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The Psychopharmacology of Hallucinogens

Henry David Abraham, M.D., Andrew M. Aldridge, M.B., Ch.B., and Prashant Gogia, M.B., B.S.

Hallucinogenic drugs have been inhaled, ingested, worshipped, and reviled since prehistory. With the purification and synthesis of bontanical preparations and the ensuing discovery of chemically unique agents, hope was raised regarding their therapeutic potential, but this hope has been clouded by an epidemic of abuse and an inventory of adverse effects. This review examines aspects of that controversy, including the history of hallucinogens, epidemiology of current hallucinogen abuse, the association of LSD use with prolonged psychoses and hallucinogen persisting perception disorder, and the efforts to demonstrate the drug's therapeutic efficacy. Human subject ramifications in hallucinogen experimentation are discussed. Future lines of research are suggested in human, animal, and tissue culture paradigms.
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Homo sapiens from the dawn of history has been omnivorous. It should come, then, as no surprise that in the never-ending quest for sustenance in hunter-gatherer societies a number of plants would come to be found whose psychotropic effects were adapted for magical, medicinal, and religious purposes. Table 1 summarizes an overview of indigenous hallucinogens that have been subjected to scholarly inquiry. The list is representative, not exhaustive. The term *hallucinogen* derives from the late Latin, *alucinari*, meaning to wander in mind, talk idly, or prate. Schultes catalogued nearly 100 plants with hallucinogenic properties, the majority of which are found in the Western hemisphere (Schultes and Hofmann 1980). Shulgin synthesized and screened 179 phenylethylamine congeners for hallucinogenic potencies in humans (Shulgin and Shulgin 1991). Glennon et al. (1984) showed a strong correlation between the affinity of hallucinogens for the 5-HT_2 receptor and their comparative potencies in humans.

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From the Department of Psychiatry, Tufts New England Medical Center, Boston, MA.

Address correspondence to Dr. Abraham, Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906.

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Hallucinogenic plants comprise fungi and angiosperms. The active agents of these plants tend to fall into surprisingly few chemical classes. Hofmann (1980) described 11: phenylpropenes, dibenzopyrans, isoxazoles, tropanes, quinolizidines, phenylethylamines, isoquinolines, tryptamines, β-carbolines, ergolines, and ibogaindoles. The indole nucleus of serotonin is commonly found in these compounds. Substituted phenylethylamines bear structural similarity to the catecholamines. Each suggests, but neither has led to, a specific mechanism of hallucinosis.

HISTORICAL PERSPECTIVE

Recent perspectives on hallucinogens have been provided by several authors (Brawley and Duffield 1972; Sankar 1975; Martin and Sloan 1977; Grinspoon and Bakalar 1979; Schultes and Hofmann 1980; Siegel 1984; Strassman 1984; Rivier 1994). As bitter and intoxicating alkaloids, hallucinogens likely played a defensive role in the evolution of plants by discouraging would-be herbivores (Siegel 1979). The history of hallucinogens is one of the more compelling in pharmacology. The oldest hallucinogen is thought to be the fly-agaric mushroom, *Amanita muscaria*, discovered in Siberia by observing the behavior of intoxicated reindeer. The ingestion of ergot alkaloids is credited with the induction of religious states in the Grecian Mysteries of Eleu-

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Table 1. An Overview of Representative Hallucinogens

Agent	Locale	Chemical Classification	Biological Sources	Common Route	Typical Dose	Duration of Effects	Abuse or Adverse Reactions
Lysergic acid diethylamide	Globally distributed semisynthetic	Indolealkylamine	Fungus in rye yields lysergic acid	Oral	100 μg	6–12 hrs	Extensive, including pandemic 1965–1975
Mescaline	Southwestern U.S.	Phenethylamine	Peyote cactus *L. Williamsii*	Oral	200–400 mg or 4–6 cactus buttons	10–12 hrs	Little or none verified
Methylene-dioxy-amphetamine (MDA)	U.S., synthetic	Phenethylamine	Synthetic	Oral	80–160 mg	8–12 hrs	Documented
Methylene-dioxy-metamphetamine (MDMA)	U.S., synthetic	Phenethylamine	Synthetic	Oral	80–150 mg	4–6 hrs	Documented
Psilocybin	Southern U.S., Mexico, South America	Phosphorylated hydroxylated DMT	*Psilocybe* mushrooms	Oral	4–6 mg or 5–10 g of dried mushroom	4–6 hrs	Little to none reported
Ibogaine	West African tropics	Indole	*Tabernanthe iboga*	Powdered root, eaten	200–400 mg	8–12 hrs	None reported
Harmine	S. American tropics	7-methoxy-β-carbolines	*Banisteriopsis caapi*	As a tea	300–400 mg, est'd.	4–8 hrs	None reported
Dimethyl-tryptamine	S. America, synthetic	Substituted tryptamine	*Virola calophylla*	As a snuff, IV	0.2 mg/kg, IV	30 min	None reported

sis (Wasson et al. 1978). Medieval witches used their brooms as vaginal applicators of hallucinogenic ointments (Harner 1973). Accidental ingestions of *Datura* are said to have poisoned Anthony's legions during a retreat in the first century B.C. Periodic epidemics of ergotism caused by the ingestion of rye infected with the fungus *Claviceps purpurea* plagued Europe, killing 40,000 in 944 A.D.

