white collar workers.⁴ There is a positive correlation with years of completed education and also greater prevalence in the metropolitan areas of the Northeastern and Western parts of the US.

Acute effects

The first use of LSD, an accidental ingestion in a laboratory, is described by Hofmann.⁵ Duration and degree of intoxication both increase with dose.⁶ The drug passes the blood-brain barrier readily, and exerts its psychological

Supported in part by USPHS grant R01 DA07120-01A2 to H. D. Abraham.

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effects at a concentration of 0.5 ng per gm of brain tissue. The drug has a biological half life in macaque plasma of 100 minutes, while its psychophysiological effects may extend from 6 to 12 hours. Symptoms correspond to signs of sympathetic arousal: increased pulse and blood pressure, dilated pupils, piloerection, hyperreflexia and slight pyrexia. Following this there is a period of increasingly intense perceptual distortion. Hallucinations can occur in any sensory modality, the most common being visual and the least common auditory. Delusions are uncommon. Orientation and cognition tend to be preserved. The perception of the passage of time is often distorted. Synesthesia, the blending of sensory modalities, while prevalent in the literature, is unusual in our clinical experience. Affective changes are profound and often take the form of an exaggeration of pre-existing mood. In many instances they are experienced as positive. The feelings of terror and depression described by Hofmann, which characterize the 'bad trip', appear in emergency rooms as drug casualties. Gradually the intensity of these effects declines, their total duration of action being between 6 and 12 hours.

There is great variation in the response to LSD both between individuals and in the same individual at different times. This is related in part to the instructional set, setting,⁷ and personality of the individual. Following multiple doses tolerance ('Gewöhnung') develops.^{8,9} Cross tolerance also is seen between LSD, psilocybin and mescaline.^{10,11} There is no evidence of a withdrawal syndrome from LSD.¹²

Acute LSD intoxication commonly presents to the emergency room as a 'bad trip'. In this instance the diagnosis is fairly straight forward: the patient, or accompanying friends, are able to give a history of ingestion, features of the LSD intoxication described above are present, usually accompanied by panic or dysphoria.

It is important to take a careful history, even in cases where the diagnosis appears evident, as illicit drugs are frequently mislabeled or misidentified. A description of the substance must be elicited; LSD is often supplied absorbed on small squares of paper, 'blotter acid' (frequently printed with fanciful 'new age' designs) occasionally in sugar cubes, aspirin tablets or dissolved in water or alcohol. The mode of administration is almost invariably oral, ocular and intravenous routes being rare. LSD is never

smoked. A history of a smoked hallucinogen should suggest phencyclidine (PCP). Ancillary factors, such as the effect of the substance on other users, the sophistication of the historian and the time of ingestion are also important.

Commonly, substances sold as 'LSD', 'mescaline' or 'psilocybin', when they include an active ingredient, contain LSD but are adulterated. Stated quantities are similarly inaccurate. Differentiation between LSD-like hallucinogens in an emergency setting is of academic interest, since they produce similar syndromes requiring identical management. This is not the case when PCP is suspected, and in which treatment is significantly different.¹³

The clinical picture of LSD intoxication may be difficult to diagnose when only part of the history is available. The history of ingestion may be absent when the patient is uncooperative, or in cases of accidental ingestion or deliberate poisoning. In these instances blood and urine toxicology may clarify the situation in retrospect.¹⁴ Unfortunately results are seldom available within the time frame of intoxication. The pattern may also be complicated by the presence of other drugs or concurrent mental illness.

The palm test, devised by one of the authors (HDA), is useful in rapidly differentiating LSD from PCP ingestion in the emergency room. Here the physician displays his open hand to the patient, at a distance of about 18 inches, and asks for a description of the colors seen in its palm. The LSD hallucinator may appear pleased by the question, and commonly describe multiple colors and imagery. This is in distinction to the PCP ingestor, on the other hand, who tends to react to the test with a labile affect and aggressive behavior. Snarling or attempted biting are not uncommon, yielding a useful diagnostic sign. Contemporary toxicology now makes it possible to test the validity of this simple maneuver.

