

# Hallucinogens, Designer Drugs, and Inhalants

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## EDITORS' COMMENTS

The epidemic of psychedelic drug use that swept the country during the Vietnam War protests and the hippie "summer of love" has largely receded, and the psychiatrist entering the field today often has little experience with problems arising from these agents. A similar problem exists with respect to inhalants and so-called "designer drugs," usually substituted opioids and amphetamines with street names such as "Ecstasy" and "Eve." Acquaintance with the effects of these drugs and treatment of untoward responses to them is largely confined to emergency room physicians and those specializing in drug abuse. As Abraham makes clear, however, large numbers of persons, particularly the young, use these drugs, and any psychiatrist may be called upon to diagnose and treat complications of their use. This excellent chapter provides the psychiatrist with invaluable information on how to cope with these often difficult situations.

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## Hallucinogens

### HISTORY

At the dawn of prehistory *homo sapiens* discovered that some plants, although relatively devoid of nutritional value, nonetheless produced psychological effects that were of value for mystical and medicinal purposes, producing alterations in perception,

thinking, and mood. Abuse of such botanical substances exerted profound effects in numerous cultures throughout history, including the use of cannabis in the Islamic world, coca in Peru, and opium in China.<sup>1</sup> In 1928 Heinrich Klüver published the classic study, *Mescal: the "Divine" Plant and Its Psychological Effects*, containing a series of observations made of the effects of mescaline, an active component of *Lophophora williamsii*, the peyotl cactus.<sup>2</sup> The discovery of the hallucinogenic properties of lysergic acid diethylamide (LSD) by Hofmann in 1943 constituted a quantum leap in available potencies, since the psychic effects achieved by 300 mg of mescaline could now be achieved with 100  $\mu$ g of LSD, a 3000-fold increase in potency. The second consequence of this discovery was that the use of hallucinogenic plants was no longer restrained by religion, region, culture, or botanical supplies. With the introduction of LSD to Western Europe and the United States in 1949, an era of scientific and therapeutic investigation of the hallucinogens began, leading to increased understanding of serotonin receptor subtypes and neuroanatomic distribution, neural signal transduction, the mechanisms of visual hallucinations, and the phenomenology of schizophrenia. More controversial were studies exploring the psychotherapeutic potential of these agents. Most unfortunate was the worldwide epidemic of abuse of these agents, which began in the 1960s and has become endemic in the United States.

### EPIDEMIOLOGY

Hallucinogenic drugs are commonly abused. Data from the 1990 National Institute of Drug Abuse

(NIDA) Household Survey reported that 7.6% of the U.S. population over the age of 12 years used hallucinogens at some time in their lives. Demographic data indicate LSD use is most prevalent between the ages of 18 and 25, with 3.9% reporting use in the past year, compared with 2.4% for the age group 12 to 17 and 0.4% for those 26 and older. Use is greater among men, whites, and Hispanics. There appears to be a positive association with urban areas in the Northeast and West and an inverse relationship with employment and education level. High school seniors, while demonstrating an inverse correlation between LSD use and college plans, also demonstrate a strong positive correlation between LSD use and parents' education. These data confirm the clinical impression of LSD users as disaffected offspring of Caucasian, white-collar parents. Surveys of 15,000 high school seniors in 1993 showed a 21.4% increase in the lifetime prevalence of LSD use over the previous year, reflecting a rising trend of abuse of hallucinogens over the preceding seven years,<sup>3</sup> in contradistinction to the use of other drugs, including marijuana and cocaine, which has continued to fall every year since 1979.

## PHARMACOLOGY

Hallucinogens may be defined as agents exerting profound alterations of mood, thinking, and perception while exerting minimal effects on orientation and memory. Brawley and Duffield<sup>4</sup> define hallucinogens by effects common to this class of drugs, including autonomic arousal, sensory distortions, and psychic changes. Chemically they represent diverse molecules commonly classified as indolealkylamines and phenethylamines. Albert Hofmann's original self-experiments remain a classical description of the subjective effects of LSD, which at a low dose included a progression from a constant flux of visual distortions, to out of body sensations, to fear and despair, all in a context of a clarity of thought.<sup>5</sup> At doses of 100  $\mu$ g or more the drug causes sympathetic arousal, intense perceptual distortion, disruption in the sense of time, and exaggeration of pre-existing moods, including euphoria, depression, paranoia, and panic. It is this last mood that has been characterized as the "bad trip," during which the user may present in the emergency room.