In 1845 Jacques Moreau published the first text on hallucinogens, in which he observed that such drugs enabled imagined thoughts to become sensory expressions. Nineteenth-century students of hallucinogens described them in exalted terms (Moreau 1845). One of Moreau's subjects, the poet Théophile Gautier, reported Moreau giving him a dose of hashish and saying, "This will be subtracted from your share in Paradise." A decade later von Bibra (1855) referred to these plants as *Genussmittel*, or "medium of enjoyment."

The work of mycologist M. C. Cooke (1860) was notable for differentiating opiates from the other "sisters of sleep," that is, hallucinogens. DeVeze (1907) a half century later first classified narcotic from hallucinogenic plants, a process that was refined definitively by the toxicologist Louis Lewin in 1924. Lewin emphasized the perceptual effects of these plants, as well as their use and abuse potential. Seeking to explore their spiritual effects, the psychologist William James received a supply of mescal buttons from Weir Mitchell, ingested them, became violently ill for 24 hours, but failed to hallucinate. His experiments with nitrous oxide and ether were more successful (James 1902). By the 1920s and 1930s ethnobotanical and psychopharmacological work had begun in earnest, with the field work of Safford, Reko, and later, Schultes (Schultes and Hoffmann 1980). Klüver (1966) pioneered an analysis of the visual hallucinatory forms associated with mescaline.

With the discovery of the hallucinogenic properties of lysergic acid diethylamide (LSD) by Hofmann in 1943, the aboriginal modes of hallucinogen use, historically limited by region, ritual, religion, and botanical origins of the plant used, gave way to the possibility of drug use no longer so constrained. With the introduction of LSD to Europe and to the United States in 1949, an era was begun in which extremely potent agents became available to millions of persons for uses that ranged from the religious to the recreational. LSD was

used to develop new insights into the mechanisms of nerve cell transmission, visual hallucinations, and the phenomenology of schizophrenia.

Hallucinogenic drugs were used to develop model psychoses. In a classic study of altered states of consciousness, Langs and Barr (1968) observed similar patterns of paranoia in schizophrenics and about a fourth of normal subjects receiving LSD. Heimann (1994) described losses of temporal and spatial organization in musicians given psilocybin. Hollister (1962), however, concluded that symptoms from a group of 59 experimental subjects receiving hallucinogens were discriminable from those in schizophrenics. The promise of a new tool in psychiatry was reflected in a flurry of publications exploring the drug's benefits. But inevitably, wide and undisciplined use of LSD soon revealed a rising tide of liabilities.

In 1968 Freedman surveyed the dangers of a casual view toward hallucinogens in a pivotal paper that concluded that the harms of using LSD outweighed the apparent benefits. Figure 1 charts all LSD publications by year in the scientific literature as noted in the *Index Medicus* from 1960 to 1994. Articles were selected by titles if classifiable as favorable or adverse reports. Positive values on the ordinate are the total number of favorable reports by year. Negative values record the number of adverse reports by year. It is noteworthy that the years 1960–1968 constituted a preponderance of favorable reports, which subsequently reversed from that point to the present. The absolute number of publications, as well as the number of favorable reports, fell off coinciding with the passsage of federal regulations limiting research with this drug. Finally, it should also be noted that the shape of the curve appears to describe a biphasic socioscientific attitude toward many, if not most, developments in pharmacology. Such a biphase is also likely to be seen in the human pattern of rising hopes followed by sober reconsideration that marks much of the recorded history of ideas.

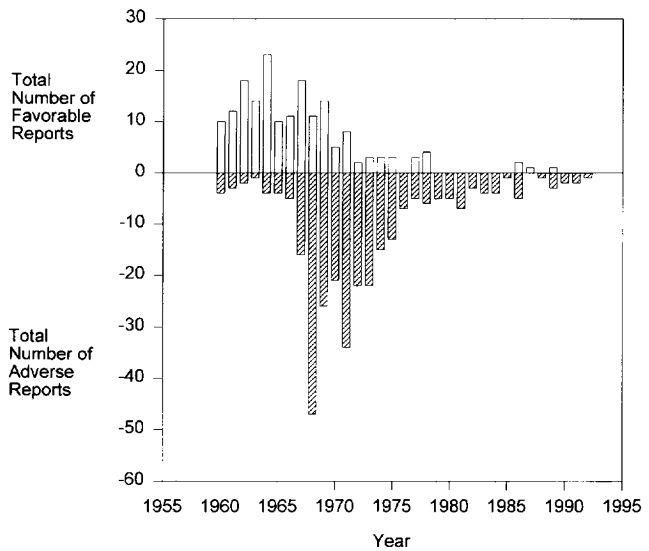

Figure 1. Scientific publications on LSD in *Index Medicus*, 1960 through 1994. Each human study on LSD was assigned a score of +1 for favorable findings (*upward open bars*) and −1 for adverse ones (*downward striped bars*) when scoring was possible. The curve is measuring not a chemotherapeutic index of the benefits and risks of LSD, but a research trend reflecting a strong cohort-period effect of scientific activity.

