Human Hallucinogenic Drug Research: Regulatory, Clinical, and Scientific Issues

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INTRODUCTION

It is likely that no other group of drugs has been subject to such intensive clinical study and to then nearly complete neglect in such a short a period of time as the hallucinogens. Mescaline, the most well-known psychoactive alkaloid of the peyote cactus, was studied in a limited fashion (Kluver 1928) before the discovery of lysergic acid diethylamide (LSD). However, Sandoz Laboratories' description of the microgram potency of LSD to induce psychotomimetic effects (Stoll 1947) generated tremendous excitement in psychiatry and may be seen as an equally important precursor to the modern era of biological psychiatry, as was the contemporaneous discovery of chlorpromazine's antipsychotic properties.

Thousands of subjects, both normal volunteers and psychiatric patients, received LSD and similar drugs in research in the United States and Europe. Szára (this volume) has summarized the research done and monetary effort expended toward understanding LSD's effects during the early 1950s through the early 1970s. Important insights into human cognitive, emotional, electroencephalographic, and perceptual functions in normal individuals and in persons with a broad range of psychiatric disorders were detailed, based on early psychopharmacologic investigations of LSD's effects (Hoffer and Osmond 1967). Drug-assisted psychotherapy, although not clearly proven efficacious before research with these drugs was stopped, had shown some promising results (Pahnke et al. 1970). Neither optimal patient selection nor psychotherapeutic approaches had been decided upon, nor had a firm theoretical basis for this type of work been developed (Grinspoon and Bakalar 1979).

There are several recently published popular histories of the psychedelic era: its beginnings, flourishing, and eventual decline within the scientific, legislative, and media communities (Lee and Shlain 1985; Stevens 1987). Unsupervised use of these drugs by millions of young adults and the

domestic instability caused by the Vietnam War combined to make use and abuse of hallucinogens a significant public health concern. In order to restrict their use by the public, hallucinogens were placed into Schedule I of the Controlled Substances Act of 1970. Drugs in this schedule have no known medical use, cannot be used safely even under medical supervision, and are highly abusable. However, the regulatory process involved in working with Schedule I compounds discouraged all but a few investigators from human research with these compounds. Recently, however, mescaline's psychological and electroencephalographic effects have been studied by a German group (Oepen et al. 1989). In addition, a group of Swiss clinical psychiatrists has been administering 3,4-methylenedioxymethamphetamine (MDMA) and LSD to psychiatric patients since 1985, but no data have been forthcoming from purely clinical use (Widmer 1992).

The confusing and often contradictory nature of the approaches taken in understanding and studying these compounds is reflected in the many names they have received. These names include but are not limited to: "hallucinogenic," "psychedelic," "psychotomimetic," "mysticomimetic," "entheogenic" (generating the divine), "psychodysleptic," "illusogenic," "phanerothyme" ("soul-feeling"), "psycholytic," "phantasticant," and "psychotogenic" (Stafford 1982). "Hallucinogenic," probably the most widely used term in the medical literature, is used in this chapter. However, it should be remembered that frank hallucinations with these drugs are rare, and hallucinogen is as much a term of convenience as of accuracy (Shulgin, this volume).

A tremendous amount of publicity and scientific discourse took place regarding the adverse effects of hallucinogenic drugs. As early as 1960, Cohen had published data on nearly 5,000 individuals exposed to LSD either as research subjects or in drug-assisted psychotherapy. These cases were obtained from his and others' research caseloads. He concluded that the incidence of psychotic reactions lasting longer than 48 hours was 0.08 percent in controls and 0.18 percent in patients; the incidence of suicide attempts was 0 percent in controls and 0.12 percent in patients (Cohen 1960). Thousands of cases subsequently were reported of individuals presenting to emergency rooms and psychiatric clinics for treatment of adverse reactions. These included acute panic reactions, the bad trip, and "flashbacks," or spontaneous eruptions into awareness of one or more features of a previous drug experience.

These reports have been reviewed carefully, and it was concluded that nearly all of these contained serious methodological flaws (Strassman 1984). These unavoidable limitations to these descriptions of adverse effects included lack of knowledge of the actual identity or dose of drug, confounding combinations of other drugs or alcohol, sparse premorbid data on the subjects' psychiatric history, and selection bias. Furthermore, it appeared that in carefully screened, prepared, supervised, and followed-up subjects, both experimental and psychotherapeutic, the incidence of prolonged or delayed adverse reactions was extremely low (Strassman 1984).

The necessary interfacing between human psychopharmacology and basic neuropharmacology has proceeded for the psychotherapeutic drugs such as minor tranquilizers, antidepressants, neuroleptics, and lithium. These parallel courses of investigation have provided clinicians with new families of drugs based upon data generated in lower animal models. Examples include the 5-hydroxytryptamine (5-HT_{1A}) partial agonist and anxiolytic agent buspirone and the selective serotonin reuptake inhibitors fluoxetine and sertraline. Such interfacing work, however, has not been possible with the hallucinogens because of the difficulty associated with human research with them.

In spite of restrictions on human use of hallucinogens, basic research has proceeded at a rapid rate. For example, the original work describing the 5-HT_1 and 5-HT_2 subtypes used LSD (Peroutka and Snyder 1979); the later discovery of the 5-HT_{1C} subtype was made with LSD (Yagaloff and Hartig 1985); and phenethylamine hallucinogens are now the standard radioligands for localization of $5\text{-HT}_2/5\text{-HT}_{1C}$ subtypes in mammalian brain (Appel et al. 1990).

Several converging factors now provide a suitable backdrop for the resumption of human research with hallucinogens (Freedman 1984). The aforementioned advances in serotonin neuropharmacology have generated one of the major thrusts in current neuroscience research; that is, the role of serotonin in normal and aberrant brain function. Much human psychopharmacologic data are being generated on the effects of 5-HT agonists and antagonists, including L-tryptophan, L-5-hydroxy-tryptophan, fenfluramine, chlorimipramine, buspirone, b-chloro-(1-piperazinyl)pyrazine (MK-212), meta-chlorophenylpiperazine (MCPP), ritanserin, metergoline, methysergide, and cyproheptadine (e.g., Murphy et al. 1991). No 5-HT active compounds generate more profound or unusual effects on mental function than the hallucinogens,

and a firmer theoretical foundation is now available to begin assessing the relative contributions of specific 5-HT subtypes in their mechanism of action. In addition, the use of hallucinogenic drugs by young adults is growing, unlike the use of other illicit psychoactive drugs (NIDA 1991). Therefore, public health issues are addressed by resumption of careful study of the hallucinogens with the possibility of developing safe, effective, and rapid antidotes to drug-induced acute adverse reactions. Finally, the approaches taken by proponents of the psychedelic revolution may have faded sufficiently into the background of the American psyche to allow the resumption of systematic, hypotheses-based research into the effects and mechanisms of action, and perhaps therapeutic utility, of these most interesting drugs.