There is considerable variation in the response to hallucinogens both between individuals and in the same individual at different times, related in part to the setting in which it is encountered and the personality of the subject. Hallucinogens exhibit

tolerance and cross-tolerance with one another.<sup>6</sup> There is no withdrawal. There are no documented toxic fatalities from LSD use. Considerable variation is found in the concentration of hallucinogens in commonly ingested botanical specimens. On the other hand, street preparations of LSD are relatively consistent in their superior potency compared with botanical hallucinogens and in their chemical purity. Forensic analyses of samples of alleged LSD by the Massachusetts Department of Public Health, using gas chromatography-mass spectrometry, yield true positive results for LSD approximately 80% of the time.

## PSYCHIATRIC SEQUELAE OF HALLUCINOGENS

Three psychiatric disorders have been described in conjunction with the use of hallucinogens. These include hallucinogen anxiety disorders, psychotic reactions, and hallucinogen persisting perception disorder. The evidence for these disorders is based on clinical observations and the results of direct human experimentation.<sup>7</sup>

### Hallucinogen Anxiety Disorder

Once a common cause of rock concert casualties, hallucinogen induced dysphoria appears to have declined as a result of lower drug doses and increasing user sophistication regarding its management. Clinically, the patient presents in the emergency room with many of the autonomic features of an acute panic attack, including extreme apprehension, tachycardia, and elevated vital signs. Mydriasis is marked. A distinguishing characteristic of post-hallucinogen panic is the presence of visual disturbances. Discriminating hallucinogens from anticholinergic drugs and phencyclidine is valuable, because treatments for each are different. The simplest test is a careful history. If that is not possible, the palm test may be used to differentiate LSD from phencyclidine. It is performed by asking the patient to describe all the colors visible in the palm of the examiner. The LSD patient sees many, whereas the phencyclidine patient more often responds with hostility. Blood and urine toxicology results may clarify the situation in retrospect. Results are seldom available within the time frame of intoxication. Historically, acute dysphoria was managed with neuroleptics or "talking down." It is now recognized that the former may intensify the experience,<sup>8</sup> and talking down often requires hours. Diazepam, on the other hand, in a dose of 20 mg by mouth, offers a rapid resolution to the crisis.

### Psychotic Reactions

Attack rates for prolonged psychotic reactions lasting more than two days after ingestion of a hallucinogen range from 0.08% to 4.6% with a trend towards higher occurrence among psychiatric patients and lower occurrence among healthy volunteers. Data derive from studies involving direct administration of hallucinogens, cross-sectional and longitudinal samples, surveys, and case reports.<sup>9-12</sup> Symptoms occupy a full range of presentations, including mood swings, auditory and visual hallucinations, mania, grandiosity, and religiosity. In two studies, psychotic hallucinogen users appeared to have healthier premorbid personalities than non-drug-using psychotics and earlier ages of onset, suggesting that in certain vulnerable individuals, hallucinogens serve as a psychotogenic trigger. The role hallucinogens play in all psychoses following their use is not always clear, since pre-existing psychoses, mistaken drug identification, and drug adulteration often confound efforts to study this problem. Kornblith<sup>13</sup> concluded in a review of this issue that prior illness was evident in many, but not all, of those with psychoses following LSD. In one of the few longitudinal assessments of three classes of drug abusers (psychostimulant, sedative, and narcotic users), McLellan and coworkers<sup>14</sup> found that psychostimulants, including LSD and amphetamine, more often were associated with the development of schizophrenia. A chart review of 176 inpatients found that more psychotic patients abused hallucinogens than did a comparable group of drug abusers without psychosis. Other differences were found among drug-abusing psychotics, including earlier ages of onset, more visual hallucinations, more depression, and more families with affective disorder. These workers concluded the data were consistent with the hypothesis that the drug abuse had precipitated a psychosis.<sup>15</sup>

