

Hallucinogenic Drugs in Psychiatric Research and Treatment

Perspectives and Prospects

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Clinical research with hallucinogens has resumed after a generation's hiatus. To place these new studies in context, this article reviews the history of hallucinogens' use and abuse, discusses their pharmacological properties, and highlights previous human studies. Research with lysergic acid diethylamide and related hallucinogens with thousands of patients and control subjects was associated with acceptable safety when subjects were carefully screened, supervised, and followed up. Data were generated regarding hallucinogens' psychopharmacology, overlap with endogenous psychoses, and psychotherapeutic efficacy. Current American and European studies emphasize systematic psychopharmacology, in addition to psychotherapy protocols. Human hallucinogen research will help define unique mind-brain interfaces, and provide mechanistic hypotheses and treatment options for psychiatric disorders. It is critical that human hallucinogen research in the 1990s make use of state of the art methodologies, or consensually define when modifications are required. Training and supervisory issues also must be explicitly addressed.

—*J Nerv Ment Dis* 183:127–138, 1995

Hallucinogenic substances found in fungi, plants, and animals have been used on all continents, and in a wide variety of cultures, both highly advanced and preliterate (Dobkin de Rios, 1984). Mescaline, from the peyote cactus, has been used in clinical research protocols from the 1890s to the present (Mitchell, 1896). The thousand-times more potent effects of LSD-25 were discovered in 1943 by Albert Hofmann, 5 years after its synthesis (Stoll, 1947). The beginning of modern "biological psychiatry" can be said to have started as much with the appreciation of LSD's "psychotogenic" effects as the contemporaneous discovery of the one-thousandth as potent "antipsychotic" effects of chlorpromazine.

The study of hallucinogenic drugs in humans was, and remains, important for several reasons. First, they elicit a multifaceted clinical syndrome, affecting many of the functions that characterize the human mind, including affect, cognition, volition, interoception, and perception. Characterizing hallucinogens' properties will enhance understanding of important mind-brain relationships, particularly relevant in this, the Decade of the Brain. Second, naturally occurring psychotic syndromes share features with those elicited by these drugs. Understanding effects and mechanisms of action of hallucinogens may provide novel insights and treat-

ments into endogenous psychoses. Third, increasing use and abuse of hallucinogens over the last several years, particularly LSD, by young adults may produce a similar spate of adverse psychiatric sequelae seen with the first wave of their illicit use in the 1960s. Treatment of these adverse effects consume scarce public resources and safe, selective, and efficacious treatments of acute and chronic negative effects of these drugs are needed. Finally, the enhancement of the psychotherapeutic process, sometimes in treatment refractory patients, reported by early studies, has relevance to current emphasis on time-limited psychotherapeutic interventions.

Nomenclature

Many terms have been used to describe the effects of these drugs, including psychedelic (mind manifesting), psychodysleptic (disturbing the mind), phantasticant, psychotogen, oneirogen (producing dreams), entheogen (generating religious experience), phanerothyme (making feelings visible), psychotomimetic, and schizotoxin (Grinspoon and Bakalar, 1979; Stafford, 1992). Psychedelic represents the nonmedical, recreational, and illicit use of these drugs, while hallucinogen refers to these compounds within a medical-legal context.

The "classical" hallucinogens belong to several chemical families: phenethylamines (*e.g.*, mescaline), indolealkylamines (*e.g.*, psilocybin and *N,N*-dimethyltryptamine [DMT]), and lysergamides (*e.g.*, LSD and morning glory seeds) (Nichols et al., 1991). 3,4-Methyl-

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This work was supported by National Institute on Drug Abuse grant RO1-DA08096, University of New Mexico General Clinical Research Center grant RR00997-15, and University of New Mexico Department of Psychiatry research funds.

ene-dioxymethamphetamine (MDMA) ("X," "XTC") is a methoxylated amphetamine (phenethylamine), and produces effects that overlap those of classical compounds (Lister et al., 1992). Low doses of the dissociative anesthetics, phencyclidine and ketamine (Siegel, 1978), and antimuscarinic agents (Ketchum et al., 1973) also share subjective properties with the hallucinogens. However, hallucinogens do not produce anesthesia at high doses, as do the former compounds, nor is there a clouding of consciousness at "psychedelic" doses, as with the latter.