WHAT IS AN HALLUCINOGEN?

This deceptively simple question is controversial (Schultes and Hofmann 1980). The more than 90 species of hallucinogenic plants afford an anthropological definition, namely, those botanical substances that have been used as primitive psychotropics (LaBarre 1975). An early classification of psychotropic substances was suggested by Lewin (1924), who grouped them into classes according to their most pronounced effect. Hallucinogens he called *phantastica*. Brawley and Duffield (1972) classified psychotropics as poisons (e.g., methanol, heavy metals, cardiac glycosides); deliriants (e.g., anticholinergics, phencyclidine); and psychotomimetics (some ergot alkaloids and phenylethylamines). Poisons induce toxic psychoses; deliriants induce a delirious state without concomitant metabolic disturbances; and psychotomimetics alter autonomic, affective, perceptual, and cognitive function while inducing neither a delirium nor a gross metabolic derangement.

Jarvik (1970) offered one of the first chemical classifications of hallucinogens, which included anticholinergics, indoleakylamines, and cannabis derivatives. Drug phenomenology has been used to deal with this question, in which hallucinogens are defined as agents altering perceptions without major autonomic or metabolic changes (Hollister 1968; Brawley and Duffield 1972; Martin and Sloan 1977; Grinspoon and Bakalar 1979). The virtue of this definition is that it significantly narrows candidate classes of drugs and helps to refine research and the consideration of social policy. This formulation has currency today. As a consequence one may define as hallucinogenic *any agent that causes alterations in perception, cognition, and mood as its primary psychobiological actions in the presence of an otherwise clear sensorium.* Most commonly this includes indoleakylamines and phenethylamines and excludes, inter alia, the anticholinergics, the arylcyclohexylamine dissociative anesthetics such as phencyclidine, stimulants such as amphetamine and cocaine, bromism and heavy metal intoxication. The term *hallucinogen* while unduly emphasizing perceptual effects connotes by convention their effects on emotion and cognition as well. What is needed are multidrug, multivariate studies to identify discriminants for this drug class. Strassman et al. (1994)

has summarized the history of efforts to quantify the effects of hallucinogens.

METHODOLOGICAL CONSIDERATIONS

The assignment of beneficial or harmful effects to a particular hallucinogenic is not simple. Causality implies a fixed temporal sequence between agent and effect and experimental evidence that unequivocally links the two. In clinical research it is sometimes useful to conceptualize four levels of increasing scientific validity. One may metaphorically refer to them as marble, brick, sticks, and mud. At the highest level is "marble," the standard of randomized assignment of subjects to a drug cohort or a control group. This is an ideal standard, impractical in many situations, and one seldom attained. It is gratifying to note that after a hiatus of nearly three decades human experimentation with hallucinogens has been renewed utilizing careful attention to experimental design (Hermle et al. 1994; Strassman and Qualls 1994; Strassman et al. 1994).

At lesser levels of validity, observational data are employed. A technique simulating a prospective cohort study is what Feinstein calls a "trohoc" study, a cohort study in reverse (Feinstein 1985). One may refer to these studies as made of "brick." They are done by establishing study groups and then examining records backward through time to test an hypothesis. Three elements strengthen the validity of this approach: (1) the strength of the statistical association; (2) the time sequence; and (3) the consistency of the finding with existing knowledge (Clark and McMahon 1967). In the research of LSD-related disorders we were able to find one such study (McLellan et al. 1979).

A third level of validity is occupied by studies in the category of "sticks." These are the case-controlled epidemiological studies, comparisons of groups by an inquiry to their past histories. A number of these studies are now available, and they comprise the lion's share of the research in hallucinogens.

At the humble end of validity are uncontrolled case reports, the "mud" of our field. Although without statistical power, case reports often become the means by which more solid edifices of knowledge are built. In hallucinogenic research, case reports fuel more systematic inquiries into the claims of beneficial and adverse drug outcomes.

EPIDEMIOLOGY

Hallucinogenic drugs are commonly abused. Data from the 1990 NIDA Household Survey (National Institute on Drug Abuse 1990) suggests that 7.6% of the U.S. population over the age of 12 years used hallucinogens at some time in their lives. The survey showed that in the previous 12 months 1.1% reported hallucinogen use. Comparative figures for other drugs were: 10.2% marijuana, 3.1% cocaine, 1.2% inhalants, and 0.2% each for phencyclidine and heroin. In 1993 a survey of 18,054 householders over the age of 12 found a higher life use of hallucinogens of 8.7% (Substance Abuse and Mental Health Services Administration 1994). The Household Survey gives figures for lifetime exposure to individual hallucinogens, with 5.5% reporting having tried LSD and 3% mescaline.

Demographic data indicate that LSD use is most prevalent between the ages of 18 to 25, with 4.9% reporting use in the past year, compared to 2.1% for the age group 12 to 17 and 1.2% for those 26 and older. Use is greater among men, whites, and Hispanics. There appears to be a positive association with urban areas in the Northeast and West, and an inverse one with employment and education level. High school seniors, while showing an inverse correlation between LSD use and college plans, demonstrate a strong positive one between LSD use and parents' education (Johnston et al. 1990). These data confirm the clinical impression of LSD users as disaffected offspring of Caucasian, white-collar parents.