The management of LSD toxicity historically involved the use of neuroleptics or emergency psychotherapy lasting 4 or more hours ('talking down'). It is now recognized that the former may intensify the experience (particularly if PCP has been ingested), and while talking down may be effective, it is a process which is not always conducive to the emergency room. On the other hand, in our clinical experience diazepam 20 mg by mouth is effective within 30 minutes, and is

to be considered the treatment of choice. There is no controlled clinical trial of this treatment as yet.

Prolonged psychoses

In 1960 Cohen described reports of complications from 44 investigators of LSD therapy.¹⁵ Eight cases of prolonged psychosis were described among 25 000 doses given to 5000 recipients of the drug, with an incidence of 0.18% for patients undergoing LSD therapy, and 0.08% for experimental subjects. Geert-Jørgenson *et al.* concluded following 3 years' use of LSD in 129 patients that "complications have been so few it seems absurd to tabulate them," (adding their cohort suffered two suicides, four parasuicides, one homicide, and several with "after-effects ... involving no particular inconvenience.")¹⁶ A similarly benign note was sounded by Levine & Ludwig in the same year who wrote that "It would seem that the incidence statistics better support a statement that the drug is exceptionally safe rather than dangerous."¹⁷

Since then incidence data have accrued in a number of studies regarding the likelihood of psychosis following LSD, at least eight of which report observations of LSD administered in clinical settings. Opitz described two patients among 66 who underwent LSD therapy and developed prolonged psychotic reactions.¹⁸ In a study in which the drug was given to psychotic subjects, Fink *et al.* found that 3 of 65 subjects given LSD developed prolonged psychoses for up to 3 months, characterized by disturbances in mood, affect and thought. Premorbidly this sample of patients had been hospitalized for a mean of 5.1 years, had a mean duration of illness of 14.6 years, and were treatment refractory. Most of the psychotic patients expressed displeasure with the experience. Patients with prolonged reactions suffered labile moods, including mania and depression, and an aggressive suicide attempt. These workers concluded, "The hazard of LSD administration appears not to be in the precipitation of a schizophrenic-like state, but rather in decreasing emotional and affective controls and inducing a persistent state of altered consciousness."¹⁹

Leuner described 3 of 82 subjects in LSD therapy suffering prolonged psychoses.²⁰ Malleon surveyed 73 physicians in the UK who had used LSD in patients. Psychosis lasting for

more than 48 hours occurred at a rate of 9 per thousand.²¹ Baker reported 4 out of 150 patients with prolonged psychoses following LSD therapy.²² And McFarling reported a delayed psychosis only once in 281 LSD recipients in US Army experiments which the author doubted was related to the drug.²³ All told, these workers concluded the incidence of prolonged psychosis following LSD in clinical settings falls in a range of 0.08–4.6%, with a median of 2.7%. It is also noteworthy that the lowest two figures are derived from experimental subjects, whereas all others are from clinical populations.

Smart & Bateman reviewed 225 reports of adverse reactions, among which were 142 (63%) cases of prolonged psychotic reactions, noted with paranoid delusions, hallucinations, and fear, 19% of these took the LSD in supervised settings.²⁴ They concluded that the rates of pre-LSD psychosis in LSD users was higher than the general population, but that LSD was precipitating prolonged psychoses in otherwise normal individuals. Most noteworthy was that 30–50% of cases became psychotic after a single dose, suggesting a peculiar vulnerability to the drug in certain individuals.