A clinically useful manner of representing hallucinogens refers to their temporal properties: onset, peak effect, and duration of action. An "ultra-short-acting" drug's onset is less than 1 minute, peak effects occur within 5 minutes, and duration is 30 minutes or less. Intravenous DMT is an example (Strassman et al., 1994). A "short-acting" hallucinogen's onset is between 5 and 15 minutes, peak effects are within 15 to 60 minutes, and duration is 1 to 2 hours (*e.g.*, intramuscular *N,N*-diethyltryptamine; Faillace et al., 1967). "Intermediate-acting" hallucinogens include the orally active tryptamine psilocybin (Rinkel et al., 1960). Onset is within 15 to 30 minutes, peak effects are at 1 to 3 hours, with duration up to 6 hours. "Long-acting" hallucinogens include oral LSD and mescaline (Hoch et al., 1952), with onset at 30 to 90 minutes, peak effects at 3 to 5 hours, and duration of 8 to 12 hours. "Ultra-long-acting" compounds include the poorly characterized African plant drug ibogaine (Fernandez, 1982). Duration of action may last 18 to 24 hours.

Prevalence of Use

Hallucinogen use in the United States remained relatively constant from the late 1960s to the late 1980s (Pope et al., 1990). However, data from the National Institute on Drug Abuse (NIDA) show an increase in any LSD use by high school seniors "within the last 12 months" from 4.8% to 5.6% from 1988 to 1992. While the magnitude of this rise is slight, it stands in contrast to the abuse of other drugs. For example, the proportion of seniors who had used any cocaine dropped from 7.9% to 3.1% during the same period (Johnston et al., 1993). Thus, the proportion of respondents who reported any use of LSD was almost twice as high as the proportion reporting any cocaine use by high school seniors in 1992. The 1990 NIDA statistics reveal that lifetime prevalence rates for hallucinogens were about the same as those for cocaine, and 7 to 8 times higher than for heroin. LSD ranked first in the categories of "most intense" and "longest" high among respondents. Between 13 and 17 million individuals in this country have used a hallucinogen at least once (NIDA, 1991).

Legal Status

Hallucinogens reside in Schedule I of the Controlled Substances Act of 1970, which is reserved for drugs with "high abuse potential," "lack of established safety even under medical supervision," and "no known use in medical treatment" (Anonymous, 1970). Compounds with "substantially similar" structure or function also are Schedule I drugs, as a result of the passage of the Controlled Substances Analog Bill of 1986 (Anonymous, 1986).

The use of mescaline-containing peyote by the Native American Church has been debated for nearly a century (La Barre, 1989). Native American Church members may possess and ingest peyote in several states, and non-Native Americans may use it in Church ceremonies in some. In response to increasing judicial restrictions on peyote use, the Religious Freedom Restoration Act became law in 1993 (Anonymous, 1993). Interpretation of this law with respect to hallucinogenic "sacraments" by traditional non-Western (Rivier and Lindgren, 1972) and other "neo-religious" groups will be of interest.

Basic Neuropharmacology

The nearly simultaneous discoveries of serotonin (5-HT) and LSD undoubtedly have had an impact on the preeminent role of this neurotransmitter in explicating hallucinogens' effects and mechanisms of action. Noradrenergic (Horita and Hamilton, 1969), dopaminergic (Ahn and Makman, 1979), and cholinergic (Cervoni et al., 1963) systems have also been investigated, but have received less attention.

Gaddum and Hameed (1954) and Woolley and Shaw (1954) first suggested that LSD antagonized the effects of 5-HT in lower animals. Soon thereafter, Freedman (1961) showed that LSD decreased particulate binding of 5-HT in the axon, raising brain levels of 5-HT and lowering those of its metabolite 5-hydroxyindoleacetic acid. 5-HT mechanisms have been demonstrated for electrophysiological (Aghajanian et al., 1968), pharmacological (Conn and Sanders-Bush, 1986), and behavioral (Glennon et al., 1985) effects of hallucinogens.

The animal model of "hallucinogenesis" most used is drug discrimination, wherein animals are trained to distinguish between a hallucinogen, usually LSD, and saline. Animal responses to a test drug as if it were LSD suggest that the "interoceptive" or "discriminative" cue is similar to LSD's (Glennon et al., 1983). However, several nonhallucinogens are LSD-like in this model, such as quipazine (Cunningham and Appel, 1987) and lisuride (Nielson, 1985), while psilocybin is not (Koerner and Appel, 1983), which emphasizes the need for human studies.

Hallucinogens were important in stimulating the burgeoning field of 5-HT receptor subtypes (Peroutka and

Snyder, 1979). Current data emphasize effects upon the 5-HT_{1A} and 5-HT_{2A/C} subtypes (Glennon et al., 1985; Spencer et al., 1987), alone or in combination (Arnt and Hyttel, 1989).

Tolerance (Freedman et al., 1958) and cross-tolerance (Appel and Freedman, 1968) to behavioral effects of hallucinogens is seen rapidly, and is accompanied by downregulation of 5-HT₂ sites (McKenna et al., 1989).

Human Psychopharmacology

Measurement of Hallucinogen Effects in Humans

Initial human studies with hallucinogens relied upon careful clinical observation, using psychoanalytic (Savage, 1952) or behavioral (Cheek and Holstein, 1971) perspectives, in normal subjects (Snyder et al., 1967) and psychiatric patients (Hoch et al., 1952). In addition, hallucinogen effects on previously validated psychological scales, such as the MMPI (Belleville, 1956), assessed change scores within individuals and allowed comparisons between hallucinogen-induced syndromes in normal subjects with other well-characterized psychopathological states.