Information on drug use among high school seniors has been collected systematically by the team at the University of Michigan Institute for Social Research since 1975 (Johnston et al. 1994). Since 1985 there has been a steady increase in hallucinogen use, reaching a decade long peak of 11.4% in 1994.

ACUTE EFFECTS

"Last Friday, April 16th, 1943, I was forced to interrupt my work in the laboratory in the middle of the afternoon, being affected with a remarkable restlessness, combined with a slight dizziness." This report of Hofmann was written shortly after accidentally ingesting a small quantity of LSD (Hofmann 1980). He then performed a self-experiment: "4/29/43, 16:30: Solution of diethylamide tartrate orally = 0.25 mg. Taken diluted with 10 cc water. Tasteless. 17:00: Beginning dizziness, feeling of anxiety, visual distortions, symptoms of paralysis, desire to laugh." From this point Dr. Hofmann was unable to record his experiences. Later he describes a terrifying journey home: Everything in his vision wavered and appeared distorted while he felt overcome by incipient dread. He felt riveted to the spot, although he was bicycling rapidly. Despite his bewilderment he described clarity of thought. Once home, familiar objects appeared grotesque and threatening. At times the whole room seemed to be in motion. Circles and spirals exploded in colored fountains, rearranging and hybridizing themselves in constant flux. Feelings of

fear, despair, and helplessness pervaded. He felt he was outside his body. Toward the end of the evening these effects gradually subsided and he was able to sleep, awakening the next morning with a feeling of well-being.

Hofmann's first description typifies the effect of a low dose, possibly 25 to 50 μg: short duration, little affective lability and visual illusions but no hallucinations. Perception is intensified, rather than distorted. At this dose meaning may be heightened to the extent that experience takes on a mystical, epiphanic quality and old memories may be reexperienced with an eidetic intensity (Busch and Johnson 1950).

His second ingestion characterizes the effect of a larger dose. Again, dizziness and anxiety may occur 20 to 30 minutes after ingestion (Abramson et al. 1955). These 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. 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 preexisting mood. In most 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 casualties. Gradually the intensity of these effects declines, the total duration of drug action being between 6 and 12 hours.

Hermle et al. (1994) have recently compared the effects of mescaline and 3,4-methylenedioxyethamphetamine (MDE) in normal volunteers using psychometric, sleep, and single photon emission computed tomography (SPECT) data. Both drugs produced a loss of ego boundaries, with mescaline producing more anxiety and more pronounced visual effects. Similar to amphetamine MDE disrupted sleep. SPECT data showed a right hyperfrontality from mescaline, distinct from the patterns of hypofrontality described in schizophrenia. Strassman et al. have recently described the effects of dimethyltryptamine (DMT) in 12 normal volunteers using a randomized, placebo-controlled, multidose, double-blind design (Strassman and Qualls 1994; Strassman et al. 1994). In addition to cardiovascular and endocrine measures, a multidimensional hallucinogen rating scale was developed that was capable of application in a variety of experimental settings.

There is considerable variation in the response to LSD both between individuals and in the same individual at different times. This is related in part to the setting. Stoll (1947) noted a much higher incidence of acute adverse effects in subjects who were unaware of its administration. Slater et al. (1960) compared group with individual administration and found the former had an excess of euphoric responses while the latter showed more anxiety, hypomotility, and speech disruption. A second set of factors that condition LSD response are related to the personality of the subject.

LSD exhibits tolerance and cross-tolerance (Stoll 1947; Isbell 1955; Isbell et al. 1961; Wolbach et al. 1962). In humans tolerance to gross behavioral changes develops in 4 to 7 days of daily administration and lasts approximately 3 days (Abramson et al. 1956). Schizophrenics may develop tolerance in 2 to 3 days (Cholden et al. 1955). Cross-tolerance has been demonstrated in humans between LSD, psilocybin, and mescaline but not to amphetamines or marijuana. This has suggested a criterion for classifying hallucinogens by the extent to which they are cross-tolerant with LSD (Martin and Sloan 1977). Although DMT produces similar effects, cross-tolerance with LSD is limited.

Hallucinogens have no withdrawal effects. There are no documented toxic fatalities from LSD use. On the other hand, at least five deaths have been reported in humans using MDMA or MDEA, presumably by arrhythmias in three cases (Dowling et al. 1987). Rodents are extremely resistant to its effects, mice having an LD_{50} dose of 150,000 μg per kg. Alternatively, an elephant was killed by an injection of 297 mg of LSD (100 μg per kg) (West et al. 1962). Chemically pure LSD was mistaken for cocaine and accidentally snorted in quantities estimated at between 10,000 and 100,000 μg (Klock et al. 1975). In this instance the eight individuals involved suffered from mental status changes characterized by confusion, hallucinations, and hemorrhage, possibly mediated by LSD antagonism of platelet serotonin function. All recovered.

Mental functions are differentially affected by LSD. The vividness of Hofmann's original descriptions testifies to the fact that memory is unimpaired, although perception, orientation, concentration, and other measures of cognition may be impaired depending on dose (Jarvik et al. 1955; Levine et al. 1955; Silverstein and Klee 1958).

