ARCHIVES OF GENERAL PSYCHIATRY

Volume 51(2), February 1994, pp 98-108

Dose-Response Study of N,N-Dimethyltryptamine in Humans: II. Subjective Effects and Preliminary Results of a New Rating Scale

[Original Article]

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Abstract

Background: Validation of animal models of hallucinogenic drugs' subjective effects requires human data. Previous human studies used varied groups of subjects and assessment methods. Rating scales for hallucinogen effects emphasized psychodynamic principles or the drugs' dysphoric properties. We describe the subjective effects of graded doses of N,N-dimethyltryptamine (DMT), an endogenous hallucinogen and drug of abuse, in a group of experienced hallucinogen users. We also present preliminary data from a new rating scale for these effects.

Methods: Twelve highly motivated volunteers received two doses (0.04 and 0.4 mg/kg) of intravenous (IV) dimethyltryptamine fumarate "nonblind," before entering a double-blind, saline placebo-controlled, randomized study using four doses of IV DMT. Subjects were carefully interviewed after resolution of drug effects, providing thorough and systematic descriptions of DMT's effects. They also were administered a new instrument, the Hallucinogen Rating Scale (HRS). The HRS was drafted from interviews obtained from an independent sample of 19 experienced DMT users, and modified during early stages of the study.

Results: Psychological effects of IV DMT began almost immediately after administration, peaked at 90 to 120 seconds, and were almost completely resolved by 30 minutes. This time course paralleled DMT blood levels previously described.

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Hallucinogenic effects were seen after 0.2 and 0.4 mg/kg of dimethyltryptamine fumarate, and included a rapidly moving, brightly colored visual display of images. Auditory effects were less common. "Loss of control," associated with a brief, but overwhelming "rush," led to a dissociated state, where euphoria alternated or coexisted with anxiety. These effects completly replaced subjects' previously ongoing mental experience and were more vivid and compelling than dreams or waking awareness. Lower doses, 0.1 and 0.05 mg/kg, were primarily affective and somaesthetic, while 0.1 mg/kg elicited the least desirable effects. Clustering of HRS items, using either a clinical, mental status method or principal components factor analysis provided better resolution of dose effects than did the biological variables described previously.

Conclusions: These clinical and preliminary quantitative data provide bases for further psychopharmacologic characterization of DMT's properties in humans. They also may be used to compare the effects of other agents affecting relevant brain receptors in volunteer and psychiatric populations.

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Recent History

Dose–Response Study of N,... GO

The "classical" hallucinogens include lysergic acid diethylamide (LSD), psilocybin, and mescaline. Above threshold doses, they reliably elicit a unique constellation of perceptual, emotional, cognitive, interoceptive, and volitional effects, in a usually clear sensorium [1]. Although other drugs might cause similar symptoms (eg, subanesthetic doses of the dissociative anesthetics ketamine hydrochloride and phencyclidine hydrochloride (PCP); amphetamines; marijuana; and anticholinergic deliriants), they can be differentiated clinically from the classical hallucinogens. For example, hallucinogens do not produce general anesthesia at high doses as do PCP or ketamine.

Despite limited cogent human psychopharmacologic studies for many years, basic neuropharmacologic work regarding hallucinogens' effects and mechanisms of action continued. Attention has focused on their serotonergic [2] in addition to dopaminergic [3] and noradrenergic [4] properties. Current research emphasizes the agonist or partial agonist properties of hallucinogens at serotonin (5-HT) receptors, specifically the 5-HT sub 2 [5,6], 5-HT_{1A} [7], and 5-HT_{1C8} subtypes.

N,N-dimethyltryptamine (DMT) is a prototypical indole hallucinogen, originally discovered in plants [9], but later found in lower animals [10] and humans [11], with well-characterized and relatively typical neuropharmacologic [12] and behavioral [13] properties. Its short duration of action, relative obscurity, history of safe use in clinical research, and unknown function in humans joined to make it an attractive candidate with which to begin a reexamination of human hallucinogenic drug effects.

Hallucinogens, as psychopharmacologic agents, can be characterized at multiple levels. Interfacing the animal and human "biological" data is possible by applying the relevant methodology to the clinical research setting. Thus, the neuroendocrine, cardiovascular, and autonomic (pupil diameter and rectal temperature) effects of graded doses of DMT, in 11 experienced hallucinogen users, were described in the preceding article [14]. However, the generalizability of animal to human data is more problematic when behavioral effects are addressed [15].

The older human literature described a broad spectrum of effects of hallucinogens, using many different methods of data collection and a variety of experimental subjects. Our approach to assessing subjective effects of DMT was to study individuals who had repeatedly used hallucinogens. We believed that experienced users would be capable of carefully observing and describing subjective effects of DMT and less prone to development of acute adverse reactions to this short-acting, highly disruptive compound

in the stressful setting of a modern clinical research center. We also thought it desirable to allow subjects, as much as possible, to use their (or a comparable cohort's) own words to describe the effects of DMT. Thus, to quantify the effects of DMT, we developed a rating scale based on descriptions of the psychological properties of DMT and other hallucinogens from similarly experienced hallucinogen users. We hoped this might provide an important "resonance" between our subjects' experiences and the words and phrases used by this independent sample.