EPIDEMIOLOGY AND PUBLIC HEALTH SIGNIFICANCE

Hallucinogen use in this country had remained relatively constant over the last 20 years but now appears to be increasing. The 1990 high school drug use survey (Johnson et al. 1991*a)* found that approximately 10 percent of high school seniors polled had used hallucinogens at least once, an increase of 0.4 percent since 1989. These lifetime prevalence rates are about the same as those for cocaine, seven to eight times higher than for heroin, almost twice as high as for sedatives, and three times higher than for steroids. LSD ranks first in the categories "most intense" and "longest" high among respondents. The comparable population estimates for young adults and college students indicate a 0.8 percent rise in lifetime prevalence rates for LSD use (0.6 percent increase in annual prevalence rates) in 1990 compared to 1989; females' use had been converging on males, but "in 1990, an important increase in LSD use among males widened the difference again" (Johnson et al. 1991*b,* p. 92). Lifetime prevalence rates in young adults for LSD are three times those for phencyclidine (PCP) and more than half those for cocaine. The 1990 National Household Survey of Drug Abuse (NIDA 1991) reports that lifetime prevalence of hallucinogen use is 7.6 percent, compared with 11.3 percent for cocaine. The number of individuals in this country, therefore, who have used an hallucinogen at least once is estimated at between 13 and 17 million. Whites use hallucinogens more (8.7 percent lifetime prevalence) than either African Americans (3.0 percent) or Hispanics (5.2 percent), with a consistent male-to-female ratio of 2-3:1 across all ethnic groups.

The compound used in the study described below, N,N-dimethyltryptamine (DMT), is used by a seemingly small proportion of hallucinogen abusers. However, DMT is a prototypical tryptamine hallucinogen. Variations on its structure have generated other short-duration parenterally active drugs such as N,N-diethyltryptamine (Szára et al. 1966) and N,N-dipropyltryptamine (Soskin et al. 1973). Furthermore, designer drugs developed to circumvent existing scheduling laws and/or produce specific qualitative effects derive from this compound (Repke et al. 1985). Other recent developments also are important. Ayahuasca, an Amazonian plant extract (McKenna et al. 1984*a*), has become popular in some circles on the coasts, being imported from Peru and Brazil. It contains DMT, found in one of the plants *(Psychotria viridis),* and monoamine oxidase (MAO) inhibiting ß-carboline harmala alkaloids in another plant *(Banisteriopsis caapi),* allowing the DMT to become orally active (McKenna et al. 19848).

Space limitations prevent a detailed discussion of the relationship between hallucinogen use and other psychiatric disorders. However, the greater incidence of use of hallucinogens by individuals with schizophrenia than by a normal population (Mueser et al. 1990), the possible role of hallucinogens in the development of borderline psychopathology (Dulit et al. 1990), the higher incidence of hallucinogen use in nondrinkers who are first- and second-degree relatives of alcoholics compared to controls (Schuckit and Sweeney 1987), and the role of hallucinogens in precipitating schizophrenic and other psychoses (Vardy and Kay 1983) all bespeak the importance these drugs have for issues of public psychiatric health.

REGULATORY ISSUES

A detailed account of the process by which an investigational new drug (IND) permit was acquired for DMT has been published (Strassman 1991). This chapter summarizes the salient points.

There were several reasons DMT, rather than longer-acting, more popular hallucinogens, was chosen for a research proposal. First, it is a very short-acting hallucinogen, with peak effects obtained within 2 to 5 minutes after intramuscular (IM) injection (Sai-Halasz et al. 1958). This attribute is an advantage in the potentially anxiety-provoking environment provided by a modem clinical research center, where a renewal of human studies with hallucinogens must take place. That is, no

matter how troubled a subject's experience on DMT might be, it would be short-lived and relatively manageable.

Second, DMT is an endogenous hallucinogen whose existence in the human nervous system has never been adequately explicated (Gillin et al. 1976). Thus, an investigation into the mechanisms of action and effects of DMT might shed some light on endogenous hallucinatory states. Along this line of reasoning, antidotes to DMT might show efficacy as treatments of disorders with hallucinations such as schizophrenia. The importance of the 5-HT_2 receptor subtype in the mechanism of action of the novel antipsychotic drugs clozapine (Meltzer and Nash 1991) and ritanserin (Gelders et al. 1986) bespeaks the relevance of this approach. Finally, DMT abuse is not a widespread phenomenon. Thus, beginning human hallucinogen research with DMT would not cause the intense public scrutiny that might result from knowledge that LSD once again was being used in humans.

In order to use a drug in humans for either nonindicated purposes or a purpose with no currently established use, it is necessary to apply to the Food and Drug Administration (FDA) for an IND permit. However, for a Schedule I hallucinogen, none of which has been used in humans for many years, there is the additional problem of locating an acceptable source of the compound. A Drug Master File for the compound must be established for the FDA to determine basic safety and manufacturing data concerning any drug for human use. This file contains manufacturing and quality control data for the drug to which FDA may refer. FDA also is charged with concurrently establishing whether the proposed course of study will yield worthwhile data.

The proposed study was to establish normative dose-response data for DMT in a group of experienced hallucinogen users in a double-blind, randomized, placebo-controlled study design.

Experienced hallucinogen users were chosen for three reasons: experienced subjects would be less likely to panic than naive subjects in response to the sudden onset and intensely hallucinogenic effects of a short-acting drug such as DMT; experienced subjects would be more capable of carefully describing the effects of DMT than would subjects with no experience with these compounds; and liability for the subsequent development of substance abuse and/or other psychiatric pathology would be less sustainable in subjects with a prior history of use of these drugs.