There is a dearth of controlled treatment studies in this population, although in many respects the treatment of post-hallucinogen psychotic disorder does not differ from conventional therapies for other psychoses. Case reports describe the most commonly effective treatments as lithium and electroconvulsive therapy (ECT), in addition to conventional neuroleptics, supporting the finding of affective symptoms made in a longitudinal study of 15 patients with LSD psychosis.<sup>16</sup> Antidepressants, carbamazepine, beta blockers, and the benzodiazepines may all have a place in the pharmacotherapy of these patients. The post-hallucinogen psychosis patient, compared with the schizophrenic patient with predominantly negative symptoms, retains considerable ability to relate interpersonally despite

major deficits in function. Supportive, educational, cognitive-behavioral, and family therapies are effective in conjunction with medication. Clinical experience suggests that treatment is best focused on four main goals, namely, the control of symptoms, minimal use of hospitalizations, establishment and maintenance of employment, and development of social relationships. Comorbid features of the disorder are likely to be dependence on alcohol and cannabis, depression, and suicide, tied in part to the patient's preservation of insight into profound cognitive and emotional deficits, often made strikingly more poignant as the patient observes his or her peers progressing productively through the life cycle.

### Hallucinogen Persisting Perception Disorder

In 1955 Cooper described long-lasting visual disturbances following the use of LSD. Originally called flashbacks because they occurred briefly and resembled visual experiences of prior LSD trips, these disturbances now are classified as symptoms of the Hallucinogen Persisting Perception Disorder (HPPD) in the Diagnostic and Statistical Manual of Mental Disorders IV of the American Psychiatric Association.

Symptomatic LSD users present primarily with visual disturbances, including geometric pseudo-hallucinations, false fleeting perceptions in the peripheral fields, flashes of color, and positive afterimagery. The visual disorder appears stable in half of the cases in an apparently permanent alteration of the visual apparatus. Precipitants include stress, fatigue, emergence into a dark environment, intention, marijuana, neuroleptics, and anxiety states. Depression is comorbidly present. The disorder may be brought on by a single dose of LSD.<sup>17</sup> A survey of self-selected LSD users in a metropolitan setting revealed that 64.3% reported symptoms of HPPD.

The pathophysiology of this disorder is unknown. There are no pre-drug, post-drug experimental designs examining this issue. Two cross-sectional studies have compared LSD users to controls on a variety of visual measures, including tests of color vision, dark adaptation, and critical flicker fusion. These studies found abnormalities in visual function consistent with the hypothesis that imagery continued to be processed centrally after the test stimulus had been removed.<sup>18,19</sup> Recently it has been suggested that this disorder may arise from an excitotoxic destruction of inhibitory interneurons that are serotonergic at the soma and GABAergic at the terminals. This is supported by clinical reports of partial help from benzodiazepines for this disorder.

der, the observation that LSD serves as a potent partial agonist to serotonin in the facial nucleus,<sup>20</sup> and the recent finding that patients with this disorder have an apparently increased affinity of LSD at the serotonin-2 receptor in platelets (Abraham and coworkers, unpublished data).

Slow clinical recognition of HPPD is not uncommon. The typical patient may consult a half dozen or so clinicians—usually an ophthalmologist, neurologist, psychiatrist, or psychologist—before the diagnosis is made. Differential diagnosis must rule out organic forms of hallucinosis, including seizures, other sources of toxicity, strokes, CNS tumors, infections, and trauma. Treatment success has been partial. Benzodiazepines ameliorate but do not eradicate the symptoms. Using addictive agents in substance abusers is not entirely without risk of further abuse. One study used haloperidol to reduce hallucinations in eight subjects, but an exacerbation of symptoms early in treatment was also noted. Psychotherapy is indicated to help patients make an adjustment to chronic visual distractions and to address the notion of “brain damage” commonly feared by these patients.