This article describes the psychological properties of different doses of DMT using descriptions of effects clustered by a clinical, mental status method. It also presents our initial attempt to quantify these effects using a newly developed rating scale, the Hallucinogen Rating Scale (HRS).

SUBJECTS, MATERIALS, AND METHODS

A detailed description of the recruitment, screening, assessment, and characterization of the 12 experienced hallucinogen users who participated in this study was presented previously [14]. Briefly, subjects were recruited by "word-of-mouth," and those with current Axis I disorders (except for one subject with an Adjustment Disorder), ongoing medical illness, or long-term medication use were excluded from participation. The number of previous exposures to hallucinogens ranged from six to "hundreds."

One of the 12 subjects was withdrawn halfway through the study because a recurrence of major depression developed that was associated with the onset of several stressors. He was treated with and responded to desipramine hydrochloride. Thus, the data described in this article are from 11 subjects (one woman and 10 men).

Six of the 11 subjects had used 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") five or more times; five had taken it twice or less. 3,4-methylenedioxymethamphetamine is a mammalian serotonergic neurotoxin [16] with equivocal long-term effects in humans [17]. To approximate equal cell sizes to assess differential responses to the "serotonergic probe" DMT, we described the six former subjects as "high exposure" and the latter five as "low-no exposure."

DRUG ADMINISTRATION

Witnessed written informed consent was obtained. The method of, and rationale for, intravenous (IV) (rather than intramuscular) DMT administration were described in detail in the preceding article. All subjects received, on separate days, low (0.04 mg/kg) and high (0.4 mg/kg) doses of dimethyltryptamine fumarate, nonblind, in the inpatient unit of the General Clinical Research Center of the University of New Mexico Hospital, Albuquerque. The DMT was infused over 30 seconds and the IV tube was flushed with sterile saline for an additional 15 seconds.

Because the effects of DMT were so brief, we (R.J.S. and a research nurse) did not attempt to question or interview subjects during the acute intoxication, allowing them an unimpeded opportunity to observe the onset, plateau, and resolution of effects. Conversation focused on the effects of the injection once subjects were able and willing to begin talking. Other issues were discussed at the subject's discretion, but we emphasized descriptive rather than exploratory or therapeutic themes. The HRS was given 30 minutes postinfusion, after the single IV line was removed.

A similar format was used in the double-blind, saline placebo-controlled, randomized phase of the study. Furthermore, a rectal temperature probe was placed 30 minutes before drug administration, as was an additional forearm catheter for blood sampling until 60 minutes after injection. The HRS was administered after the last blood sample was drawn, and the probe and IV lines were removed. Double-blind treatments were 0.05, 0.1, 0.2, and 0.4 mg/kg of dimethyltryptamine fumarate, and sterile saline.

Sessions were separated by at least 1 week for men, and at least 1 month for the only woman, who always was studied during the early follicular phase of her menstrual cycle.

HALLUCINOGEN RATING SCALE

The details of the development, drafting, modification, scoring, and analysis of the HRS are described in an "Appendix" available on request from the authors. Briefly, 19 experienced hallucinogen users, who had also used DMT, were interviewed, providing a thorough description of the effects of smoked DMT free base, its usual form of "street" use [18]. In drafting the HRS, we attempted to include effects of DMT common to other hallucinogens, as well as those believed unique to DMT. The version finally used for the double-blind study contained 126 individual items. When filling out the HRS, subjects were asked to recall their experiences from the immediately preceding session. Almost all questions were scored 0 to 4: 0, "not at all"; 1, "slightly"; 2, "moderately"; 3, "quite a bit"; and 4, "extremely."

STATISTICS

Statistical procedures were performed using PC-SAS Version 6 (SAS, Cary, NC). Two-tailed $P<.05$ were considered significant.

In screening for dose effects, a one-way analysis of variance (ANOVA) with the factor dose, without repeated measures (because SAS discards observations with even one missing value in its repeated measures procedure), was performed for each question. All questions were retained for further analyses if they demonstrated a dose-related response at $P<.05$.

Two methods were used to place HRS items into groups. The first was a clinical mental status method, choosing six conceptually coherent "clusters." These were as follows: (1) Somaesthesia--interoceptive, visceral, and cutaneous/tactile effects; (2) Affect--emotional/affective responses; (3) Perception--visual, auditory, gustatory, and olfactory experiences; (4) Cognition--alterations in thought processes or content; (5) Volition--a change in capacity to willfully interact with themselves, the environment, or certain aspects of the experience; and (6) Intensity--strength of the various aspects of the experience.

In addition, we obtained factors using a principal components factor analysis with a variance maximum (VARIMAX) rotation. The number of factors was set at six, to correspond to the number of clinical clusters.

The major analysis was a one-way ANOVA with repeated measures, with factor dose repeated, performed on the values for each set of clusters and factors. To assess whether extent of prior MDMA use affected these quantified subjective responses to DMT, a two-way repeated measures ANOVA, with repeated factor dose and class variable MDMA history, was performed.