The literature on the biological and psychological effects on humans and animals of hallucinogens in general and DMT in particular was reviewed, primarily from the perspective of recent advances in 5-HT neuropharmacology and psychopharmacology. Several hypotheses were then generated regarding what variables would be affected by DMT, what the interpretation of these effects would be, and subsequent experiments that would help prove or disprove these interpretations. The variables of interest were easily observable and verifiable. They included several neuroendocrine functions, cardiovascular effects, autonomic effects (pupil diameter and core temperature), and rating scale scores.

The first step in the application process for use of DMT was to submit a protocol to the Human Research Review Committee of the University of New Mexico School of Medicine's Institutional Review Board (IRB). The IRB is responsible for the protection of human subjects involved in any clinical research. Although the IRB is concerned primarily with risk-to-benefit ratios, it also may offer suggestions regarding the scientific quality of the proposed study. This latter function usually is subsumed by the Scientific Advisory Committee of the General Clinical Research Center (GCRC) of the University of New Mexico Medical School, where the actual study was to take place.

The IRB places great emphasis on the nature of the informed consent document and, at first, was inclined to have this document state that DMT "had no known medical use," one of the criteria for placement into Schedule I. However, the suggestion was made that, if FDA approval were subsequently obtained, this would not be the case, as DMT would have been approved as a medically useful compound (i.e., as a probe of human serotonergic psychopharmacology and neuroendocrinology). The IRB accepted this reasoning and did not insist on including this phrase, which would have unnecessarily alarmed the subjects who were already approaching the study with some trepidation. The IRB also wanted a statement in the informed consent document regarding what effects subjects might experience while under the influence of DMT.

Interviews had previously been conducted with 19 experienced DMT free-base smokers in order to draft a new rating scale for this study (see below). Thus, a relatively balanced account of the subjective effects of DMT could be provided without going into too much detail. The subjects interviewed spoke most frequently of positively charged effects, so these predominated in the informed consent. However, panic, fear, confusion, and other unpleasant experiences also were listed as possible

outcomes. Prolonged (> 24 hour) reactions to hallucinogenic drugs do occur in carefully controlled settings, although such reactions never have been reported for DMT. However, their overall incidence is quite low. The informed consent document, then, included a statement concerning the fact that subjects might experience prolonged adverse responses to the drug and that psychiatric hospitalization was available.

Finally, the IRB was told that local approval was necessary before applying for Federal permission to begin this study. Once Federal permission was acquired, the principal investigator (PI) would notify the IRB and begin, and not before.

The issues of confidentiality and anonymity also were of concern, since admitting to the use of Schedule I drugs is a crime, and a relatively high-functioning group was expected to volunteer for the study based on the socioeconomic status of the initial interviewees. Meetings with the university hospital counsel, directors of medical records and hospital admissions, GCRC head nurse, and administrative assistants led to a coding scheme by which subjects' confidentiality and anonymity were maintained, with only the PI having the key to the code.

The next step was presenting the protocol to the GCRC Scientific Advisory Committee for a thorough scientific critique. Issues of informed consent and ethical review were not taken up, except in a general way, as these concerns were the purview of the IRB.

After approval from both university committees charged with scientific and ethical issues, State Pharmacy Board approval was necessary to obtain and use a Schedule I drug. The protocol and the appropriate approvals had previously been submitted to the Drug Enforcement Administration (DEA) in Washington, DC, but approval had not yet been received. However, the State Pharmacy Board approved the protocol after it was explained that Federal DEA approval could not be received until State approval was obtained and that the project could not begin until all the requisite Federal permits were in hand.

The Federal approval process required simultaneous interaction with the FDA and the DEA. The applications for a Schedule I permit for DMT were sent to DEA, and the IND application was sent to FDA at the same time. Nearly 2 years were required to keep both of these processes on track until they were finally approved.

The application process to the DEA was complicated by requests for DMT for two separate reasons, possibly from two different sources, and of two different grades. DMT was required for the development of a laboratory assay for DMT in human blood and could be purchased from one of several chemical supply houses. However, laboratory grade DMT could not be used for human studies, even if it were purified to FDA standards. Thus, an additional source of pharmaceutical quality DMT was necessary for human administration. DEA was reluctant to approve the Schedule I application to ***possess*** laboratory grade DMT until the IND was received from the FDA. FDA could not decide whether to approve the IND request until pharmaceutical quality DMT was on hand and its appropriateness for human use could be confirmed. FDA finally wrote a brief letter to DEA saying that the science of the study was reasonable and that human studies of DMT would not begin until the FDA had deemed it safe to begin, but that DEA could approve the Schedule I permit to *obtain* laboratory grade DMT (so assay development could begin) and pharmaceutical grade DMT (to which the appropriate quality control procedures could be applied).

The next major effort involved finding a source of DMT approved by the FDA. The FDA required a pedigree of the DMT if it were to be administered parenterally, the only way DMT alone is active. The pedigree is a description of all precursors, intermediates, and impurities in these compounds, en route to the final synthesis of the DMT. A detailed chemical analysis of the final product also is required. Additionally, the manufacturer must provide FDA with details concerning the manufacturing and cleanup procedures to assure FDA that "good manufacturing procedures (GMP)" were followed. The National Institute on Drug Abuse (NIDA) had some DMT "on the shelf," as did Sigma Chemical (from which the laboratory grade DMT was purchased). Either sample could be purified to > 99 percent purity, but FDA would not accept DMT without a pedigree. Neither NIDA nor Sigma had the pedigree information. Several other possible sources also proved to be either legally or economically unfeasible.

Finally, the DEA determined that regulations allow the synthesis of small batches of Schedule I drugs by previously licensed research laboratories if the drug was for research rather than fiduciary purposes. The "coincidental activities" clause frees synthesizers of small batches of scheduled drugs from the much more rigorous and costly security arrangements required for manufacturers with primarily commercial interests. A colleague with a Schedule I permit for DMT then agreed to

make a small batch of DMT for this study and to provide the requisite documentation, a collaboration with which FDA was satisfied in principle.

The DMT was formulated for intravenous (IV) administration by the inpatient pharmacy of the University of New Mexico Hospital. The DMT then had to be put through the quality control steps required by FDA. Since pharmaceutical companies work with much larger lots of drugs than this small batch, it took some creative problem solving to determine the number of vials of injectable DMT that needed to be tested for pyrogenicity, sterility, and content uniformity. The last issue concerns both the concentration of representative samples of the product being within 5 to 10 percent of the hypothetical value (in this case 40 milligrams per milliliter [mg/ml]) and the maintenance of this concentration over time.