## Inhalants

Inhalants have been called “the ten-cent hallucinogen,” attractive for their cheapness and ability to alter states of consciousness. They represent four classes of abusable substances: (1) volatile solvents, including glue, lighter fluid, degreasing compound, gasoline and exhaust fumes, paint thinners, and countless ordinary household items; (2) aerosols, including spray paints, hair sprays, deodorants, and vegetable frying lubricants; (3) anesthetics such as ether, chloroform, and N<sub>2</sub>O; and (4) the volatile (amyl and butyl) nitrites. The virtually limitless varieties of aliphatic and aromatic agents that are found in modern industrial products means that a precise linkage between specific agents and psychiatric sequelae is often not possible. Nevertheless, abuse of particular agents in epidemiologic clusters in the last two decades, along with the rise of AIDS, has prompted lines of inquiry into the patterns of inhalant use and their medical consequences.

Inhalants are self-administered by sniffing (the nasal route) or huffing (the oral route) from a paper bag, can, rag, or inflated balloon. There is little of the alleged romance or mystique of cocaine or heroin to be found in inhalant abuse. Breathing solvents from a soaking rag in the description of Oetting and col-

leagues is a “grubby, dirty cheap way to get high. Inhalant users are, therefore, likely to be the social rejects, the emotionally disturbed, the disadvantaged minorities, the maladjusted, as well as the angry and alienated.” Sniffers of hydrocarbons, excluding gay men using nitrites, tend to fall into three classes: (1) adult inhalant abusers for whom inhalants are the drugs of choice; (2) adolescent polydrug abusers; and (3) young inhalant abusers who abuse no other drugs except for alcohol or cannabis.<sup>21</sup> From the point of view of the user, inhalants are associated with low cost, high availability, small packaging, rapid intoxication, and relative freedom from legal entanglements.

## EPIDEMIOLOGY

The use of inhalants in the United States has been stable over the last decade, with approximately 12% of young adults ages 19 to 28 reporting a lifetime prevalence of inhalant use.<sup>22</sup> On the other hand, Frank and coworkers<sup>23</sup> found that during a nine-year period from 1974 to 1983 solvent abuse in New York secondary school students increased from 1.9% to 10.6% for six-month prevalences. Among high school students there has been a decline in the use of amyl nitrite, from 4.7% to 1.7% in the years 1986 through 1990. Student surveys do not reflect trends among truants and drop outs. Drug use, and inhalant use in particular, correlate with high truancy rates and poor school performance, suggesting underreportage.

Inhalants have an earlier age of onset compared with tobacco and alcohol, with a peak use in small groups between the ages of 11 and 13. Highest prevalences are found in relatively isolated communities such as Indian reservations or smaller Hispanic communities. Adult users in a Philadelphia study, by comparison, tended to be white, male, with a 10th-grade education or less, and minimal job skills. Inhalant-dependent adults tend to be solitary users. Inhalant users are disproportionately from troubled and fragmented families and have a lower socioeconomic status.

Amyl and butyl nitrite use commonly has been associated with gay male night life, in which the drugs are used as “poppers,” small glass vials which are popped between the fingers to permit inhalation of the nitrite. The euphoria is alleged by some to enhance sexual and dancing pleasure. First described by Brunton in 1859 as a vasodilator, inhalable nitrites demonstrated utility in the treatment of angina pectoris.<sup>24</sup> The abuse of amyl and butyl nitrites increased significantly during the years 1974

to 1977. By 1979, over 5 million people in the United States used these drugs more than once a week.<sup>25</sup> In 1980 a conservative estimate was that 250 million recreational doses a year were consumed in the United States.

## PHARMACOLOGY

Inhalable compounds with demonstrated toxicity include acetones, benzene, petroleum hydrocarbons, toluene, dichloro- and trichloro-fluoromethanes, and ketones. The maximum allowable airborne concentration of toluene for industry, for example, is 200 parts per million. That from glue inhaled in a bag, on the other hand, is fifty times greater. Alkyl nitrites are flammable and explosive. Room odorizer products taken orally show an unusually steep lethality function.