RESULTS

The main findings were that 0.2 and 0.4 mg/kg IV dimethyltryptamine fumarate elicited the nearly instantaneous onset of visual hallucinatory phenomena, bodily dissociation, and extreme shifts in mood, which totally replaced subjects' previously ongoing mental experiences. Auditory effects were noted in about half the subjects. Effects resolved quickly; the time course paralleled DMT blood levels described previously. Lower doses, 0.05 and 0.1 mg/kg, were not hallucinogenic; emotional and somaesthetic effects predominated. Analyses of preliminary HRS data suggest its ability to quantify and statistically distinguish dose effects.

In this section, we emphasize effects of the highest, 0.4 mg/kg, hallucinogenic dose. Effects are presented by clinical cluster, to demonstrate the heuristic value of such grouping.

0.4-MG/KG DOSE

Subjects were almost uniformly overwhelmed at the intensity and speed of onset of this dose given for the first time nonblind. All subjects described an intense, rapidly developing, and usually transiently anxiety-provoking "rush" throughout their body and "mind." This developed before the 45-second infusion was completed. The rush, compared with a "freight train" by several subjects, immediately and completely disrupted normal mental function, replacing it with hallucinogenic effects. This rush progressed rapidly to a state wherein most subjects lost awareness of their bodies, and many were not cognizant of being in the hospital or participating in an experiment for the first minute or two of the experience. The three subjects who had smoked DMT free base agreed IV effects were more overwhelming and rapid in onset.

PERCEPTION

Visual imagery predominated in all subjects. At this dose, there was little difference between what was "seen" with eyes opened or closed. Examples of this phenomena included the following comments. "I tried closing my eyes but I saw the same things with my eyes closed as I did with them open." "(The visions were so real) I had to open my eyes to reorient. When I did, the visions were overlaid on top of you. I closed my eyes and then that removed the interference with what I had been seeing." Visual imagery included concrete, formed, more or less recognizable visual images. These were both familiar and novel, such as "a fantastic bird," "a tree of life and knowledge," "a ballroom with crystal chandeliers," human and "alien" figures (such as "a little round creature with one big eye and one small eye, on nearly invisible feet"), "the inside of a computer's boards," "ducts," "DNA double helices," "a pulsating diaphragm," "a spinning golden disc," "a huge fly eye bouncing in front of my face," tunnels, and stairways. Many subjects described kaleidoscopic geometric patterns that were not obviously representational; for example, "beautiful, colorful pink cobwebs; an elongation of light;" "tremendously intricate tiny geometric colors, like being 1 inch from a color TV." Subjects described the colors as brighter, more intense, and deeply saturated than those seen in normal awareness or dreams: "It was like the blue of a desert sky, but on another planet. The colors were 10 to 100 times more saturated." Foreground-background distinctions were merged in these visions: "As far as I could see, all the way to the visual 'horizon,' there were hundreds of forms of beautiful women. Then, they became superimposed onto a (pastoral) scene that one might sketch. The figures made it a three-dimensional or four-dimensional scene."

As effects resolved, subjects would open eyes and note that the visual field was overlaid by geometric patterns, with undulating movement and intensification of colors of external objects. Several described a curious "decomposition" of external visual perceptual continuity that altered their ability to process normally what they saw. For example, one subject said, "I looked up and saw how mechanical and essentially soul-less you were. Your movements were not your own, they were no longer smooth and coordinated." There was also an enhancement of depth perception, most subjects referring to the room, and particularly a door in the room, as being "much more three-dimensional."

Auditory effects were noted in about half the subjects. They were not formed (eg, music or voices) but were usually high-pitched, "whining/whirring," "chattering," "crinkling/crunching," or at times comical, such as the "boing, sproing" sounds heard in cartoons. They were heard at the onset of effects, simultaneous with the rush and resolved just as quickly. Some subjects' auditory acuity seemed enhanced: "I was hyper-aware of all the sounds you were making in the room; settling in your chair, the blood drawing equipment, the blood pressure cuff inflating." For others, outside auditory stimulation receded far from awareness. One subject said, "I was just totally overwhelmed. If there were noises next door, I couldn't hear them, they didn't matter."

SOMAESTHESIA

These effects were typical of a highly stimulatory "fear response." Several commented on their "breath catching in the throat," or the "wind being knocked out of me" at the onset of effects. Many described a transient heaviness in the chest, a sense of constriction and pressure. One subject said, "I was worried that the vibration would blow my head up. The colors and vibration were so intense, I thought I would pop. I didn't think I would stay in my skin." Another said, "There's that feeling of the dip in the road, swinging on a swing, your stomach sinks. The flushes run through you, your legs twitch." One subject exclaimed, before the infusion was complete, "Here we go!" This rush often progressed to a sense of detachment or dissociation from the body. The loss of awareness of physical experience coincided with the most intense display of hallucinatory images. Comments such as "I no longer had a body"; "I thought I had died"; "My body dissolved; I was pure consciousness"; "I sensed you hovering over me trying to resuscitate me as if I had just come into an emergency room" were typical.

Some male subjects described a sexual effect of the highest dose: a hot and pleasurable sensation developing in the genital area. No one experienced orgasm or ejaculated. Some subjects described a sense of "flying," "falling," a decrease in sense of bodily weight, or rapid movement. Sensations of hot, cold, and alternations between the two were common.