Satisfied with the quality of the DMT for human use and the scientific rigor of the study, FDA gave approval to begin. DEA was notified at this time. Amendments to this protocol, if not substantive, were discussed and approved by telephone. More substantial amendments, such as combining DMT with another drug, required both written and telephone consultation as well as formally requesting the manufacturer of the additional drug to provide written authorization for FDA to access *its* Drug Master File and IND information. DEA was sent copies of all changes to the original DMT protocol.

CLINICAL ISSUES

Recruitment, Screening, and Orientation of Subjects

Experienced hallucinogen users were recruited for this study by word of mouth, except for the last subject who responded to an announcement sent through the psychology department graduate student training office of a local university. Although this particular issue has not yet arisen, it was decided to take no more than two subjects from any particular department or division to prevent the development of cliques, an unfortunate occurrence in previous human hallucinogen studies using graduate students. Subjects initially called the PI to discuss the protocol. They were asked about current medication use or drug abuse and whether they had experience with hallucinogens. Those who were taking medication chronically, had an intercurrent medical illness, or were

currently abusing cocaine or alcohol were not accepted for further screening. Occasional marijuana use was accepted. The subjects were then interviewed in person to screen more carefully for current medical and psychiatric conditions and to assess the level of experience with hallucinogenic drugs. This interview assessed adaptive and maladaptive responses to dysphoric experiences with these drugs. That is, the investigators were interested in knowing how subjects managed bad trips and whether they repressed and denied, or acknowledged, the relevance of these experiences to their personal lives. Examples of this type of adaptive response to an acute adverse reaction are being more careful with whom the person takes hallucinogens and deciding not to take these drugs in a busy metropolitan setting.

Subjects would have been withdrawn if they currently suffered from a severe Axis I disorder (e.g., schizophrenia, major affective disorder, substance abuse, or anxiety disorder) or had a history of psychosis not due to either drugs or fever. One subject with an adjustment disorder related to divorce proceedings was included, as he appeared to be managing these stresses adaptively. A past history of major depression or substance abuse was not necessarily cause for exclusion from the study if subjects were in good remission for at least 1 year, understood the nature of their episode(s), and were not in life circumstances that could precipitate a recurrence during the study.

Subjects also were required to have relatively good object relations, as determined by stability of work, school, and interpersonal functions. In this study, the subject with the most chaotic life circumstances was the person who developed an intercurrent depression midway through the protocol and had to be withdrawn from further participation. Such individuals are not believed suitable for this type of project until their personal and/or work lives are more stable.

Subjects were interested in why this work was being done, the expected results, and the hypotheses. Honesty and tact are very important when orienting and preparing subjects for hallucinogenic drug studies. Such subjects, during the intoxication, may be exquisitely sensitive to interpersonal nuances, attempts to obscure or lie, and personal discomfort with particular issues. Any approach with these subjects that hints of deviousness, dishonesty, manipulation, or callousness is multiplied several times over when the actual drug intoxication is underway. Thus, starting off on the right foot is not only desirable but will prevent paranoid, panic, and dysphoric reactions later during the actual study.

At that time, the nature of the study was described, and subjects received a copy of the informed consent to review. The subjects were asked to think over their participation and were told to call the PI with their decision or any further questions. Prospective subjects were instructed to discuss their participation with their spouse or significant other. The handful of subjects with fearful and reluctant spouses needed more time to decide to participate; some required a meeting between the spouse and study staff to prevent study participation from generating unnecessary friction within a couple. Such friction could not help but carry over into the drug sessions and affect the quality of drug effects.

The informed consent document stated that the primary effects of DMT were psychological, although high doses can cause a transient moderately elevated blood pressure. Auditory and/or visual hallucinations might occur, and other unusual effects were likely. Sense of time might be altered; very powerful emotions, both pleasurable or unpleasant, might be experienced, including opposite feelings or thoughts at the same time. Extreme sensitivity to the environment and people, including frank paranoia, could occur; on the other hand, subjects might not notice anything at all in the environment. Separation of mental processes from all physical sensations could occur. Extreme changes of mood are not uncommon. The incidence of prolonged (> 24 hr) adverse reactions to hallucinogenic drugs in well-screened, prepared, and followed-up subjects was described as quite low. If prolonged adverse reactions to DMT did develop, 24-hour emergency psychiatric consultation was available. Psychiatric hospitalization could also be arranged.

Only 3 of the original 12 subjects had previous experience with DMT, and all were extremely interested in knowing as much about it as possible. Each subject received a copy of a chapter on the history, botany, chemistry, and effects of short-acting tryptamines written for an educated lay audience (Stafford 1982, pp. 308-331).

Prospective subjects then received a structured clinical interview (SCID) of the *Diagnostic and Statistical Manual of Mental Disorders III-Revised* (DSM-III-R), Outpatient Version (Spitzer et al. 1987), by a trained psychiatric research nurse. First-degree relatives' psychiatric histories were obtained during the SCID. Diagnoses were confirmed by discussion with two research psychiatrists. A medical history, a physical examination, and laboratory screening tests then were performed by the PI. Laboratory tests included a complete blood count with differential, 24-item chemistry panel, thyroid functions (including thyroid stimulating

hormone), routine urinalysis, and electrocardiogram (EKG). Subjects were withdrawn who demonstrated any significant abnormalities in this screening, including thyroid disorder, high blood pressure (diastolic over 90 mm Hg), heart disease/abnormal EKG, hepatitis, peptic ulcer disease, diabetes, or other serious medical problems.

The PI administered the medical work-up personally to establish a hands-on relationship with subjects that would facilitate their ability to more comfortably regress under the effects of DMT under supervision in a clinical research setting, and because the personal relationship might prove helpful. This was also the first opportunity for subjects to meet the research nurse who was to assist in the drug sessions. She introduced herself, drew the requisite screening blood samples, performed the EKG, and gave subjects a brief tour of the inpatient unit. This allowed subjects to initiate a relationship with the nurse and become accustomed to her manner of performing potentially painful, uncomfortable, and embarrassing procedures (even more so in the midst of the DMT intoxication). Subsequently, the PI and nurse discussed initial impressions of the subjects.