Three rating scales were developed specifically for LSD effects in the 1960s. "Normative" data for all three scales were generated from effects in unexperienced hallucinogen users who were not told what the effects of LSD might be, making the data difficult to interpret, particularly when an attempt is made to determine their reinforcing properties in those who use them recreationally.

The Abramson et al. (1955) scale emphasized somatic, cognitive, and perceptual effects of LSD, while the Linton-Langs scale (Linton and Langs, 1962) assessed effects predicated on a psychoanalytic theory of consciousness. The Addiction Research Center Inventory (Haertzen et al., 1963), the standard rating scale for assessing effects of drugs of abuse, used LSD as one of several mind-altering compounds. Its LSD scale is known as the dysphoria scale, reflecting its emphasis on unpleasant effects (Haertzen and Hickey, 1987).

We have developed a new instrument, the Hallucinogen Rating Scale (HRS), that differs from these previous scales. It was drafted by interviewing experienced hallucinogen users, and modified during pilot studies with DMT in an additional cohort of well-prepared, educated, well-functioning, experienced hallucinogen users (Strassman et al., 1994).

The HRS also differs from other rating scales in its emphasis on a "mental status examination" clustering of items. In the Abramson et al. scale, derivative factors, such as paranoid ideation and generalized inhibitory effects, are used. The Linton-Langs scale also uses this manner of grouping items: feeling less inhibited and suspiciousness are examples. In the Addiction Re-

search Center Inventory, similarities or differences between a test drug and "reference" drugs are made, without determining the nature of these similarities or differences. In the HRS, items are grouped into six "clinical clusters": somesthesia (somatic/interoceptive/visceral cues), affect, perception, cognition (thought content and processes), volition (willful ability to interact with one's mental and physical self and the environment), and intensity (a global measure of robustness of response). These clinical clusters provided better resolution of subtle dose effects for DMT than multiple biological measurements in initial dose-response studies. Principal components factor analysis, choosing six factors to correspond to the clinical clusters, also proved superior to biological variables in differentiating among DMT doses, but generated a less heuristically useful grouping of individual items (Strassman et al., 1994).

Route of Administration

Whether LSD and longer-acting compounds produce their effects directly, or require secondary, "downstream" mechanisms, has been debated, because of the delay in onset of effects of LSD even with intravenous administration (Aghajanian and Bing, 1964). However, Hoch (1956) described nearly instantaneous onset of LSD effects with intraspinal administration, and intravenous DMT effects also are immediate (Strassman et al., 1994). Thus, access of drug to relevant brain sites, lipid solubility, clearance, and other pharmacokinetic factors determine the time course of drug effects, rather than secondary processes. However, there may be systems downstream from 5-HT receptor agonism that require extremely short time domains for activation.

Tolerance

LSD and other classical compounds elicit behavioral tolerance (Isbell et al., 1956) and cross-tolerance (Abramson et al., 1960a) after several daily doses. The exception is DMT, for which no behavioral tolerance has been demonstrated (Gillin et al., 1976), and which elicits a fully hallucinogenic response in LSD-tolerant subjects (Rosenberg et al., 1964).

Human Hallucinogen-Neurotransmitter Interactions

Serotonin. Bromo-LSD, a potent 5-HT antagonist in lower animals (Cerletti and Doepfner, 1958), although psychoactive in humans at much higher doses than LSD (Isbell et al., 1959b), antagonized LSD effects in both normal subjects (Ginzel and Mayer-Gross, 1956) and psychiatric patients (Turner et al., 1959). Cyproheptadine, a 5-HT_{2A/C} antagonist (Hoyer and Schoeffter, 1991), prevented the subjective effects of DMT in two of three normal volunteers (Meltzer et al., 1982).

5-Hydroxytryptophan loading studies attempted to surmount the 5-HT antagonism of LSD in humans, but did not demonstrate clinically relevant effects (Pare and LaBrosse, 1963). Chronic monoamine oxidase inhibition reduced LSD's effects in humans (Resnick et al., 1964), perhaps relating to downregulation of 5-HT sites. MAO inhibition also reduced DMT effects (Sai-Halasz, 1963). This latter phenomenon may relate to inhibition of DMT metabolism (Sitaram et al., 1987). Reserpine, if administered at adequate dosage and duration, enhanced responses to LSD in humans (Isbell and Logan, 1957; Resnick et al., 1965), supporting a functional "upregulation" of relevant mechanisms.