AFFECT

Subjects initially were anxious as the rush developed. However, they quickly settled into the experience within 15 to 30 seconds after injection. Many subjects, perhaps due to their experienced nature, were able to dissociate their emotional responses from the physical fear response. For example, "I felt the familiar body reaction, the fear, but there was no emotional response on my part. I didn't panic"; or "I tried to get myself worked up over what I was seeing, but I just wasn't able to respond emotionally."

Most described the high dose as exciting, euphoric, and highly positively charged. "I feel great, like I had a revelation or something." These qualities were often associated with the visual hallucinatory display: "The bird and I just flew. Wings! Aaaah! It was slow, majestic, grand, slow and lovely. So much beauty! So much richness!" It was not unusual for subjects to describe extremely different emotional reactions alternating with each other, or existing simultaneously, such as fear and euphoria, anxiety and relaxation.

COGNITION

Subjects found the high dose to be compellingly novel and unusual, if not somewhat disorienting. For example, "It was so alien. You immediately try to associate something familiar to it, but you can't." Another commented, "Things are coming into focus. I'm feeling human again. I had no idea what was going on. I was in the middle of the galaxy and there was no one to help me. For a second, I needed help. It just happened so fast."

However, subjects also found they were able to maintain, after some initial confusion, a watchful, observing ego. They almost uniformly remarked at how qualitatively unchanged their thinking processes were (although many described a speeding up of these processes). For example, "My intellect wasn't altered at all. I was just alert to what was unfolding during the experience"; "My mind was definitely at a different place, but it was commenting on the state as it was going on along"; "As I started to come down a little, I got journalistic. I became an observer."

Reality testing was affected inasmuch as subjects were often unaware of the experimental setting, so

absorbing were the phenomena. For example, in response to a nurse describing a dream of hers at the end of a subject's double-blind 0.4-mg/kg session, he said, "What you are describing was a dream. This is real. It's totally unexpected, quite constant, and objective." Despite this subject's claim, many others remarked on the degree of similarity between dreams and their experiences at this dose. "This was a dream, not a hallucination. Dreams have story lines such as I experienced today; hallucinations do not."

Some subjects emerged from the intoxication with new perspectives on their personal and/or professional lives. One said, "It changed me. My self-concept seemed small, stupid and insignificant after what I saw and felt. It's made me admit that I can take more responsibility; I can do more in areas I never thought I could. It's so unnatural and bizarre you have to find your own source of strength to navigate in it." Another "saw clearly how the personal self and consciousness are just slowed down and less refined versions of 'pure consciousness.' "

Others, however, found the cognitive effects less sanguine, noting an unpleasant discrepancy between their observation of everyday reality and their apperception of it. For example, "Everything looked right but just a little off. It was as if the room were designed to make me feel uneasy. The wall colors were malevolent; the clock looked all right, but weirdly so, not quite right, as if it were just starting to move every time I glanced at it. It was like a New Age horror film, because things didn't really look that different." Another said, "It didn't feel like my normal mode of thinking. You know how schizophrenics talk about different meanings to things? A leaf on the ground takes on new meaning, and they get into it in a big way? That kind of thing."

Some found these effects emotionally unsettling, their intellectual and emotional bases for everyday experience having been severely disrupted. Parts of subsequent drug sessions were sometimes spent "working through" responses to previous high dose(s).

Many subjects referred to a sense of an "other intelligence" present within the hallucinatory state. This was usually described as "supra-intelligent," but "emotionally detached." " 'They' were aware of me, but not particularly concerned. It was like what a parent would feel looking into a playpen at his 1-year-old laying there"; or "It was business as usual for them, there was a lot to do." Others had a clear view of "alien beings": "The 'elves' were prankish and ornery in their nature. There were four of them by the highway; they totally commanded the scene--it was their territory. They were about my height and held up placards, showing me all this incredibly beautiful, complex, swirling geometric stuff."

VOLITION

Almost every subject found the high dose to cause an almost complete loss of control. They felt quite regressed, more or less completely helpless, and unable to function either physically or psychologically in a normal manner. For example, "I'm glad you two were on both sides of me. It was reassuring. I don't know what I would have done if I were alone in that state"; "The blood pressure cuff was sort of refreshing, reminding me I was being looked after, that I had a body. I had to remember to breathe"; "I knew enough to open my eyes to get reoriented"; "I felt like an infant."

Subjects were not capable of affecting willfully the progression of effects during the earliest stages. For example, one said, "I tried telling myself to let go, but even that thought was swept aside in the rush of effects." Several described being "forced" to attend to certain aspects of the experience, by the "other intelligences." For example, "There was a sense of being told: 'Look at this, look at that, pay attention!' I tried to let go, which helped"; "One of the elves made it impossible for me to move. There was no issue of control; they were totally in control. They wanted me to look here and there. That was all I could do"; "I wanted to focus to the left, but something was forcing me to view the hallucinations to the right."

INTENSITY

Many subjects described a wavelike pattern of intensity levels with this dose. For example, "There would be alternating an awareness, or consciousness, of the scene at hand. Then there would come another wave, like the ocean, knocking me over." Many subjects, including those with experience smoking DMT, said they had been "higher than ever before" with this dose of DMT.