Nature of the Research Team

The importance of one clinical nurse being involved with subjects from start to finish of the protocol cannot be overemphasized. The nurse's presence is important to the development of subjects' trust and ability to attend completely to the effects of the drug, just as the subjects' trust and confidence in the PI as the only one ever to administer the drug is important. On the rare occasion when the nurse was unavailable for inpatient studies, things never went as smoothly, subjects were not as relaxed, and verbal and nonverbal signals between the substituting nurse and PI were not as clear and unimpeded as with the regular nurse. All of these issues are significant when subjects are in an extremely regressed, suggestible, and, at times, disoriented state.

In addition, the nurse preferably should be of the opposite gender to that of the PI. The regressed state induced by hallucinogens greatly enhances the subjects' tendency to project and overly identify with the experimental team. The presence of two authority figures of opposite genders may help provide a soothing transference template for subjects who may be experiencing helpless infantile feelings.

The PI for human hallucinogen studies should be a psychiatrist with experience in the interviewing, diagnosis, and treatment of psychotic (drug-induced or otherwise) states. The PI should have extensive psychotherapeutic expertise, as the transference and countertransference issues involved in dealing with childlike and regressed conditions requires great tact and sensitivity. If at all possible, the PI should also have had a successful course of psychotherapy/psychoanalysis in order to learn about his/her interpersonal style, nuances, idiosyncracies, and their effect on others.

DMT Sessions and Their Supervision

Before entering into the double-blind, placebo controlled, randomized arm of the study, all subjects received nonblind administrations of 0.04 and 0.4 milligrams per kilogram (mg/kg) IV DMT, usually on consecutive days. The DMT solution (40 mg/ml) was drawn into a sterile tuberculin syringe at a dose range of 0.04 to 0.4 mg/kg, and diluted with sterile saline to 1.0 ml before administration. Tolerance was not a concern, as previous work demonstrated no tolerance to twice daily IM administration of fully hallucinogenic doses of DMT for 5 consecutive days. The drug was administered IV rather than IM as had been reported previously (Szára 1957) because of the results of the initial dose-finding studies using a subject with experience smoking DMT free base, the usual form and route of administration by recreational users (Stafford 1982). The onset and intensity of effect of 1.0 mg/kg IM DMT fumarate were described by this subject as significantly less intense and hallucinogenic than a previous experience with the smoked drug. Further dose-finding studies with this subject and another experienced DMT smoker established that 0.4 mg/kg IV DMT fumarate produced a rush and hallucinogenic effects comparable to or slightly greater than those seen with a full dose of smoked DMT free base.

Subjects were admitted to a dimly lit (about 100 lux) room by 9:00 a.m. after having fasted since midnight. A butterfly style small gauge metal needle was inserted into a forearm vein and kept patent with heparinized saline. Subjects were allowed to relax for 30 minutes before the drug was given. DMT was infused over 30 seconds and flushed with 5 ml of sterile saline over the next 15 seconds. Blood pressure and heart rate were taken with an automatic cuff several times before and frequently during the 30 minutes following drug administration. IV diphenhydramine and diazepam and sublingual nitroglycerin were available for severe allergic, emotional, and hypertensive reactions, respectively. The

research team (a nurse and psychiatrist) sat quietly on either side of the subject, attentive to verbal and nonverbal cues, but did not offer any direction or advice unless absolutely necessary during the first several minutes, the time of peak effects of the drug. Verbal and emotional support were provided as necessary, but drug sessions were not exploratory or therapeutic in intent nor nature. The experienced nature of the subjects, their relatively stable object relations, and the consistent emphasis on objective data collection was helpful in focusing subjects' expectations toward these goals. As drug effects resolved, discussion focused on the nature of the subject's experiences, The butterfly catheter was removed at 30 minutes postinjection, and the Hallucinogen Rating Scale (HRS, see below) was administered. After the subjects ate a snack or meal, they were discharged.

Subjects felt the onset of effects before the 45-second infusion was completed. Peak hallucinogenic effects of 0.4 mg/kg doses occurred usually before the first vital sign check at 2 minutes postinjection, a useful temporal reference point for subjects. Peak effects began resolving at 90 to 120 seconds postinjection. Subjects remained moderately intoxicated by the 0.4 mg/kg dose for another 5 to 15 minutes and felt relatively normal by 25 to 30 minutes postinjection.

The nonblind days served several purposes. They allowed assessment of the cardiovascular and subjective effects of both subclinical and fully hallucinogenic doses of DMT in a novel and potentially anxiety-provoking setting. These days also provided the research team and subjects an opportunity to become acquainted and familiar with each others' styles without the extensive blood drawing and use of the rectal thermistor that could exaggerate any potentially paranoid reactions. Subjects were also able to calibrate themselves to what to expect regarding minimal and maximal effects of the drug, one of the purposes of the double-blind study being to determine whether subjects could distinguish among incremental doses of DMT. Finally, these nonblind days provided subjects with the opportunity to drop out of the study before extensive data had been collected. None withdrew, although one subject was dropped because his diastolic blood pressure rose to >100 mm Hg after a low dose.

Double-blind study days were quite similar to the nonblind days. Two IV lines were inserted, the second for frequent blood drawing, as was a flexible reusable rectal thermistor for core temperature measurement. Pupil diameter was measured against a standard card with black circles of

1 millimeter gradations near the subject's face. DMT and sterile saline placebo dosages of 0.05, 0.1, 0.2, and 0.4 mg/kg were administered. Dosages of 0.4 mg/kg were assumed to be fully hallucinogenic, 0.05 mg would be barely distinguishable from placebo, and the intermediate doses were equally spaced on a log scale. Blood samples were drawn and later assayed for beta-endorphin, adrenocorticotropic hormone (ACTH), cortisol, prolactin, growth hormone, and melatonin. Pupil diameter and vital signs (VS) (i.e., heart rate and blood pressure) were measured 2, 5, 10, 15, 30, and 60 minutes after drug administration. Since the last blood sample was at 60 minutes postinjection, the HRS was administered 30 minutes later than for the nonblind sessions. This second 30-minute period was usually taken up by more relaxed conversation, although when possible, attention was repeatedly turned back toward the subjects' drug experience.

Study sessions occurred at an interval of at least 2 weeks from January to September, 1991. The one female subject was studied during the early follicular phase of her cycle. A negative result to a pregnancy test drawn the night before her study days was always ensured before drug administration.