Acute LSD intoxication commonly presents to the emergency room as a "bad trip." A careful history is essential, even in cases where the diagnosis appears evident, as illicit drugs may be misrepresented 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), less often in sugar cubes, aspirins, or dissolved in water or alcohol. The mode of administration is oral. Ocular and intravenous routes are rare. LSD is not smoked. A history of a smoked "hallucinogen" should suggest PCP.

Chemical analyses of illicit specimens by the Massachusetts Department of Public Health using gas chro-

matography mass spectrometry yield true positives for LSD 53.5% of the time. Adulteration is surprisingly uncommon, although mistaken attribution is common. Distinguishing between hallucinogens in an emergency setting is of academic interest; they produce similar syndromes and are managed conservatively. Attention is warranted to rule out other agents capable of simulating hallucinogens, such as anticholinergic drugs and PCP. Blood and urine toxicology may clarify the situation in retrospect. Results are seldom available within the time frame of intoxication. A recently described palm test administered at bedside may be useful in such situations (Abraham and Aldridge 1993).

LSD toxicity historically has been managed with neuroleptics or "talking down." It is now recognized that the former may intensify the experience (Schwartz et al. 1967), and talking down may entail a disproportionate time commitment from a busy emergency room clinician. Personal experience by the authors has found that benzodiazepines (e.g., diazepam 20 mg by mouth) appear to offer a rapid and effective alternative, with resolution of the bad trip within 30 minutes. No controlled studies are yet available to support this impression.

PSYCHOTIC REACTIONS

The earliest suggestions that hallucinogens might be associated with long-term disorders came in the decade following Hofmann's discovery of his "Problem Child" (Sandison et al. 1954; Elkes et al. 1955). But apparently low attack rates of psychosis following LSD during the period of early human experimentation (Geert-Jörgenson et al. 1964) led researchers to suggest that, "the drug is exceptionally safe rather than dangerous" (Levine and Ludwig 1964). Can hallucinogens cause protracted psychoses? And how can one attribute causality when studies are likely to be clouded by such factors as street drug adulteration, false or mistaken drug identification, polypharmacy, and preexisting psychopathology?

Since the 1960s evidence has accrued that has addressed the issue of the validity of the diagnostics of posthallucinogen psychosis. Psychosis has been described in studies that included direct administration of LSD to patients and experimental subjects (Opitz 1963; Fink et al. 1966; Leuner 1967; Baker 1967; McFarling 1980). There are at least two longitudinal studies of psychosis following psychostimulants including LSD (McLellan et al. 1979; Bowers 1977). Eight studies have made cross-sectional comparisons of patients with LSD users and controls (Abraham 1980; Smart and Jones 1970; Breakey et al. 1974; Bowers 1972a, 1972b; Safer 1987; Tsuang et al. 1982; Vardy and Kay 1983). Psychosis has been surveyed or reported in case series of LSD complication rates (Cohen 1960; Medical Society of the County of New York 1966; Ungerleider et al. 1966; Blumenfield and Glickman 1967; Smart and Bateman 1967; Tietz 1967; Hekimian and Gershon 1968; Frosch 1969; Malleson 1971; Sanborn and Daniels 1971; Abruzzi 1977; McLellan and Druley 1977; Kornblith 1981). Finally the literature yields case reports on 75 patients presenting with post-LSD psychoses (Cooper 1955; Cohen and Ditman 1963; Frosch et al. 1965; Metzner 1969; Hatrick and Dewhurst 1970; Muller 1971; Dewhurst and Hatrick 1972; Fookes 1972; Reich and Hepps 1972; Horowitz 1975; Lake et al. 1981; Bowers 1987; Abraham 1983b; Schwartz et al. 1987).

Attack rates for psychoses following experimentally administered LSD range from 0.08% (Malleson 1971) to 4.6% (Fink et al. 1966), with a trend toward higher rates among psychiatric patients and lower among volunteers. To test this trend, we performed a metaanalysis on six studies reporting psychoses following LSD administration (Opitz 1963; Fink et al. 1966; Baker 1967; Leuner 1967; Malleson 1971; McFarling 1980). Cases were combined into four cells, (1) patients' and (2) volunteers' and (3) psychotic and (4) nonpsychotic reactions. We used a 2×2 contingency table to calculate a chi-square value ($\chi^2 = 6.97$, $p < .01$). Keeping in mind the limitations inherent in metaanalysis of data from diverse sources and methods, we conclude that psychiatric patienthood may be a risk factor for prolonged psychoses following LSD.

The clinical nature of psychoses following LSD appears to resemble schizoaffective disorders with the not-infrequent addition of visual disturbances. Fink et al. (1966) noted in an early experiment with chronic psychotic patients that, "the hazard of LSD administration appears not to be in the precipitation of a schizophreniclike state but rather in decreasing emotional and affective controls and inducing a persistent state of altered consciousness." A sample of 105 users of LSD from a psychiatric outpatient department as described: 23% had diagnoses of schizophrenia characterized by visual disturbances, good relatedness, mild thought disorder, and mystical preoccupations suggestive of temporal lobe disorder (Abraham 1980). Bowers found that schizophrenic drug users had healthier premorbid personalities than nondrug-using schizophrenics and an earlier age of onset (Bowers 1972a), a finding confirmed by Breakey et al. (1974).