Both *meta*-chlorophenylpiperazine (Kahn and Wetzel, 1991) and 6-chloro-2-(1-piperziny)pyrazine (MK-212) (Murphy et al., 1991) share pharmacological characteristics with the classical hallucinogens, and elicit "hallucinogenic" effects in patients with schizophrenia (Krystal et al., 1993) or alcoholism (Lee and Meltzer, 1991), but not in normal subjects (Murphy et al., 1991). Higher doses in normal subjects may produce more typical responses.

Dopamine. LSD has agonist effects at postsynaptic receptors (Burt et al., 1976), and DMT has dopamine-releasing properties (Haubrich and Wang, 1977). While chlorpromazine was suggested to be a "specific antidote" to LSD effects (Isbell and Logan, 1957), it may enhance LSD's effects if given during the acute intoxication (Abramson et al., 1960b; Schwartz, 1967). Similarly, haloperidol pretreatment enhanced the neuroendocrine and subjective effects of DMT in one subject (Meltzer et al., 1982). In addition, methamphetamine (a dopamine agonist) ameliorated acute LSD effects (Hoch, 1956). Thus, affinities of hallucinogens for dopamine receptors, relative to primarily dopaminergic or antidopaminergic compounds, may determine the end result of manipulating dopaminergic neurotransmission on responses to hallucinogens.

Other. Little data exist regarding manipulating cholinergic (Isbell et al., 1959a) and adrenergic (Murphree, 1962) systems on hallucinogen effects in humans, and require further study.

Hallucinogens and Schizophrenia

The association between ingestion of hallucinogens and onset of acute schizophrenic episodes is discussed below (see *Adverse Effects*).

One of the initial indications for LSD in clinical research was for elicitation of a time-limited "psychotomimetic" syndrome. However, the degree of overlap has been vigorously debated (Hollister, 1962; Langs and Barr, 1968; Vardy and Kay, 1983; Young, 1974). The criticism that visual effects were relatively uncommon in functional psychoses has been tempered by the high

incidence of these symptoms in later studies (Bracha et al., 1989). It appears that acutely ill, positive-symptom patients show more "psychedelic" symptoms than do chronic, undifferentiated, negative-symptom predominating patients, particularly in the prodromal state (Bowers and Freedman, 1966).

Hallucinogens also were administered to psychotic patients and comparisons were made between drug effects and preexisting symptoms (Cholden et al., 1955). These studies were limited by the highly anecdotal nature of ratings of "subjective" effects. Some studies reported that hallucinogens produced different symptoms than those patients were normally experiencing (Fink et al., 1966; Turner et al., 1959), while others reported an exacerbation of preexisting psychopathology (Hoch et al., 1952; MacDonald and Galvin, 1956). A relatively consistent finding was that "burned out," predominantly negative symptom-laden patients showed blunted responses to hallucinogens (Boszormenyi and Szara, 1958; Hoch et al., 1952). This latter finding supports lower levels of 5-HT₂ sites in the cortex of schizophrenics (Mita et al., 1986). It also prompted a search for "endogenous schizotoxins," in which case "tolerance" to naturally occurring psychotomimetics would confer resistance to exogenously administered agents in patients.

The short-chained tryptamines, DMT and 5-methoxy-DMT, were leading candidates for endogenous hallucinogens (Corbett et al., 1978; Franzen and Gross, 1965). Requisite enzymes for DMT biosynthesis were found in human blood (Wyatt et al., 1973), brain (Saavedra and Axelrod, 1972), and lung (Axelrod, 1962). Although correlations were seen between acute symptomatology and DMT excretion in patients (Murray et al., 1979), interest waned because peripheral DMT levels were not consistently different between normal and psychotic subjects (Gillin et al., 1976). However, peripheral levels do not accurately reflect either concentrations at discrete brain areas, nor differential sensitivity to comparable levels between normal subjects and patients with psychoses. Lack of tolerance to its psychological effects, given either twice-daily for 5 days (Gillin et al., 1976) or every 30 minutes four times,² strengthens its importance as a putative schizotoxin.

Psychotherapy Research

Relatively few studies used LSD as a "psychopharmacotherapeutic" agent in humans, *i.e.*, daily dosing regimens. Daily LSD elicited robust antidepressant responses in depressives in an uncontrolled study, while tolerance to its psychedelic effects developed rapidly (Savage, 1952). These data are consistent with similar

² Strassman RJ, Qualls CR, Berg LM (1994) Unpublished data.

effects of chronic LSD and antidepressants on 5-HT receptor function (Buckholtz et al., 1990; Stolz et al., 1983). Beneficial responses to daily dosing in some autistic children also were seen (Bender, 1966; Freedman et al., 1962; Simmons et al., 1966).