SCIENTIFIC ISSUES

Serotonergic Mediation of Biologic and Behavioral Effects

Hallucinogenic drugs have multiple effects on central neurotransmission. The area currently of greatest interest is serotonin and its receptors, specifically the 5-HT_2, 5-HT_{1A} and 5-HT_{1C}, subtypes (Heym and Jacobs 1987). Noradrenergic (Horita and Hamilton 1969) and dopaminergic (Ahn and Makman 1979) effects of hallucinogens have been described but are not now receiving comparable attention.

Hallucinogenic drugs, as primarily serotonergic agonists or partial agonists, have diffuse and relatively well documented physiological effects. Growth hormone, prolactin, beta-endorphin, ACTH, and cortisol are all affected by serotonergic stimuli (Van de Kar 1991). Many of these hormones rise with the administration of hallucinogens in lower animals (Koenig et al. 1987) and humans (Demsich and Neubauer 1979) and are believed modulated by 5-HT_{1A}, 5-HT_{1C}, and/or 5-HT_2 receptor subtypes. Cardiovascular variables (McCall and Humphrey 1982), core temperature (Horita and Dillie 1954), and pupillary diameter (Greiner et al. 1958) also

are affected by serotonergic hallucinogens, with the majority of data suggesting 5-HT_2 mechanisms of action.

Studies in Animals. Animal behavioral studies use several models of hallucinogenicity to pharmacologically characterize known hallucinogens and to assess whether novel compounds have hallucinogenic properties. These models include drug discrimination (DD) (Appel et al. 1982) (consistent with 5-HT_{1A} [Spencer et al. 1987] and 5-HT_2/5-HT_{1C} [Glennon, this volume] effects); the serotonin syndrome (mediated by the 5-HT_{1A} subtype [Smith and Peroutka 1986]) and one of its components, head shakes (mediated by the 5-HT_2 subtype [Peroutka et al. 1981]); the abortive limb flick in cats (Jacobs et al. 1976); and the characteristic exploratory behavior patterns of rodents placed in a novel environment (Geyer, this volume). All these models, although generating much relevant data, lack requisite specificity. For example, apomorphine (Geyer et al. 1979) and quipazine (Kuhn et al. 1978) appear hallucinogenic in some of these models, and psilocybin (Koerner and Appel 1983) is sometimes not found to be so.

The 5-HT_2/5-HT_{1C} subtype is now of most interest regarding mediation of hallucinogenic drug effects. For example, ritanserin, a potent and selective 5-HT_2/5-HT_{1C} antagonist (Sahin-Erdemeli et al. 1991), blocks the discriminable effects of LSD in lower animals (Colpaert et al. 1985). It also blocks certain neuroendocrine (Lee et al. 1991) and subjective (Seibyl et al. 1991) effects of serotonergic agonists in humans, effects that may be mediated by 5-HT_2/5-HT_{1C} receptors. Finally, anecdotal reports indicate that ritanserin pretreatment blocks the hallucinogenic effects of LSD in humans. However, the 5-HT_{1A} receptor subtype also is important. DMT (Deliganis et al. 1991) and LSD (Pierce and Peroutka 1989) have almost equal affinities for the two subtypes.

An endogenous human hallucinogen, 5-MeO-DMT (Smythies et al. 1979), used in many animal studies of hallucinogenic drug effects, has greater affinity for the 5-HT_{1A} receptor than for the 5-HT_2 receptor (McKenna et al. 1990). Additionally, the discriminative effects of 5-MeO-DMT, which generalize to LSD (Young et al. 1982) and the selective 5-HT_2/5-HT_{1C} agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) (Glennon et al. 1979; Glennon et al. 1986), are blocked by the 5-HT_{1A} antagonist pindolol (Spencer et al. 1987), which is essentially devoid of 5-HT_2/5-HT_{1C} effects (Hoyer 1988). The 5-HT_{1A} receptor may therefore contribute necessary effects that produce the *characteristic* hallucinogenic drug syndrome. Although DMT's

neuroendocrine and behavioral effects were inconsistently blocked by cyproheptadine (Meltzer et al. 1980), the lack of specificity of this antagonist makes assessment of relative contributions of the 5-HT_2 and 5-HT_1 subtypes difficult.

Experimental Results of DMT Administration. Full details of the effects of DMT administration on multiple biological variables have been presented (Strassman and Qualls 1994). Generally, DMT was physically well tolerated by the subjects participating in this study. There were no episodes of nausea or vomiting with the dose range used, something that cannot be always said for longer-acting drugs (Denber 1956). One subject's diastolic blood pressure rose to >100 mm Hg after a screening, nonblind dose of 0.04 mg/kg; that subject was withdrawn from further participation. As one other subsequent subject had to be dropped from further study after a similar rise in response to 0.05 mg/kg DMT, this test dose of drug is necessary if higher doses are to be used.

As expected, based upon lower animal and clinical data, there were dose-dependent elevations in several neuroendocrine variables in response to DMT. Beta-endorphin, ACTH, cortisol, and prolactin were stimulated. The rise in POMC peptides was nearly 4 to 5 times baseline, with peak effects occurring within 5 minutes of DMT administration. Growth hormone rose relative to placebo, but the effects of the 0.05 mg/kg dose were no different than those of the 0.4 mg/kg dose. Melatonin levels in six subjects whose 0.4 mg/kg dose blood samples were analyzed demonstrated no daytime stimulation of this pineal hormone. The negative melatonin data are inconsistent with DMT's biological effects being mediated by nonspecific stress rather than by selective serotonin receptor subtype activation. The rise in beta-endorphin seen in this study is more than twice that seen after a 28.5 mile mountain race in which daytime melatonin levels doubled (Strassman et al. 1989). The earlier study proposed that massive sympathetic drive (i.e., catacholamine release) was responsible for the observed rise in melatonin. In the present study, a greater rise in beta-endorphin was seen in circumstances eliciting no effect on melatonin levels. These two sets of data make it unlikely that a stress effect (i.e., purely sympathetic activation) drove the neuroendocrine variables; if that were the case, melatonin levels would have risen, which they did not.

Additionally, there were dose-dependent elevations in mean arterial blood pressure, heart rate, rectal temperature, and pupil diameter. For nearly all of these biological dependent variables, the dose at which statistically

significant differences could be seen between DMT and placebo was 0.2 mg/kg, the threshold dose for hallucinogenic effects.