The clearest description of post-LSD psychotic disorder comes from 75 case reports in which clinical features were described in detail (Table 2). What emerges is that the commonest symptoms reported include mood swings, visual hallucinations, mania, grandiosity, and religiosity. The most effective treatments were electroconvulsive therapy (ECT) and lithium. Bowers's longitudinal study of 15 patients with LSD psychosis prompted him to conclude that a major affective component was present (Bowers 1977).

Other reports describe post-LSD psychotics appear-

Table 2. Post-LSD Psychoses

	n	Life Dose	Symptoms	Duration	Treatment
Cooper (1955)	8	NA	Mood swings, somatic concerns, hallucinations	NA	NA
Cohen (1960)	1	75 μg	Transient acute schizophreniform reactions, prolonged psychosis	NA	Chlorpromazine
Cohen & Ditman (1963)	3	NA	Grandiosity, hyper-religiosity, visual hallucinations	2 yrs.	NA
Frosch (1969)	3	1	Prolonged psychoses	NA	NA
Metzner (1969)	1	6	Catatonia	3 wks.	ECT
Hatrick & Dewhurst (1970)	2	1	Depression, auditory hallucinations, paranoid delusions	NA	ECT chlorpromazine
Dewhurst & Hatrick (1972)	19	1–6	Schizoaffective disorder, philosophical delusions, visual hallucinations	NA	ECT chlorpromazine
Muller (1971)	3	NA	NA	12–17 days	ECT
Reich & Hepps (1972)	1	Occasional	Motiveless assaults, homicide, psychosis	8 days	Phenothiazines
Fookes (1972)	1	3	Depression, delusions, suicide attempt	NA	ECT
Muller (1971)	4	Heavy	Mania, psychosis, hallucinations	NA	ECT
Horowitz (1975)	4	NA	Mania, coterminous with LSD use	NA	Lithium
Bowers (1977)	15	NA	Manic-depressive, schizoaffective spectrum	NA	NA
Lake et al. (1981)	1	NA	Religiosity, mania, grandiosity, aggression	3 wks.	Lithium
Schwartz (1967)	8	NA	Prolonged psychoses	>48 hrs.	NA
Abraham (1983b)	1	5	Grandiosity, auditory, visual hallucinations	2.4 yrs.	5-Hydroxytryptophan

ing as schizophrenic (Blumenfield and Glickman 1967; Vardy and Kay 1983). Heikimian and Gershon (1968) likewise noted that a majority of their 47 inpatients with a drug abuse history were diagnosed as schizophrenics, with half describing psychosis prior to drug use.

Four additional studies found post-LSD psychotics with prior psychosis but also patients in whom the drug precipitated psychosis without a prodrome (Public Health Committee 1966; Ungerleider et al. 1966; Smart and Bateman 1967; Frosch 1969). One group reported cases of psychosis following a single dose, suggesting a peculiar vulnerability to the drug in certain individuals. A review of this problem concluded that prior illness was evident in many, but not all, psychoses following LSD (Kornblith 1981).

Comparison studies have found LSD psychotics to display abnormal Minnesota Multiphasic Personality Inventories (Smart and Jones 1970) and Rorschachs (Tucker et al. 1972) and decreased 5-hydroxyindoleacetic acid in spinal fluid (Bowers 1972b). Studies examining the association of specific psychiatric diagnoses to specific classes of drugs found schizophrenia most frequently tied to amphetamine and hallucinogen abuse (McLellan and Druley 1977; McLellan et al. 1979). A chart review of 176 inpatients found that more psychotic patients abused hallucinogens than did a comparable group of drug abusers without psychosis. The drug-abusing psychosis were also differentiated from drug-abstinent psychotics by earlier ages of onset, more visual hallucinations, depression, and families with af-

fective disorder. These workers concluded that the data were consistent with the hypothesis that the drug abuse had precipitated a psychosis (Tsuang et al. 1982).

It may be concluded that in certain vulnerable individuals LSD must be viewed as a psychotogen. Clues to the nature of that vulnerability may be found in schizoaffective and visual symptoms, the apparent genetic loading for affective disorder, and possible involvement of the serotonin system of neural connections in the central nervous system (CNS) (Bowers 1972b; Smart and Bateman 1967).

HALLUCINOGEN PERSISTING PERCEPTION DISORDER

In 1954 Sandison et al. first described LSD-like recurrences following therapeutic use of the drug. In 1958 Eisner and Cohen described LSD users reporting spontaneous recurrences of LSD-like states in subjects days to weeks following drug use. Subsequent reports described persistent hallucinosis (Rosenthal 1964) that could last as long as a year following drug use (Robbins et al. 1967). Holsten (1976) described patients who experienced flashbacks 4 years following drug use. Horowitz (1969) appears to have been the first to introduce the term *flashback* into the literature. He described perceptual distortions, spontaneous imagery, and recurrent unbidden images. Other workers described flashbacks as perceptual, somatic, and emotional (Shick and Smith 1970). A third report suggested that flashbacks appeared to be a misnomer, as patients described cases of continuous, rather than paroxysmal, visual disturbances from LSD (Anderson and O'Malley 1972).