The first, nonblind, high dose usually was more anxiety ridden (particularly for the first 30 seconds after injection) than the subsequent high dose. That is, subjects were prepared to "lose control" after having been in that state previously. Their understanding that the drug experience was essentially safe, that they "would live" and not "lose their minds" was strengthened by having had the high dose before. Finally, their confidence in the research team to unobtrusively support their regressed state grew as their participation in the study progressed.

0.2-MG/KG DOSE

This was the threshold dose for hallucinogenic effects. Nearly all subjects had some visual hallucinations, but auditory ones were less common. Some found this to be their "dose of choice," being less frightening than the 0.4-mg/kg dose, but generating enough perceptual and affective responses to be interesting, novel, and pleasurable. The rush was difficult to distinguish, at the onset, from the 0.4-mg/kg dose, but it soon became apparent that the intensity of the experience would be less than the highest dose.

0.1-MG/KG DOSE

This dose was least enjoyed by subjects. They felt the somaesthetic sensations of excitation and the "drive to discharge" more striking than the perceptual or affective changes. They were "physically" expecting a hallucinogenic effect, but were left only with uncomfortable physical tension. One subject remarked, "You'll never sell this dose. It had all of the physical effects without any of the mental ones." Another said, "My body feels like pepper tastes."

0.05-MG/KG DOSE

Several subjects mistook this dose for placebo. Those who were able to distinguish it from saline remarked on its relaxing, comforting, and "warm" physical effects. One former heroin user likened it to the "soft cotton batting" of IV heroin. There were no perceptual (auditory or visual) effects at this dose.

Subjects were relatively consistent in their styles of reacting to all doses of DMT. That is, those who began speaking early did so after receiving all doses; those who preferred a longer period of silence with eyes closed did so after receiving all doses, too. Many, even if they were able to speak early on, chose to remain silent with eyes closed so as to be able to follow carefully the progression of effects.

HALLUCINOGEN RATING SCALE

Seventy-five of 126 questions demonstrated a significant effect of dose by a one-way ANOVA. All but one of these 75 ("What dose do you think you received today?") were included in computations choosing factors and clusters and in assessing the effects of dose on these groups of questions. Tables containing questions grouped by clinical cluster and principal components factor are contained in the Appendix available from the authors on request.

The results of a one-way ANOVA with repeated measures on mean raw scores for each cluster, with repeated factor dose, are presented in Table 1 and graphically displayed in Figure 1. Five of the six

clusters discriminated between placebo and the lowest dose of DMT (0.05 mg/kg). Two clusters, Intensity and Cognition, discriminated among all doses.

The hallucinogenic "break point," between 0.2 and 0.1 mg/kg, was statistically separable for four clusters: Intensity, Affect, Perception, and Cognition. Volition, Perception, Affect, and Intensity demonstrated significant differences between 0.4 and 0.2 mg/kg.

Three of the six principal components factors discriminated between placebo and 0.05 mg/kg of dimethyltryptamine fumarate, whereas two factors discriminated among all five doses. However, they were better able to discriminate between the hallucinogenic 0.2-mg/kg and nonhallucinogenic 0.1-mg/kg dimethyltryptamine fumarate doses (six of six, compared with four of six clinical clusters). Table 2 displays these results.

A two-way repeated measures ANOVA, with repeated factor dose and class variable MDMA history, demonstrated no effect of degree of prior MDMA exposure on either set of item groupings, across all doses.

TECHNICAL COMMENT ON ASSESSMENT OF SUBJECTIVE EFFECTS

Human studies assessing the psychological and subjective effects of hallucinogens used many approaches. Complicating these different observational and data collecting models were issues regarding the (1) subject sample and (2) purpose of drug administration. As no drug's effects are as responsive to environmental cues as are the effects of hallucinogens [19-21], "set" and "setting" issues should be considered when interpreting these data [22]. Set refers to the psychophysiologic state and the expectations of the subject; setting refers to the physical environment and experimenters' expectations within which sessions occur.

Clinical observations by skilled clinicians were among the first attempts to describe a general pattern of the effects of hallucinogens in humans. These observations used behavioral-descriptive [23,24] and psychodynamic [25,26] perspectives, providing colorful and provocative descriptions. However, it was difficult to transfer these observational techniques from one research center to another. Attempts were made to quantify some of these psychological effects [27], but similar problems arose attempting to generalize scores on, for example, "echolalia" or "regression to infancy" from study to study.

A parallel course of research applied previously validated psychological instruments to the hallucinogenic drug state. These included, for example, the Minnesota Multiphasic Personality Inventory (MMPI) [28], Rorschach [29], Weschler intelligence tests [30], and the Clyde Mood Scale [31], and provided comparisons between hallucinogen effects and previously characterized psychopathologic syndromes. Additionally, these studies quantified effects of these drugs on relatively well-characterized psychological functions. However, none of these tests were originally developed specifically for quantification of hallucinogenic drug effects.

Three rating scales were used most frequently to quantify the psychological properties of hallucinogens. Two were developed specifically for LSD--the Linton-Langs questionnaire and the Abramson et al questionnaire. The Addiction Research Center Inventory (ARCI) was developed to assess the characteristics of several drugs, one of which was LSD.