Although sublingual nitroglycerin and IV diphenhydramine were available at the bedside for every session, there was never an occasion to use them for hypertensive or allergic reactions. However, the author believes these drugs and IV diazepam should be readily available during all hallucinogenic drug sessions.

Subjective Effects

The study protocol was designed to generate normative dose-response data for DMT in nonpsychiatrically ill volunteers. The data were to include biological and psychological variables. There was little difficulty deciding upon which biological variables to study, based on human and basic data regarding 5-HT regulation of multiple physiological processes.

Rating Scale. The author decided to develop a new rating scale to carefully assess the subjective effects induced by the powerful, short-acting hallucinogen DMT rather than using previously developed instruments. The goal was to devise a scale developed from a population different than that used to develop normative data for the standard drug effect questionnaire, the Addiction Research Center Inventory (ARCI) (Haertzen and Hickey 1987). The ARCI subjects were former narcotic addicts serving prison sentences for violations of narcotics laws, and they were not informed what drugs were administered or what effects were expected. The subjects were not necessarily experienced with, or prone to use hallucinogens.

Other LSD rating scales' development also suffered from both a lack of truly informed consent and subjects' lack of previous experience with hallucinogens (Linton and Langs 1962; Abramson et al. 1955). The author believed it important to develop a questionnaire based on what respondents got out of using DMT (and other hallucinogens). The LSD scale on the ARCI is also known as the dysphoria scale, and although users of hallucinogens usually experience some dysphoria while intoxicated, they do not take these drugs for their dysphoric effects. Thus, a less pathological approach to scale development was also thought useful.

Nineteen experienced DMT free base smokers, who were also experienced with a wide variety of other hallucinogens, were interviewed

to provide a detailed description of the physical, perceptual, emotional, and cognitive effects of smoked DMT. A draft of the new scale, the HRS, was developed. It was administered to subjects in 13 nonblind low dose (0.04 mg/kg) and 12 high dose (0.4 mg/kg) DMT sessions. One low dose subject did not receive a high dose because of his blood pressure response to 0.04 mg/kg DMT. The HRS was modified based on the experiences reported during these sessions and upon suggestions of the subjects, all but two of whom had college degrees. The final questionnaire contained 126 questions. It generally took 15 to 20 minutes to fill out. The HRS was administered to subjects after all drug effects had resolved; subjects usually would fill out the questionnaire while eating or relaxing in bed. The brief duration of drug effect and incapacitating nature of the higher doses precluded subjects answering the questionnaire during the acute intoxication.

Two methods were used to create a more manageable number of groups of questions. The first method for developing factors was the clinical method. Based upon initial interviews with DMT smokers, the subjects' narrative accounts of their experiences, and a mental status descriptive approach to mental functions, six clusters of conceptually coherent questions were created. These clusters were: (1) affect, (2) somatesthesia/interoception, (3) intensity, (4) perception, (5) cognition, and (6) volition.

The second method of developing clusters was based on principal component factor analysis with varimax rotation, allowing the computer to create relevant factors equal in number to the clinical clusters. A detailed description of the development of the HRS and the derivation of factors/clusters has been published previously (Strassman et al. 1994).

Results. These data were described in more detail by Strassman and colleagues (1994). Behaviorally, DMT caused no troublesome effects in the dose range 0.04 to 0.4 mg/kg. No subject dropped out after the nonblind screening administration of the low (0.04 mg/kg) and high (0.4 mg/kg) doses. Only one subject was withdrawn halfway through the study because of the development of a major depressive episode. However, he had a history of recurrent major depression, acute episodes being triggered by stressful personal circumstances similar to those he was experiencing while in the study. Followup of 11 of the 12 subjects has not revealed any delayed negative effects of participation. The one subject lost to followup had gone through the protocol with no difficulties.

A brief summary of each dose's effects follows.

0.4 mg/kg: All subjects described an intense, rapidly developing rush that was both pleasurable and transiently anxiety-provoking, felt throughout the body and mind. Visual effects, noted by all subjects, ranged from intensely colored, rapidly moving, concrete, formed, more or less recognizable images with eyes open or closed, to abstract geometric patterns that were not obviously representational. With eyes open, the visual field was overlaid by geometric patterns, with undulating movement and intensification of colors of objects. Auditory hallucinations were noted in more than half the subjects but were not clearly familiar (i.e., music or voices). Subjects described usually high-pitched, whining, chattering, crinkling/crunching, or at times comical noises, such as "boing" and "sproing" sounds heard in cartoons. Somatesthetic effects were of a highly stimulatory fear-response nature, although all subjects distinguished between their physical reaction to the drug and the less emotional subjective response to this reaction.

As effects resolved, the physical sensations became pleasant and relaxing. Some subjects (N=2) described a sexual effect of the highest dose, a sensation of heat developing in the genital area; no one experienced orgasm or ejaculated. After the initial anxiety associated with the onset of high dose effects, all but one subject (11/12) described exciting, euphoric, and highly positively charged feelings, often related to the visual hallucinatory display. One-third to one-half of the subjects also described the emotional valence as bland, impersonal, and journalistic in nature, the experience developing and resolving so quickly that there did not seem to be time for subjects to react or modify it in any way. Subjects described their thoughts and evaluative capacities as relatively unimpaired and likened the experience to a dream in which, although awareness of the outside world was abolished, they were alert and attentive to the hallucinatory effects, remembering them quite well and in detail.

The first nonblind high dose was more anxiety-ridden (particularly for the first 30 seconds postinjection) than was the subsequent high dose. Subjects were better prepared to lose control after having been in that state once before. Their understanding that the drug experience was physically safe and that they would not lose their minds was strengthened by having had the high dose before. Finally, their confidence in the research team to unobtrusively support their relatively helpless state grew as their participation in the study progressed.

0.2 mg/kg: This generally was the threshold dose for hallucinogenic effects. The majority of subjects had some visual hallucinations, but auditory hallucinations were rare. Some found this to be their dose of choice, being less disorienting and anxiety provoking in onset than the 0.4 mg/kg dose, but generating enough perceptual and affective effects to be interesting and pleasurable.