Pharmacologically, nitrites dilate cerebral vasculature, increase intracranial pressure, and create a transient euphoria. They exert a relaxing effect on the smooth muscle of bronchi, gut, and rectum proper, facilitating anal intercourse.<sup>26</sup> They are also alleged to enhance sexual performance, although this last is not strongly supported by evidence. A survey of 173 polysubstance users reported that nearly half the users described isobutyl nitrite as "unpleasant" because of lightheadedness and dizziness, rapid heartbeat, blurred vision, facial flushing, and headache. Thirty-four percent reported severe pulsatile headache, 17% reported burning in the nose, and 11% reported nausea immediately after inhalation of the drug. Only 56% described the euphoria as fair to good.<sup>27</sup>

Other adverse effects of nitrite inhalants include nausea, ataxia, symptoms of anoxia, short lived and prolonged pulsatile headaches, hypotension, flushing, and syncope. Methemoglobinemia has been shown experimentally to play a role in lethality, preventable by methylene blue.<sup>28</sup> Amyl nitrite may be particularly dangerous to persons prone to cerebral hemorrhage, hypotension, glaucoma, and myocardial disease.

While occasional use of certain inhalants, such as glue, may be medically innocuous, toxic neuropathies ("Huffer's neuropathy"), renal dysfunction, aplastic anemia, hepatotoxicity, and sudden death have all been described in association with inhalants. Deaths have been described from inhaling typing, cleaning, and lighter fluids, and these are thought to be related to either suffocation or cardiac arrhythmia, intensified by hypercapnia or physical activity.<sup>29</sup> Agents most often involved have been trichlorofluoromethane, dichlorodifluoromethane,

and cryofluorane, in respiratory circumstances analogous to those of operating room anesthetic deaths. That is, users may commonly place a rag soaked with a volatile hydrocarbon in a bag, which is then tightly held over the airway, causing a fall in  $pO_2$  and a rise in  $pCO_2$ . Deaths then occur when the abuser attempts to run or dance violently, ostensibly releasing norepinephrine, which then further destabilizes cardiac rhythm to the point of ventricular fibrillation.

Prolonged administration of these substances may lead to several disorders of the blood and blood-forming organs, including Heinz-body hemolytic anemia and splenomegaly. Ingestion produces a more rapid and malignant methemoglobinemia than inhalation and has been lethal. Shesser and coworkers<sup>30</sup> reported a case of a man who inhaled butyl nitrite and presented with combativeness and cyanosis. He was treated with oxygen, ascorbic acid, and methylene blue, with resolution of his symptoms. Studies show that nitrites impair lymphocyte and monocyte function and decrease helper cells. The use of nitrite inhalants has been considered a risk factor in the development of AIDS-related Kaposi's sarcoma, but this remains unproven.<sup>31</sup>

## PSYCHIATRIC SEQUELAE

Disorientation, dizziness, and euphoria are common subjective effects of inhalants. Aggressive behavior and criminal activity have been strongly associated with inhalant abuse.<sup>32</sup> Psychological studies using the Minnesota Multiphasic Personality Inventory show that chronic users have high scores for the schizophrenia, mania, and psychopathic deviance scales. Young inhalant users are reported to appear clinically more anxious, depressed, and suicidal than young marijuana users. It is not clear whether inhalant use is an effort on the part of a child to self-medicate a pre-existing clinical condition or whether use of the hydrocarbon leads to depression, anxiety, and aggression. The long term effects of chronic inhalant use are inconclusive, although the chronic inhalant abuser has a reputation for bizarre, impulsive, and dangerous behavior. In one survey, one third of those children failing a grade were inhalant users. Family turmoil and poverty have been shown in a number of studies to correlate with inhalant use.

## TREATMENT

While primary prevention is the most rational theoretical approach to the problem of inhalant use,

total prevention is not feasible in a society permeated with multiple, accessible organic inhalants. Treatment involves consideration of the patient from a medical, neurologic, and psychological perspective and is likely to be multifocal in its efforts. Acute effects of inhalants, including anoxia, cardiac arrhythmias, and other life-threatening sequelae of inhalants need to be ruled out or treated. In older inhalant abusers, other confounding drug use must be addressed. A thorough psychiatric evaluation is always indicated for the solvent-abusing child. Pre-existing depression, anxiety, and environmental stressors should be identified, and appropriate psychotherapeutic and psychopharmacologic interventions initiated. Evaluation of the family may reveal patterns of childhood abuse or neglect warranting investigation by social service agencies. Arroyo<sup>33</sup> has identified commonly occurring factors that inhibit rehabilitation of inhalant abusing children, including poverty; broken homes; distrust of the claim of confidentiality of clinic records; continued drug use; and poor group relatedness, school performance, and verbal skills. Long-term treatment and follow-up data are needed for chronic inhalant abuse.