Tietz reported that of 49 patients admitted to a county hospital as a result of LSD, 57% had extended psychoses.²⁵ A study of 25 patients seen in the emergency ward of the Kings County Hospital for LSD related disorders reported that 60% had diagnoses falling within the schizophrenic spectrum. Two of 13 admissions had prolonged psychotic reactions.²⁶ Sanborn & Daniels reviewed 53 medical records of LSD related psychiatric admissions. The largest category of diagnosis at discharge was for LSD psychosis (42%).²⁷ Abruzzi summarized 136 patrons at rock festivals who presented for treatment of an acute adverse reaction to LSD, and found that 18% continued to have psychotic residua at 1 year.²⁸ And Abraham described a sample of 105 users of LSD from a psychiatric outpatient department, 23% of which had diagnoses of schizophrenia, compared to 12% of the usual clinic prevalence.²⁹

Seventy-five case reports of post LSD psychosis from 16 separate clinical observers yield a number of common features of syndromic significance.^{18–33} Commonest symptoms reported included mood swings, visual hallucinations, mania, grandiosity, and religiosity best conforming to diagnoses of hallucinogen mood, hallucinogen

delusion, schizoaffective and atypical psychotic disorders using DSM-III-R nomenclature. The most commonly effective treatments were ECT and lithium.

The confounding of these findings with prior psychopathology has been observed in many, but not all, cases of psychosis following LSD. In a survey of drug reactions in New York County, 77% of LSD psychoses were not predictable from previous psychotic disturbances.³⁰ Ungerleider *et al.* reported that 27 of 70 patients with mixed adverse LSD reactions had previous psychiatric treatment, including 25 who had prior diagnoses of psychosis.³¹ Robbins found that 8 of 11 patients with prolonged psychosis following LSD had been psychotic prior to use.

In a study of 47 subjects who had ingested a hallucinogen within 48 hours of admission, 50% had a previous admission for psychosis, and 92% were currently admitted for psychosis following use of the drug. At discharge 68% carried a diagnosis of schizophrenia.³² Frosch found that many, but not all, patients with LSD psychoses had prior histories of psychosis.³³ Kornblith summarized three studies which showed that previous psychiatric treatment in hospitalized LSD psychotics occurred from 37 to 49% of the time.³⁴

Case controlled experimental studies have likewise yielded mixed results attesting to an association between LSD use and psychosis. In an MMPI study of users and non-users Smart & Jones³⁵ found significant elevations in the LSD group on the schizophrenia, mania and psychopathic deviance scales.

Breakey *et al.*³⁶ interviewed two groups of schizophrenic patients and a group of normal volunteers matched for age and sex. The patients comprised 26 users of drugs prior to their first psychotic illness, and 14 schizophrenics with no drug histories. Schizophrenic drug users had healthier premorbid personalities than non-drug users, but abnormal ones when compared to non-psychotic controls. Moreover, the age of onset of psychosis was earlier by 4 years in the drug users, as was the age of first admission. The drugs most commonly used in this sample were hallucinogens.

Bowers studied 12 patients developing an acute psychosis 2-7 days following LSD use, by comparing them to 26 acute psychotics with negative drug histories. The LSD group had better scores on a scale for prognosis in

schizophrenia, but a younger age for the onset of psychosis, and a briefer period of onset.³⁷ These subjects also showed a decrease in CSF 5-HIAA, a serotonin metabolite.³⁸ A 2-6 year follow-up study of 15 patients with LSD psychosis found that two had committed suicide, and half had improved. He suggested that LSD might be related to a genetic vulnerability to an illness in the manic-depressive/schizo-affective spectrum, implicating central serotonergic systems.³⁹

Safer found that current substance abusers had statistically higher rates of hospitalization compared to past users and non-users. Among psychotic patients, users of LSD, phencyclidine, or amphetamines had the highest rates.⁴⁰

McLellan & Druley, noting that approximately 50% of psychiatric patients admitted to a VA hospital admitted covert substance abuse, interviewed 279 additional veterans who were being treated for psychiatric, but not primarily substance use, disorders. The hypothesis was that specific psychiatric diagnoses were likely to be linked to the specific drugs of abuse. The findings were that, *inter alia*, 64% of the patients using hallucinogens had diagnoses of schizophrenia, compared to 64% for amphetamines, 45% for alcohol, 41% for heroin, and 22% for barbiturates.⁴¹

In a follow-up study McLellan *et al.* retrospectively compared three groups of drug abusers over a 6-year period for the development of psychopathology in association with three specific classes of agents: psychostimulants, including LSD; sedatives; and narcotics. At the start of the 6-year period there were no measurable differences in psychopathology between the three groups. At the end of the study period, the stimulant group led the other two in measures of schizophrenia, mania, and paranoia.⁴² While this study was not limited to hallucinogens, their association with psychoses developmentally over time were consistent with cross-sectional data reporting the same association.