The first suggestion that LSD may hasten psychotherapy was made in the early 1950s (Busch and Johnson, 1950), and series of cases soon followed (Eisner and Cohen, 1958). LSD was believed useful in recovering early memories, enhancing associative processes, reducing repression, intensifying affective responses, and magnifying aspects of the transference (Chandler and Hartman, 1960; Hollister et al., 1962; Snyder et al., 1968). These early protocols utilized relatively low doses (25 to 100 µg) within the context of ongoing psychoanalytic psychotherapy. This was termed the psycholytic approach, and utilized multiple sessions over months or years. These studies were hampered by lack of adequate control groups and impartial raters, small sample size, and primarily anecdotal data. However, their emphasis on repeated sessions merits attention when assessing results from "psychedelic" research protocols. This latter approach, described below, may have limited efficacy by depending inordinately upon one or two highly charged sessions, without the benefit of "working through" available in the psycholytic model.

The psychedelic approach, favored by North American researchers, involved administration of a single, or at most a small number of, high dose (300 to 1500 µg) LSD session(s) after a relatively short course of psychotherapy (Pahnke et al., 1970). This psychotherapy encouraged the patient to undergo a "psychedelic experience," which had many aspects of a religious epiphany. As many "spontaneously recovered" drug abusers report similar spiritual-mystical experiences (Ludwig, 1985), this approach was turned to substance abuse treatment (Hollister et al., 1969; Savage and McCabe, 1973). Uncontrolled, often anecdotal reports from psychedelic studies also demonstrated some promise in the treatment of sociopathy (Shagass and Bittle, 1967), prisoner recidivism (Leary and Metzner, 1967-68), and the pain and despair associated with terminal illness (Grof et al., 1973; Kast and Collins, 1964).

Substance abuse treatment studies were numerous, and while initial reports were enthusiastic (Kurland et al., 1967; MacLean et al., 1961; Smith, 1958), studies using control groups and longer follow-up demonstrated less impressive results (Cheek et al., 1966; Hollister et al., 1969; Johnson, 1969). However, a review of 31 studies involving 1100 alcoholics concluded that meaningful generalizations could not be reached because of the inconsistent designs and criteria for improvement (Abuzzahab and Anderson, 1971).

In summary, many of the initial studies suggesting enhancement of psychotherapy with hallucinogens

were hampered by lack of methodological rigor. However, placebo/control treatments are problematic. For example, when 50 µg of LSD were used as "active placebo" against 450 µg of LSD in an alcoholism treatment study using the psychedelic model, minimal differences in outcome among groups were discerned (Kurland et al., 1971). That many of the low-dose group also underwent a "peak experience" emphasizes the importance of assessing the interplay between pharmacology, psychotherapy, and subjective experience. Minimum requirements for future studies should include independent raters of effects and outcome, identical (non-drug) treatment in the control group, and adequate follow-up (at least 1 year) (O'Brien and Jones, 1994). The choice of inactive and/or active placebo must be given careful consideration. Finally, a hybrid of the psychedelic and psycholytic models, in which more frequent high-dose sessions are used, may provide additional flexibility and allow more psychotherapeutic work to take place than either model alone.

Adverse Effects

The profoundly altered mental status elicited by hallucinogens requires astute clinical management, including thorough screening and preparation of prospective patient or volunteer subjects, careful supervision of drug sessions, and consistent and responsive follow-up which may require psychotherapeutic intervention.

Early clinical investigators provided reassuring safety data. A survey of American clinical research documented in normal volunteers a rate of attempted suicide of 0/1,000, completed suicide of 0/1,000, and "psychotic reactions over 48 hours" of .8/1,000. Corresponding figures in patients were 1.2/1,000, .4/1,000, and 1.8/1,000 (Cohen, 1960). These data were derived from over 5,000 subjects who had received LSD or mescaline more than 25,000 times, single individuals taking between 1 and 80 doses, using LSD doses from 25 to 1,500 µg. A British survey reported comparable results (Malleon, 1971).

Once hallucinogens escaped from the laboratory, however, emergency rooms and clinics were quickly impacted by adverse effects in unprepared, unsupervised, and psychiatrically ill individuals taking hallucinogens, especially LSD (Frosch, 1969; Ungerleider et al., 1968). LSD was nearly always of uncertain quality and dose, and combinations of LSD and other drugs and alcohol were usual (Frosch et al., 1965).

These adverse consequences may be classified temporally as acute, subacute, and chronic (Strassman, 1984).

Acute

Acute adverse effects include: a) brief panic reac-

tions to effects of the drug, which generally responded to verbal reassurance and protection of the patient, and only in severe instances, to medication (Taylor et al., 1970); and b) psychotic reactions, disorganized states that lasted longer than 24 hours and required more intensive management and often hospitalization. These psychotic reactions usually were superimposed on pre-existing psychotic disorders in polydrug-abusing patients (Blumenfield and Glickman, 1967; Hekimian and Gershon, 1968; Hensala et al., 1967; Vardy and Kay, 1983). They typically responded to treatments appropriate to the non-drug-induced syndromes they resembled (Strassman, 1984).