The Linton-Langs questionnaire [32,33], developed in 1962, was drafted by reviewing current literature on LSD and on the psychoanalytic theory of consciousness. A preliminary version of the scale was administered to the researchers and their colleagues who took LSD; the scale was modified based on their experiences. Experimental subjects had no previous hallucinogen experience, and they were not told

what drug they were to receive or what the effects might be. The questionnaire was administered by members of the research team. Four "empirical" scales were developed from the experimental data, factoring questions that showed a high degree of correlation. For example, Scale "A" contained items related to "impaired control or attention," "loss of inhibition," "elation," and "subjective feeling of having developed new powers of insight." This scale was used by other investigators and for other hallucinogens [34].

The Abramson et al questionnaire [35], developed in 1955, was drafted by reviewing the literature on LSD. It was administered to subjects, volunteer "non-psychotic" adults, by a member of the research team. Subjects received saline placebo or one of two doses of LSD. Sessions took place in groups, known to affect an individual's response to LSD, relative to taking it alone [36]. Only five of 47 questions could distinguish between "high dose" LSD (usually 100 micrograms) and placebo. Emphasis was on somatic and perceptual symptoms such as dizziness, unsteadiness, sweating, paresthesias, blurred vision, "inner trembling," and weakness. Groups of questions were clustered in an a priori manner among "physiological," "perceptual," and "cognitive" categories. This scale was used at the Addiction Research Center, Lexington, Ky [37], where several questions were included in the development of the ARCI.

The most commonly used rating scale for drug effects is the ARCI [38], a 550-item, true-false test, developed in 1958. Subjects whose responses were used in drafting the ARCI were detoxified opiate addicts serving prison terms for violations of narcotics laws. Subjects' responses on sentence completion tasks under multiple conditions were used in drafting this scale as were some MMPI and other rating scale items [39]. Treatment conditions of these prisoner-subjects in the initial ARCI study included no-drug, saline placebo, two doses of LSD, and several other psychoactive drugs. Five "Group Variability" scales [40] were derived, characterizing common properties of a particular drug or drugs. These scales ultimately were used to describe novel compounds as, for example, more or less "morphine-like" or "LSD-like," rather than having effects on perception or cognition per se. The LSD scale contained items related to symptoms of anxiety, tension, depersonalization, and changes in perception and sensation (the "dysphoria" items). Regarding dose effects, little difference was noted between 1 and 1.5 micrograms/kg of LSD in non-LSD scales, whereas higher scores on the LSD scale were noted with the latter dose. A short, early version of the ARCI was used to assess two doses of DMT [41], demonstrating less positive responses after the lower dose. The ARCI also was used to characterize the effects of the phenethylamine hallucinogen 2,5-dimethoxy-4-methamphetamine (DOM) [42].

Our description of subjective effects of DMT used reports obtained by experienced hallucinogen users who were well prepared for the effects of the drug. In addition, these subjects (and those whose descriptions provided the initial data for development of the HRS) found hallucinogens highly desirable. Thus, our sample differed from those used to characterize hallucinogens' effects in previous studies, and the experimental expectations were such that the entire gamut of effects could be reasonably assumed covered by our methodology. We believe the clustering of symptoms, as reflected by items on the HRS, provides a clinically useful manner of capturing some of the subtleties of DMT's effects. However, qualitative effects on clusters were not quantified in this preliminary report of the HRS. That is, affect was measured only relative to the multiple treatment conditions, and we did not parse affective changes into qualitative categories, such as "euphoria," dysphoria, or "anxiety." However, further refinement of scoring the HRS may provide these data.

The HRS was designed to assess the effects of hallucinogens, but our data concern only DMT, an unusually fast and short-acting compound. Additional testing of its ability to similarly characterize other hallucinogens is necessary. Validating the DMT-derived factors/clusters with an independent sample of DMT studies also is important.

COMMENT

We describe the subjective effects of multiple doses of the short-acting, endogenous hallucinogen, DMT in 11 experienced hallucinogen users, in a double-blind, placebo-controlled, randomized design. We also present preliminary data suggesting the utility of a new instrument, the HRS, to quantify DMT's effects.

The effects of DMT were nearly instantaneous in onset, paralleling blood levels of DMT, described in the preceding article [14]. Our subjects' descriptions comported well with previous human studies of intramuscular DMT [43,44] and with "field" reports of smoked free base [18]. The two "hallucinogenic" doses, 0.2 and 0.4 mg/kg, elicited an intensely colored, rapidly moving display of visual images, formed, abstract, or both. Auditory hallucinations were less common and well constituted than the visual ones. A physical rush, commonly progressing to a sense of bodily dissociation, also was noted with the higher doses. Alternating and sometimes simultaneous experiences of fear, anxiety, euphoria, and calm characterized the affective properties of DMT in our subjects. Reality testing was powerfully affected at higher doses, subjects usually ascribing a more compelling nature or greater "validity" to the drug experience than either dreams or everyday waking phenomena. These hallucinogenic doses were where statistically significant differences in biological responses between placebo and active drug, previously described, were seen most consistently.