This last observation was confirmed in a study of 123 LSD users. These patients presented primarily with visual disturbances, including geometric pseudohallucinations, false fleeting perceptions in the peripheral fields, flashes of color, and positive afterimagery (Abraham 1983a). The visual disorder was stable in half of the sample over a 5-year period. Precipitants included stress, fatigue, a dark environment, intention, marijuana (Favazza and Domino 1969) or neuroleptics use, and anxiety states. Depression was comorbidly present. The disorder could be brought on by a single dose of LSD. It was theorized that these visual disturbances represented visual seizures brought about in vulnerable persons. Recently Aghajanian suggested that this disorder may arise from an excitotoxic destruction of inhibitory interneurons that are serotonergic at the soma and GABAergic at the terminals (Abraham and Aldridge 1993). This is supported by the usefulness of benzodiazepines for this disorder and the observation that LSD serves as a potent partial agonist at the serotonin-2 receptor in the facial nucleus (Garratt et al. 1993). Alternatively, vulnerability may be mediated through protein kinase C blockade, which enhances LSD action at this receptor (Aghajanian 1994).

There are no predrug, postdrug experimental designs examining this issue. Two cross-sectional studies have compared LSD users to controls on a variety of visual measures (Abraham 1982; Abraham and Wolf 1988), including tests of color vision, dark adaptation, and critical flicker fusion. These studies found abnormalities in visual function consistent with the hypothesis that imagery continued to be processed centrally after the test stimulus had been removed.

Slow clinical recognition of post-LSD perceptual disorder is not uncommon. The typical patient may consult a half-dozen or so clinicians—usually an ophthalmologist, neurologist, psychiatrist, or psychologist—before a proper diagnosis is made. The authors have seen a number of patients who in desperation read the medical literature or DSM-III-R and made their own diagnoses. Differential diagnosis must rule out organic forms of hallucinosis, including other sources of toxicity, strokes, CNS tumors, infections, and the sequelae of trauma (Abraham 1984). Treatment success has been partial. Benzodiazepines ameliorate, but do not eradicate, the symptoms. Using addictive agents in substance abusers is not entirely without risk of further abuse (Abraham in press). One study of eight subjects used haloperidol to reduce hallucinations, but an exacerbation of flashback symptoms early in treatment was noted as well (Moskowitz 1971). Psychotherapy is indicated in assisting patients in making an adjustment to chronic visual distractions and addressing the common notion of "brain damage" commonly feared by these patients. Pharmacotherapy is indicated for comorbid conditions, such as depression, psychosis, and panic disorder. The use of the term *flashback* has been supplanted by the diagnostic entity *hallucinogen persisting perception disorder* in 1994 by the Substance-Related Disorders Work Group of the DSM-IV.

HALLUCINOGENS AS THERAPEUTIC AGENTS

Most experimental studies of hallucinogen therapy have been with LSD. First marketed by Sandoz in 1949, LSD had two applications: analytical psychotherapy and experimental study of the nature of psychoses (Hofmann 1980). Busch and Johnson (1950) first recommended the use of LSD in psychotherapy as a tool to uncover repressed memories. Sandison et al. (1954) described the abreactive qualities of LSD and suggested use in neurotics, a treatment later called psycholytic therapy (see also Leuner 1994). It gained support in Europe and was reserved usually for psychotherapeutically resistant patients. LSD achieved widespread therapeutic use until 1965 when it was curtailed by the passage of the Drug Abuse Control amendments to the

Harrison Narcotics Act. Prior to legislative restriction, LSD was combined with numerous modes of psychotherapy, given in different dosage regimens, and used for a wide range of indications, including chemical, psychological, mystical, religious, and recreational purposes. In the years following the virtual halt to hallucinogen research in humans, numerous methodological advances occurred in psychiatry, including in neuroimaging, genetics, messenger systems, and most important, psychiatric classification and outcome schemata. Accordingly, nearly all of the data on the human effects of hallucinogens were gleaned from a period with far fewer investigative tools than are available now. This has created something of a Rip van Winkle effect in the field, in which the corpus of data in the field is several decades behind the methods currently available to acquire it.

LSD has been explored as a treatment for neuroses, phobic and obsessive-compulsive disorders, childhood schizophrenia, sociopathy, alcoholism, and as an adjunctive therapy with the terminally ill (Mascher 1967; Abuzzahab and Anderson 1971; Grinspoon and Bakalar 1979; Hollister 1984). A metaanalysis of 1,603 patients in 42 studies scored the studies in "very good/good" outcome ranges of 40% to 62.5% of cases (Mascher 1967). Hallucinogenic treatment of alcoholism was most closely studied. Fourteen representative studies are summarized in Table 3.