Toxicology laboratories now can measure sub-nanogram/milliliter concentrations of LSD in body fluids (Nelson and Foltz, 1992), aiding diagnosis of acute adverse reactions.

Subacute

Subacute effects requiring clinical intervention are flashbacks, which refer to unbidden re-experiencing of certain aspects of hallucinogen-induced effects, often visual, but partaking of all psychic functions (Wesson and Smith, 1976). They occur after an intervening period of normalcy after a drug experience (Horowitz, 1969). Not all flashbacks are felt to be adverse, and many members of the psychedelic subculture find brief "free trips" pleasurable (Wesson and Smith, 1976). The incidence is reported to vary between 15% and 77% of individuals who have had at least one LSD experience (Strassman, 1984).

In our DMT studies with experienced hallucinogen users, we have seen an incidence of 5% to 10% in volunteers with at least one high-dose DMT session. These sessions, it should be noted, are almost uniformly regarded as "higher than I have ever been," and thus may be considered traumatic. Meditation, smoking marijuana, and falling to or waking from sleep are the most common precipitants. Several volunteers willfully attempt to re-experience aspects of the DMT state by these means.

The etiology of flashbacks is not known, but organic, psychological, and social hypotheses have been proposed (Alarcon et al., 1982). Their presence in posttraumatic stress disorder and elicitation by lactate infusion (Rainey et al., 1987) suggest a complex interaction of anxiety and stress with memory processes (McGee, 1984). Flashbacks are usually self-limited, if psychoactive drugs, especially hallucinogens and marijuana, are avoided. Persistent or particularly disturbing symptoms (Abraham, 1983) require a neurological evaluation.

Chronic

Chronic adverse effects may be divided into functional and organic. Functional syndromes rarely may

be quite debilitating and treatment resistant, resembling an ego-syntonic, negative symptom-laden schizophrenic disorder (Glass and Bowers, 1970).

More difficult to diagnosis confidently as directly related to LSD use are changes in lifestyle and interpersonal behaviors associated with hallucinogen use (Blacker et al., 1968). The confluence of drugs and pre-existing personality styles is suggested in McGlothlin and Arnold's (1971) 10-year follow-up of psychotherapy patients and normal volunteers who participated in sanctioned LSD studies. This study suggested a catalytic effect of LSD use in individuals predisposed to unconventional aesthetic and philosophic ideas (McGlothlin and Arnold, 1971).

LSD-induced organic central deficits have been difficult to document with certainty, because of no premorbid data and an inability to control for other substances of abuse (Acord and Barker, 1973). Statistically, but not clinically, significant decrements were reported in several studies. Lower Halsteads' Category and Reitan's Trail Making A test scores were reported in hallucinogen users compared with control subjects; however, both of these tests were within normal ranges in drug users (Culver and King, 1974; McGlothlin et al., 1969). Nonspecific EEG changes also were described (Blacker et al., 1968).

Chronic visual disturbances, posthallucinogen perceptual disorder, akin to chronic flashbacks, may partake of functional and organic bases. The validity of this diagnosis is uncertain because of lack of premorbid data and inability to control for other drugs of abuse. Its responsiveness to benzodiazepines (Abraham, 1983) support an anxiety/functional rather than organic disorder (McGee, 1984).

Mutagenicity/Teratogenicity

Initial reports of chromosomal (Cohen et al., 1967) and reproductive (Jacobson and Berlin, 1972) disorders in LSD users were not replicated in later studies (Dishtsky et al., 1971; Muneer, 1978). Until more controlled data are forthcoming, however, women who are pregnant or not using reliable contraception are not suitable candidates for hallucinogen research protocols.

Conclusions and Recommendations

Hallucinogens are powerful drugs, with the potential to elicit or exacerbate psychiatric symptoms. Particularly aversive or overwhelming acute effects may traumatize or sensitize the individual, setting up the potential for flashbacks akin to those seen in posttraumatic stress disorder. The use of experienced hallucinogen users may reduce the traumatic nature of high-dose hallucinogen sessions, and is recommended for psychopharmacological research. Additionally, truly informed consent is possible only in experienced users. Studies

comparing responses in normal subjects with those in psychiatric patients (see below) should use the lowest doses that will generate requisite data.

Psychotherapy protocols require a careful assessment of risk to benefit ratios balancing morbidity or mortality of an untreatable psychiatric condition with the likelihood of psychological sequelae of hallucinogen exposure. The risk associated with psychotherapy research protocols may be lessened by using the lowest possible dose of drug. If high-dose administration is necessary, it may be prudent to gradually build up to this dose over several sessions.