Lower doses of dimethyltryptamine fumarate, 0.1 and 0.05 mg/kg, were not hallucinogenic, and they produced primarily somaesthetic and emotional responses. The former dose elicited a tensely dysphoric state partaking of the physical stimulation of DMT without providing the desired "breakthrough" into the novel perceptual effects. These results validated "field" data on the unpleasant nature of "too little" DMT [18]. The lowest, 0.05 mg/kg, dose had mildly mood elevating and calming properties, likened by one subject to IV heroin.

Results of the HRS, which must be considered preliminary, provided a quantitative approach to these phenomena. The analysis of these pilot data generated better separation of DMT doses using either clinical clusters or principal components factors of items than did the biological variables (neuroendocrine, cardiovascular, and autonomic) described in the preceding article.

We chose to study DMT in this initial attempt to begin a careful characterization of hallucinogen effects in humans. It has a short duration of action, established clinical safety, and lack of widespread abuse. It also meets electrophysiologic [45], pharmacologic [46], and human [47] and animal [48] behavioral criteria for hallucinogenicity. However, there are few data directly comparing human responses to DMT with other hallucinogens, particularly in the same individual(s). Rosenberg et al [41] described "similar subjective and autonomic effects" of DMT and LSD in six prisoner-subjects. The self-experiments of Szara [49] using mescaline, DMT, and LSD revealed the primary differences to be in onset and duration, but not in the quality, of the subjective experiences. However, the situation is not straightforward, as subjects tolerant to LSD showed limited cross-tolerance to DMT [41].

Of note was the rapid onset and peak effects of IV DMT and its extremely short duration of action. This was in contrast to LSD administered by a 60- to 90-second "slow" infusion, where initial peak effects were not seen until 20 to 30 minutes after injection [50], when a sudden shift in visual apperception and autonomic response took place [15]. Freedman [15] also described the onset of LSD effects as even quicker (within 2 to 3 minutes) when given by "rapid IV push," and effects were nearly instantaneous after Hoch [51] gave it intraspinally. The "lag" and sudden onset of LSD effects have been evident in rat behavioral studies [52] in which onset can be inferred to correlate with peak brain levels of drug [53]. Thus, the time necessary to reach peak brain LSD levels, that are then promptly followed by a slower

clearance of drug, may explain the lag between administration and onset of LSD's "march of effects." In humans after a rapid IV "push," a "rehearsal" of subsequent effects took place during the first 2 to 3 minutes, perhaps related to "equilibration" of LSD with relevant receptors [15], followed by the march of effects over the subsequent hours as LSD leaves the brain.

The active transport of DMT into rat cortex [54,55] may explain its nearly instantaneous sudden onset. Its rapid metabolism by monoamine oxidase in rat brain [56] is consistent with the brief duration of subsequent effects noted in our and previous studies.

High levels of hallucinogen binding at, and localization of, 5-HT receptor sites exist in human central tissue in areas known to subserve emotional, perceptual, and somatosensory functions [57]. Human in vitro autoradiographic studies on autopsied brain using LSD, with almost equal affinity for the 5-HT_2 and 5-HT sub 1A subtypes [46], showed high density binding to raphe [58], presumably a 5-HT_{1A} effect. The 5-HT_2 receptors were found in human cortical areas, mammillary bodies, claustrum, amygdala, caudate, putamen, nucleus accumbens, and hippocampus with in vitro autoradiography [59-61], while positron-emission tomographic studies with Fluorine-18-setoperone suggested 5-HT_2 receptors in cortex and striatum [62]. The 5-HT_{1C} receptors have been found in human choroid plexus, cortex, striatum, hypothalamus, and hippocampus [60,63,64].

The nonhallucinogenic, but clearly psychoactive, properties of the lower doses of DMT may reflect the relative contributions of several 5-HT receptor subtypes. For example, different levels of 5-HT_{1A} compared with 5-HT_2 agonism on the same cortical cell's electrical activity may selectively enhance responses to stimuli of varying strength [65].

Although 5-HT mechanisms are currently deemed primary in mediating hallucinogens' effects, older human data were limited by lack of specificity of modifying agents used and lack of careful characterization of "psychological effects" being modulated. Examples include pretreatment protocols using 5-hydroxytryptophan [66], cyproheptadine [67], reserpine [68], monoamine oxidase inhibitors [69], and 2-bromo-LSD (BOL) [70] (a nonhallucinogenic LSD analogue with poorly characterized subjective effects).

More selective and better characterized serotonergic agonists, with binding profiles overlapping those of the classic hallucinogens, have been administered to humans, but they have not produced classic "hallucinogenic" or "psychedelic" symptoms. For example, m-chlorophenylpiperazine (m-CPP), with high affinity for the 5-HT_2 and 5-HT_{1C} subtypes [71], caused anxiety, nausea, activation, "functional deficit," "altered self-reality," depression, and fear in normal subjects [72,73]. Exacerbation of schizophrenic patients' psychotic symptoms by m-CPP [74] has not been seen consistently [75]. 6-Chloro-2-(l-piperazinyl) pyrazine (MK-212), another substituted phenlypiperazine with greatest affinity for the 5-HT_3 subtype [76], but significant affinity for the 5-HT_{1A}, 5-HT_{1C}, and 5-HT_2 subtypes [77], caused anxiety and dysphoria in normal subjects [78], but "LSD-like" effects only in alcoholics [79]. This group of observations will require more work before the clinical response picture is understood clearly.