In 1982 Tsuang *et al.*⁴³ compared 72 hospital records of drug abusers with psychosis to records of drug abusers without psychosis, and schizophrenics without drug abuse. Drug abusers whose psychoses had predated hospitalization by 6 months or longer had greater family risks for schizophrenia and affective disorders than those with psychoses for less than 6 months, which suggested there were several subgroups of drug abusers with psychosis.

Hallucinogens had been abused by 40% of the drug abusers, 58% of the drug abusers with long standing psychosis, and 81% of the drug abusers with psychosis of less than 6 months' duration. This reflected a 67% increase in hallucinogen use by the psychotic group, compared to those abusers without psychosis. Supporting Breakey *et al.*, ages of first onset of psychosis and first hospitalization were significantly earlier for drug abusers than for non-drug abusing schizophrenics. Seven of eight comparisons of subjects with psychosis and drug abuse to subjects with schizophrenia were "consistent with the hypothesis that drug abuse has a precipitating role in the onset of psychotic illness." Why certain individuals are vulnerable to LSD psychosis and others are not is an enduring question.

Post-hallucinogen perceptual disorder

Post-hallucinogen perceptual disorder (PHPD) (was first described by Eisner & Cohen who observed spontaneous recurrences of LSD-like states in subjects days to weeks following cessation of drug use.⁴⁴ Rosenthal described patients suffering from post-drug visual hallucinations lasting as long as 5 months from the time of drug use.⁴⁵ In 1962 Hollister studied a group of 59 experimental subjects receiving hallucinogens. Thirty-nine percent continued to describe visual hallucinations when examined "when the drug experience had cleared."⁴⁶ Robbins, Frosch & Stern noted that flashbacks could occur up to a year after last ingestion, and suggested their basis seemed to be both physiological and psychological.⁴⁷

In a survey of 65 LSD users, Holsten found 50 who described post-LSD disturbances.⁴⁸ One and a half to 4 years later, 35% of the patients still experienced flashbacks, although milder ones. Horowitz presented seven clinical examples of flashbacks, and concluded that they represented perceptual distortions, spontaneous imagery, or recurrent unbidden images.⁴⁹ Shick & Smith described 3 years' experience among LSD users in a clinic with over 50 000 patient visits, and concluded flashbacks were of three types: perceptual; somatic; and emotional.⁵⁰ Anderson & O'Malley suggested flashbacks appeared to be a misnomer, describing a case of continuous, rather than paroxysmal, visual disturbances from LSD.⁵¹

A phenomenological study of 123 LSD users in 1983 described the disorder as being predom-

inantly visual, characterized by altered perceptions lasting from fractions of a second to 5 years in duration.⁵² Symptoms included geometric pseudohallucinations, false fleeting perceptions in the peripheral fields, flashes of color, and positive afterimagery. These visual disorders were stable in half of the sample over a 5-year period, and comprised more enduring phenomena than momentary 'flashes' of previous LSD trips. They were precipitated by emergence into a dark environment, intention, marijuana,⁵³ neuroleptics, and anxiety states. The disorder was considered slowly reversible or irreversible, and could arise from a single LSD ingestion. Benzodiazepines ameliorated, and neuroleptics exacerbated, visual symptoms. The author theorized that these visual disturbances represented a disinhibition of central visual processors brought about in genetically vulnerable persons. A study by Moskowitz found haloperidol reduced hallucinations in seven of eight patients, but noted an exacerbation of flashback symptoms early in treatment.⁵⁴