Current Research

In the United States, we have been administering DMT since late 1990 (Strassman, 1991) in psychopharmacologic studies utilizing experienced hallucinogen users (Strassman and Qualls, 1994; Strassman et al., 1994). The University of Miami has begun phase I studies of ibogaine in preparation for substance abuse treatment research. Similar phase I studies have begun at UCLA with MDMA, also in anticipation of therapeutic applications. Psychopharmacological studies using subanesthetic, psychotomimetic doses of ketamine in normal volunteers and patients with schizophrenia are ongoing at Yale University (Krystal et al., 1994). A substance abuse treatment amendment to the University of Maryland's inactive LSD protocol has been approved, and may begin within a year.

In Europe, group and individual psychodynamic psychotherapy with LSD or MDMA has been taking place in Switzerland since 1985, but no research data have been generated. The University of Zurich is studying the effects of psilocybin and ketamine on positron emission tomography and neuropsychological responses in normal volunteers (Vollenweider, 1994). In Germany, several sites are studying mescaline and MDE (the N-ethyl derivative of MDMA) effects in normal volunteers, studies in which multiple neurobiological variables are characterized (Hermle et al., 1992, 1993).

Areas for Future Research

As described previously, a wide range of temporal characteristics are available with the hallucinogens, and may be exploited for research with different goals. For example, psychotherapy protocols might be best served using short-acting drugs whose effects last between 1 and 2 hours, while neuroendocrine challenge studies would benefit from using ultra-short-acting drugs and keeping interactions with the environment to a minimum. Protocols requiring multiple within-individual assessments could use long- and ultra-long-acting drugs.

Measurement Variables

Recent DMT studies demonstrate the superiority of subjective (HRS) responses to biological ones with respect to subtle dose effects (Strassman et al., 1994). Thus, despite better characterization of mechanisms of action for neuroendocrine, cardiovascular, and other autonomic variables, sensitivity for effects of experimental manipulations is relatively low. This emphasizes the importance of introspection and subjective data in characterizing the effects of hallucinogens, especially using a within-subjects design.

Psychopharmacology

Human hallucinogen psychopharmacology requires further study, for both clinical and heuristic purposes. Research should assess the role of non-5-HT neurotransmitters, particularly dopamine. Risperidone, with potent 5-HT₂ and D₂ antagonism, is more potent than ritanserin, a pure 5-HT_{2A/C} agent, in antagonizing animal responses to LSD (Meert et al., 1989). The importance of combined 5-HT/DA antagonism corresponds to efficacy in schizophrenia treatment with "atypical" antipsychotic medications (Meltzer, 1989), and suggests that antagonists to hallucinogens' behavioral effects in humans may be efficacious in schizophrenia.

Pretreatment blockade studies, based upon relevant animal and human data, will suggest interruption strategies for acute adverse reactions in the emergency setting. Blockade strategies (Kosten and Kosten, 1991) also could be utilized to prevent subjective effects in those prone to chronic abuse of hallucinogens in a manner similar to naltrexone.

Although most classical hallucinogens' qualitative psychopharmacological properties are believed identical (Isbell, 1959), little data exist for within-subject studies using multiple drugs. Many congeners of classical compounds have been administered safely to humans (Isbell et al., 1959b). Assessment of salient similarities and differences will suggest structure-activity relationships for design of drugs with desirable functional profiles for clinical research purposes (Nichols, 1987).

Responses to hallucinogens in psychiatric populations with presumed abnormalities in neurotransmitter systems relevant to hallucinogen action may be tested, if appropriate safeguards are in place. Such studies would generate unique human data relating disturbed subjective experience in psychiatric patients to pharmacological manipulations, generating both therapeutically and mechanistically valuable data.

Studies exploiting recently developed hallucinogen-induced animal models of information-processing defects in schizophrenia (Braff and Geyer, 1990) could be applied to normal volunteers' responses to these drugs,

further comparing the two syndromes. In addition, the HRS could be applied to more carefully characterized schizophrenic patients at various stages of the disorder, allowing novel comparisons between functional and drug-induced psychoses.

Advances in *in vivo* brain-imaging techniques may better characterize hallucinogen effects and mechanisms of action. These include topographic pharmacoelectroencephalography, positron emission tomography (assessing metabolic effects of psychoactive doses, and distribution of low doses of labelled compounds), and magnetic resonance imaging (spectroscopy and functional imaging).

Psychotherapy

Economic constraints create increasing pressure for cost-effective medical psychotherapy (Krupnick and Pincus, 1992). Sophisticated psychotherapy protocols with proven efficacy (Frank et al., 1990) provide a strong foundation upon which hallucinogen-assisted psychotherapy research may be re-examined. Courses of therapy utilizing adjunctive, high-dose, hallucinogen-assisted sessions should be considered in a model combining the psychedelic and psycholytic models. This would be a logical extension of earlier work that suggested robust short-term improvement, but less impressive maintenance of therapeutic effects, in high-dose models.