0.1 mg/kg: This dose was not enjoyed by about half of the subjects. They felt the somatesthetic sensations of excitation and a tense, dysphoric "drive to discharge" more striking than the perceptual or affective changes.

0.05 mg/kg: One-third of the subjects mistook this dose for placebo. Those who were able to distinguish the dose from saline remarked on its uniformly relaxing, comfortable, and warm physical effects. One former heroin user likened it to the "soft cotton batting" of heroin. There were no perceptual (auditory or visual) effects at this dose.

Either method of grouping questions, the clinical clustering or the principal components factor analysis, provided better statistical separation of doses than did the biological factors described above. Two factors, intensity and cognition, separated all five treatments. Two of the principal component factors also could distinguish among the five treatments. The clinical clusters were more capable of separating placebo from 0.05 mg/kg effects; the principal component factors were more sensitive in distinguishing between hallucinogenic doses (0.2 mg/kg) and nonhallucinogenic (0.1 mg/kg) doses.

SUMMARY AND AREAS FOR FUTURE RESEARCH

This study demonstrated that if experienced hallucinogen users are carefully screened, prepared, supervised, and followed up, the naturally occurring short-acting hallucinogen DMT can be safely administered repeatedly in a clinical research setting. Normative dose-response data for multiple biological variables were generated, including neuroendocrine, cardiovascular, and autonomic (temperature and pupil diameter) variables. Data generated from a new rating scale, the HRS, provide a detailed account of subjective effects using several factors/clusters that demonstrate better resolution of dose effects than did the biological variables. Statistically significant effects of DMT on biological variables relative to placebo were almost always associated

with hallucinogenic effects. These biological and psychological data will provide the bases for further pharmacologic characterization of hallucinogenic drugs' properties.

Selective Blockade

A logical series of followup studies involve selective blockade of 5-HT receptor subtypes before DMT administration. Ritanserin or a similar 5-HT_{1C}/5-HT_2 antagonist could be used in this manner, and effects on DMT's biological and psychological perturbations could be assessed. If ritanserin does block DMT's neuroendocrine and/or behavioral effects, basic neuropharmacologic data will be confirmed in humans regarding the primacy of the 5-HT_2/5-HT_{1C} receptor(s) in mediating hallucinogenic drug effects. Second, a selective and safe antagonist might be available for hallucinogenic drug crises (Sadzot et al. 1989). Third, if ritanserin pretreatment *enhances* any effects of DMT, as might be hypothesized based on the enhancement of neuroendocrine responses to L-tryptophan by ritanserin in humans (Charig et al. 1986), an understanding of the functional interactions between 5-HT_2/5-HT_{1C} and 5-HT_{1A} receptors in humans will be advanced. Fourth, less related to drug abuse but also of clinical import, would be justification for the previously mentioned use of ritanserin in endogenous hallucinatory states.

Pindolol, a beta-blocker with potent 5-HT_{1A} antagonistic effects, has been used in humans to block presumptive 5-HT_{1A} agonists' neuroendocrine and other biological effects (Anderson and Cowen 1992; Lesch et al. 1990). No data exist on whether pindolol blocks serotonergic agonists' psychological effects in humans. Modulation of DMT's biological or psychological effects would also provide data validating or refuting the role of the 5-HT_{1A} receptor in the mechanism of action of hallucinogens.

Tolerance

Repeated or chronic administration of behaviorally active drugs often results in decreased responsiveness to their acute effects. Tolerance to LSD's behavioral effects was established in the rat (Freedman et al. 1958) and behaviorally and physiologically in humans (Isbell et al. 1956). Current emphasis is on receptor downregulation, particularly with respect to the 5-HT_2 subtype, which can occur within 2 to 3 days (Buckholtz et al. 1990).

DMT is unique in human hallucinogenic drug research in that tolerance to its effects has never been demonstrated (Gillin et al. 1976). These investigators administered a fully hallucinogenic IM dose of DMT twice a day for 5 days and found no tolerance to psychological, cardiovascular, or pupillary effects. Additionally, DMT's relatively undiminished effects in subjects tolerant to LSD (Rosenberg et al. 1964) is puzzling and may be associated with differential 5-HT_{1A} versus 5-HT_2/5-HT_{1C} effects. Illicit users describe variable tolerance depending on frequency of smoked administration. In animals, heroic regimes may be necessary to induce tolerance (Kovacic and Domino 1976). DMT's electroencephalographic (EEG) effects, in fact, may be potentiated by repeated administration (Gillin et al. 1973). In addition, 5-MeO-DMT's prolactin-raising effects are enhanced with repeated administration (Simonovic and Meltzer 1979), in contrast to LSD's effect on rat corticosterone showing tolerance (Halaris et al. 1976). Clearly the situation is complex and requires human studies with special attention to dose and interval.

Gender Differences

Animal data suggest a role for sex steroids in modulating several facets of serotonergic neurotransmission. Female rats are more sensitive than males to 5-HT_2-mediated hyperthermia (Bigeon et al. 1979) and show' a more robust prolactin response to the hallucinogen 5-MeO-DMT (McBride et al. 1990)

Human data also suggest sex differences in several parameters of 5-HT function. However, many studies demonstrating effects of gender on serotonergic variables do not control for menstrual state; for example, womens' less robust cortisol response to 5-hydroxy-tryptophan (Maes et al. 1989). Recent data do suggest menstrual phase effects of responsivity to 5-HT agonists (O'Keene et al. 1991). Prevalence of hallucinogen use in males in all ethnic groups is two to three times that in females (see above). Is this due to unpredictable effects of hallucinogens in women because of differential sensitivity across the menstrual cycle? A study of hallucinogenic drugs' effects across the cycle will provide additional data relating human and animal psychopharmacology and neuroendocrinology. More importantly, it will also establish norms by which data on human male and female hallucinogenic drug responses can be compared.

Other Hallucinogens

Now that systematic dose-response data for the biological and psychological effects of DMT in experienced hallucinogen users have been generated, a similar approach may be taken with other drugs. These could include psilocybin, the primary hallucinogen in "magic" mushrooms (Beug and Bigwood 1982); LSD; and phenylethlyamines such' as DOM, DOB, and DOI. These latter compounds are generally included with the classical hallucinogens, but little or no systematically acquired human data have been published to support or refute this classification. The biological and psychological data obtained with DMT could be compared and contrasted to that generated by similar dose-response studies with other similar compounds.

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