Empirical testing of several hypotheses generated by animal or previous human studies can be performed in humans, using our "normative" dose-response data for DMT, and preliminary results with the HRS. Other psychoactive drugs might be amenable to characterization with the HRS, particularly those with stimulant, dissociative, or less classical hallucinogenic effects; eg, ketamine and PCP, marijuana, sigma opiate agonists, amphetamines and cocaine, methoxylated amphetamines, and anticholinergic deliriants. In addition, "nonhallucinogenic" serotonergic probes' properties could be characterized using this scale.

The phenethylamine hallucinogens, DOM, 2,5-dimethoxy-4-iodo-phenylisopropylamine (DOI), and 2,5-dimethyoxy-4-bromo-phenylisopropylamine (DOB), are often placed together with the tryptamine and lysergamide classic compounds. Psilocybine, DMT, mescaline, and LSD also are believed to be more or less phenomenologically indistinguishable, based on the small number of human studies or extant animal literature. Carefully characterizing effects using well-prepared and experienced hallucinogen users may help determine degree of similarity and areas of differences. Selective blockade of relevant receptors, and noting effects on functions quantified by the HRS, might help tease apart the relative contributions of these receptors in mediating hallucinogens' effects. Patients with psychiatric conditions with presumed abnormalities of serotonergic function could be administered DMT, and differences in sensitivity to its psychological effects could be assessed. These data could help relate hypothetical neurotransmission disorders with subjective symptoms in psychiatric conditions.

Finally, in our study, there was no modulating effect of the extent of prior MDMA exposure on HRS responses to DMT and placebo, and there were minimal modulatory effects on our measured biological variables [14]. 3,4-methylenedioxymethamphetamine is a mammalian serotonergic neurotoxin [16]. Since the 5-HT_2 receptors implicated for hallucinogen effects are postsynaptic [59], a "functional denervation hypersensitivity" [80] might have been exposed with DMT in MDMA users. Appel and associates [81-83] have shown that the threshold dose for behavioral effects of LSD in rat can be lowered fourfold by pretreatments that reduce presynaptic 5-HT levels; ie, reserpine, p-chlorophenylalanine, or raphe lesions. Our data, however, do not suggest functional consequences of prior moderate MDMA use. Additional studies using control subjects with no history of drug abuse are necessary for a more rigorous assessment of MDMA effects on human serotonergic function.

Accepted for publication January 25, 1993.

This investigation was supported by grant RO3-DA06524 from the National Institute on Drug Abuse, Rockville, Md; the Scottish Rite Foundation for Schizophrenia Research, NMJ, Lexington, Mass; grant RR00997-13 from the National Institutes of Health General Clinical Research Center, Rockville; the Scott Rogers Fund of the University of New Mexico, Albuquerque; and University of New Mexico Department of Psychiatry research funds.

We thank Cynthia Geist, RN, and the nursing staff of the General Clinical Research Center, 5E, University of New Mexico Hospital, for nursing support; and Paul Salkovskis, PhD, assisted with helpful discussions regarding questionnaire development.

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Anxiety; N,N-Dimethyltryptamine; Dissociative Disorders; Dose-Response Relationship, Drug; Euphoria; Hallucinogens; Injections, Intravenous; Volition

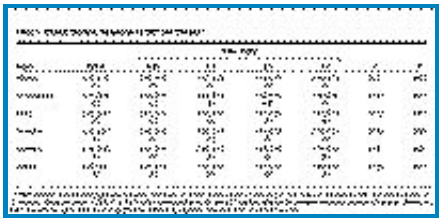

Table 1. Clinical Clusters: Responses to DMT and Placebo

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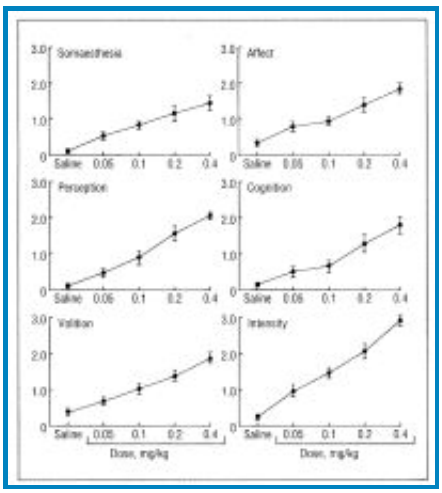

Figure 1. Mean (+-/SEM) raw values for the six clinical clusters derived from the Hallucinogen Rating Scale, in 11 subjects, after four doses of intravenous N,N-dimethyltryptamine (DMT) and saline placebo

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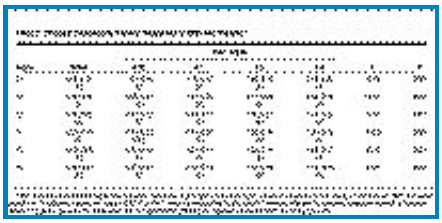

Table 2. Principal Components Factors: Responses to DMT and Placebo

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