The growing numbers of terminally ill cancer and acquired immune deficiency syndrome patients who require palliative, quality-of-life treatment suggest additional areas for future psychotherapy research that would build upon older, uncontrolled studies indicating beneficial responses. The reported elements of increased pain control, improved family relationships, and greater acceptance of illness and impending death, if verified by controlled studies, would provide additional clinical support for these patients. The use of "flooding" to treat posttraumatic stress disorder in both combat veterans (Grigsby, 1987) and others (Saigh, 1989) may also provide a unique interfacing of hallucinogenic drug effects with an established treatment modality for a particularly pernicious and common disorder. Hallucinogen-enhanced imagery and associations, and associated affective responses to these, could be used to enhance the efficacy of this treatment.

Set and Setting

Although complex and potentially controversial, set and setting issues require further study. Set refers to the personality, state, and expectations of the subject, and setting to the environment in which the session takes place. Setting partakes of the physical surroundings, *e.g.*, inpatient, high-technology research unit or comfortable outpatient consultation suite; nuances of

the investigator/therapist presentation, including clothing, appearance, odor, and other physical characteristics; being belted to the bed (Smart et al., 1966) or able to move about freely; and eyes open or blindfolded (Denber, 1958). In addition, it involves the "set" of the research team members, including the nature of countertransference and empathy (Day, 1957), type and amount of training in psychotherapy and working with regressed/psychotic individuals, and the theoretical model and expectations of the research, psychotomimetic, psychedelic, or otherwise.

Finally, research team members' experience with hallucinogens may affect the nature of the results of research/treatment protocols. Swiss and German health authorities require that the principal investigators first take study drugs at doses to be used in their protocols, both for safety issues and to provide more adequate informed consent.³ In the United States, self-experimentation by research teams initially was encouraged (Cerletti and Rothlin, 1955; Johnson, 1969; Szara, 1957). However, in response to highly publicized cases of self-experimentation and extraresearch drug taking with volunteers (Leary, 1968), this practice was discontinued. Future research must carefully account for these setting variables in assessing outcome measures, and the European practice of "going first" should be considered.

Training Issues

The small number of protocols using hallucinogens allows for very close contact between investigators and regulatory agencies overseeing this work. However, renewed examination of these compounds may generate a large number of requests to use them in clinical studies. State of the art methodologies are no guarantee against disasters resulting from imprudent administration of hallucinogens to humans.

Transference and countertransference issues are rarely discussed in psychopharmacology research, and increasingly less so in psychotherapy research. However, the regressed, suggestible, and unusual behavior of subjects under the influence of hallucinogens is easily observable. Interpersonal exchanges that would be readily overlooked in a normal state of awareness may assume extreme and confusing meaning. The clinical investigator not only may become the object of infantile wishes and fears, but may, in the subject's mind, actually look, smell, feel, and sound identical to highly emotionally charged people in his or her life. In addition, the clinical researcher may have multiple, conflicting, and more-or-less conscious motivations for administer-

³ F.X. Vollenweider, Department of Psychiatry, University of Zurich, personal communication, 1993; L. Hermle, Department of Psychiatry, University of Göttingen, personal communication, 1993.

ing incapacitating drugs to humans. These may include narcissistic, grandiose or sadistic, and voyeuristic impulses. Callous, offhand, or teasing remarks made for these and other, less malignant, but similarly unexamined, motivations can dramatically alter the course of a volunteer's hallucinogenic drug experience, from a psychedelic to psychotomimetic. Sexual relations between clinician and subject, during or after a hallucinogenic drug session, the most disastrous acting-out of both parties' drug-altered sensibilities, do occur.

Regulatory agencies determine professional qualifications and adequacy of facilities for conducting this research. However, I believe that specialized training, and perhaps certification, is necessary for clinical investigators performing human hallucinogen research. Such training/certification and ongoing periodic supervision would reduce the likelihood of subtle or flagrant misuse of these compounds by unknowing or unscrupulous clinical investigators. Specific proposals regarding the nature of this training and supervision is beyond the scope of this article. This suggestion is meant to stimulate further debate and discussion at institutional and governmental levels.

Conclusion

The renewal of human hallucinogen research is encouraging. However, it must be tempered with an appreciation that the controversial nature of these drugs caused a suspension of nearly a generation's worth of research in the field (Dahlberg et al., 1968). Ongoing studies are taking a painstaking, systematic approach, and are avoiding claims that cannot be substantiated by data. Careful attention to selection, screening, preparation, supervision, and follow-up of subjects undergoing hallucinogenic drug sessions is absolutely necessary. In addition, the training, characteristics, and research setting of clinical investigators desiring to work with these compounds must be addressed directly.

These precautions will provide a safety net to minimize many of the mistakes and false leads that plagued the first round of human studies. If appropriate circumspection is practiced, the re-examination of the role of hallucinogens in clinical research and treatment will be substantial.

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