Ludwig et al. (1970) concluded in an LSD study that all treatments for alcoholism appeared equally effective, including that using LSD. Researchers at the Spring Grove Hospital in Baltimore studied 175 alcoholics given either 150 μg of LSD as "an active placebo" or 300 to 500 μg as the active treatment. At 12- and 18-month follow-ups no differences were found between the groups (Kurland et al. 1971). Such a design may have masked a drug effect, because a "placebo" of 150 μg of LSD in most humans exerts a profound psychedelic effect in its own right (Klee et al. 1961). A controlled study of LSD in alcoholics failed to find a drug effect in 10 subjects (Smart et al. 1966). This finding was weakened by a sample size too small to avoid the high probability of a Type-II error. A study testing the therapeutic effects of LSD on narcotics addicts reported a benefit, but LSD cases were also given residential treatment, whereas controls were not (Savage and McCabe 1973). Finally, a review of 31 studies failed to favor LSD above conventional therapies for alcoholism (Abuzzahab and Anderson 1971).

Despite a profusion of early efforts, it is difficult to find compelling evidence demonstrating positive outcomes from the combination of LSD with psychotherapy. Seldom have there been studies using random assignment, placebo controls, double-blind observations, standard techniques of assessment, and other accepted design features of controlled clinical trials. In the esti-

Table 3. Representative Studies of LSD Therapy in Alcoholism

Study		*n*	Study Type	LSD Dose (μg)	Follow-up	Result
Smith	(1958)	29	Open trial	200–400	—	About 50% improvement
MacLean et al.	(1961)	61	Open trial	40–1,500	3–18 m.	48% much improved and another 26% some improvement
O'Reilly	(1962)	68	Open trial	200	38 wk.	38% improvement
Jensen	(1962)	58	Open trial	200	6–18 m.	Significantly more abstinence in LSD group
Smart & Bateman	(1967)	30	Controlled trial	800	6 m.	No statistical difference
Kurland et al.	(1967)	69	Open trial	450	6 m.	33% abstinent
Van Dusen et al.	(1967)	71	Controlled trial	100–800	18 m.	No difference in abstinence
Hollister	(1968)	45	Controlled trial	600	6 m.	LSD group better at 2 months; no difference at 6 months. Both groups improved
Johnson	(1969)	95	Controlled trial	300–500	12 m.	No difference
Ludwig et al.	(1970)	176	Controlled trial	3/kg	12 m.	All groups improved
Bowen	(1970)	81	Controlled trial	500	12 m.	No statistical difference
Denson and Sydiaha	(1970)	51	Controlled trial	50–300	12 m.	No benefit proven with LSD
Pahnke et al.	(1970)	135	Controlled trial	50–450	6 m.	High dose LSD better than low dose
Tomsovic & Edwards	(1970)	220	Controlled trial	500	12 m.	No statistical difference

mate of Leuner (1994), one of the field's pioneers, these early studies do not, "meet the standards of modern psychotherapy research." On the other hand, with the growing consolidation of methods in psychotherapy research and the emergence of alternative hallucinogens, cautious reexamination of their therapeutic potential may be in order.

HUMAN SUBJECT CONSIDERATIONS

Although controversy exists about whether hallucinogens should ever be used in humans, established principles governing the use of experimental agents serve as guidance in such questions. These principles include review of any proposed experiment by a scientifically and ethically conversant institutional board and the acquisition of informed consent from study participants. Imbedded within informed consent is a proper discussion of possible risks and benefits, ideally presented as quantitative probabilities, and a discussion of treatment alternatives, among other considerations (Annas 1989; Federal Register 1991). The application of these considerations may justify the experimental use of hallucinogens in certain situations, for example, when the condition being treated is more dire than the risk of long-term adverse effects of the treatment. Historically, controversies arose prior to the widespread acceptance of such principles, as in the administration of hallucinogens to autistic children, normal adolescents, or covertly to individuals in the military or penal systems. An added problem not often addressed is the use of unquantified outcome measures, such as marital harmony, personal well-being, or creativity, a research path that although laudable in its goals, has been dubious in its means.

O'Brien and Jones (1994) recently reviewed essential criteria for evaluating medication in psychotherapy. These include specific diagnosis; severity measures; informed consent; placebo controls; random assignment; standardized psychotherapy; "blind" raters; and follow-up. These standards are not so lofty as to be beyond the reach of conscientious investigators.

CONCLUSION

It is perhaps ironic to note that since the 1940s, even though our understanding of the mechanisms of action of hallucinogenic drugs has vastly increased, we have yet to clarify the original debate as to whether hallucinogens are clinically useful. On the other hand, the prospect of new insights into the molecular mechanisms of hallucinogens is excellent. Not unlike epilepsies, hallucinogens sit at the crossroads of the mind-brain interaction. There are two advantages to their use experimentally. In humans a relatively clear sensorium lends insight into psychological processes. In animal models there is accessibility to neurons, membranes, messengers, and genes. The challenge will be to integrate each approach into a single experimental paradigm. Why is it that certain individuals can use these agents with impunity, whereas others apparently become adversely affected for life? What is the basis of such vulnerability? Is it genetic, excitotoxic, or possibly related to kindling? Studies in ligand-specific neuroimaging are in their infancy (Lever et al. 1989; Vollenweider 1994). Techniques from molecular genetics and tissue culture may be used to study subjects with differing responses to hallucinogenic drugs, including those with psychiatric illnesses. Such explorations may illuminate the mechanisms of psychoses, affective disorders, and hallucinoses. Techniques of verifiable effects of drugs on psychotherapy may be applicable in selected human populations. Such new strategies may uncover at least some of the keys of mental illness.

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