Two additional studies have shed light on the etiology of post-hallucinogen perceptual disorder. In one, LSD users were observed to need a larger stimulus than LSD naive controls in identifying the white color of a test object in a bright yellow surround.⁵⁵ It was suggested that as the LSD user's eye scanned the field saccadically, the fovea was stimulated by the yellow background, and when gaze fixated on the white test object, the yellow visual signal failed to be inhibited. This hypothesis was then tested psychophysically in a second population of users and controls. In this study past LSD users had decreased critical flicker fusion thresholds, particularly in peripheral fields, suggesting that once a square wave stimulus was perceived, its termination in the environment tended not to be recognized, as if visual information once again was not being physiologically inhibited. Similarly, LSD users had abnormal dark adaptation curves, requiring more than three times as much light to see a test flash than controls. This observation was consistent with the hypothesis that a pre-adaptive exposure to light continued to be processed centrally once the subject was in the dark, creating an increase of visual noise which interfered with proper dark adaptation.⁵⁶ The chronic, stable nature of many of these perceptual phenomena suggest that the term flashback may be but a subtype of a more long lived

disorder, now termed post-hallucinogen perceptual disorder in DSM-III-R.

Genetic effects of the hallucinogens

This topic has been amply reviewed by Cohen & Shiloh.⁵⁷ *In vitro* early studies found that LSD was clastogenic, but no consensus could be arrived at which supported the hypothesis that LSD caused chromosomal breakage *in vivo*. In animal models evidence has been consistent that LSD is either a weak mutagen, or not mutagenic. LSD is clearly not teratogenic, and no evidence exists that it is oncogenic.

Molecular aspects of hallucinogenic neurotoxicity

Clinical and epidemiological evidence links LSD use to long term alterations in CNS function, the clearest link being found in post-hallucinogen perceptual disorder. The pathophysiology of this disorder is unclear, though a number of observations suggest mechanisms which may be operating to bring about this condition.

A widely examined hypothesis suggests that hallucinogenic effects are related to the disruption of central serotonergic activity, based in part on structural similarities between LSD and serotonin,⁵⁸ and also on observations that LSD antagonized serotonergically innervated peripheral tissues.^{59,60} This model was undermined by studies in which LSD was demonstrated as an agonist in other serotonergic systems.⁶¹ Additional doubt was cast on the antagonist model when drugs such as 2-bromo LSD, which are potent serotonin antagonists, were shown not to have corresponding hallucinogenic effects.^{62,63}

Work by Glennon *et al.*⁶⁴ in 1984 correlated the affinity of hallucinogens for various receptors with their potency in humans. Affinity for the 5-HT₂ receptor related most closely with hallucinogenic potency. The evidence for agonism at the 5-HT₂ receptor is derived from discrimination studies, in which rats are conditioned to recognize administration of an hallucinogen. Specific 5-HT₂ antagonists are then used to block hallucinogen discrimination.⁶⁵ Agonist and partial-agonist activity has been favored by Sanders-Bush *et al.*,⁶⁶ Sadzot *et al.*,⁶⁷ and Sheldon & Aghajanian,⁶⁸ while antagonism has been favored by Pierce & Peroutka.⁶⁹ Recently Sanders-Bush & Breeding have reported finding

a potent effect of hallucinogens at the 5-HT_{1C} receptor.⁷⁰

It is plausible to hypothesize that the pathophysiology of PHPD to a mild degree recapitulates the acute LSD experience, implying that related neurons may be affected. In animals LSD causes an acute drop in 5-HT₂ receptor density, which can be made long lasting with a continuous eight day infusions,⁷¹ a finding which has been found in LSD binding of 5-HT₂ receptors in platelets of drug free PHPD patients (Abraham & Arora, personal communication).

Aghajanian (personal communication) has suggested that neurones involved may be small inhibitory cortical interneurons receiving serotonergic inputs, with GABA-ergic outputs. It is hypothesized that LSD causes death of these neurones by means of an intense, LSD generated current.⁷² This hypothesis is consistent with the clinical permanence or semi-permanence of PHPD, its partial responsiveness to GABA agonism, and its transient exacerbation by neuroleptics known to antagonize serotonin receptors. Further exploration of receptor and secondary messenger characteristics in psychiatric patients with hallucinogen related disorders would appear to be a most promising strategy for deepening our understanding of substance use and its clinical consequences.

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