## Designer Drugs

### HISTORY

Compounding the tasks of diagnosis and treatment of substance abuse has been the emergence of so-called "designer drugs," chemical variants of abusable and addictive agents often synthesized under crude and clandestine circumstances and yielding dangerous or unpredictable effects. Classes of agents that have assumed public health significance include substituted opioids (*e.g.*, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] and 3-methylfentanyl or "China white"), cocaine (methcathinone and 4-methylaminorex), and the amphetamines (3,4-methylenedioxyamphetamine [MDA]; 3,4-methylenedioxymethamphetamine [MDMA] or "Ecstasy"; and 3,4-methylenedioxyethamphetamine [MDE] or "Eve"). Occasionally, adverse effects have resulted in spectacular consequences, as in the case in 1983 of the inadvertent synthesis of the neurotoxin MPTP, which led to an epidemic of drug-induced Parkinsonism.<sup>34</sup> With perhaps the exception of MDMA, use and after-effects of designer drugs appear to be sporadic with a tendency toward regional clusters of abuse activity.<sup>35</sup> Among designer drugs in current

use, MDMA and MDA have been given particular attention by a controversial claim concerning their adjunctive benefit in psychotherapy. As a consequence, a number of insights into the pharmacology and human effects of these drugs now are in the literature.

### PHARMACOLOGY

Patented in 1914 in Germany as an appetite suppressant, MDMA gained currency when it was reported being abused by college students in the United States. MDA and MDMA are ring-substituted derivatives of amphetamine and methamphetamine, respectively, and are reported to enhance emotions and empathy in ways distinct from hallucinogens or psychostimulant phenethylamines. MDA at high doses is hallucinogenic, while at lower doses it is reported to decrease anxiety and increase one's sense of self-awareness and desire to be with people and talk.<sup>36</sup> One study employed the drug as an adjunct to psychotherapy.<sup>37</sup>

Acutely, MDMA is reported by college students to increase interpersonal closeness, although a majority of those surveyed reported tachycardia, dry mouth, bruxism, and trismus. Twenty percent reported visual hallucinations. Untoward effects were noted most often on the following day, with muscle aches, fatigability, depression, and difficulty concentrating noted by 21% to 36% of subjects. Two thirds noted that positive effects decreased with successive use, while adverse effects increased.<sup>38</sup>

A retrospective survey of 20 psychiatrists who had personally experimented with the drug reported benefits of improved social function, religious orientation, and life values. Adverse effects included trismus, decreased desire to perform mental tasks, and decreases in appetite, sleep, and libido.<sup>39</sup>

The duration of action of MDA is 10–12 hr, and for MDMA, 3–5 hr. The retention of MDMA-like activity by the alpha-ethyl analog of MDMA, MBDB, as well as differences between these agents and hallucinogens in studies of quantitative electroencephalography, led Nichols to suggest that such agents represent a unique pharmacologic class that he called "entactogens."<sup>40</sup> Glennon likewise concluded that few phenylethylamines were strictly amphetamine-like or hallucinogen-like but could represent combinations of effects or a unique class of agents.<sup>41</sup>

MDA and MDMA are neurotoxic in animal studies. Both are potent releasers of 5-HT from synap-

somes. MDMA depresses firing in serotonergic and noradrenergic neurons. Large doses of MDA in rats have been found to deplete the forebrain of serotonin. O'Hearn and colleagues showed that repeated doses of MDA or MDMA caused a profound loss of serotonergic axons throughout the forebrain, including the neocortex, striatum, and thalamus.<sup>42</sup> Neurochemical and neuroanatomic studies demonstrate long-lasting degeneration of serotonin neurons in brain, in primates more than in rodents.<sup>43,44</sup> Recovery of neuronal terminals has been observed in some studies following cessation of drug administration. In human users of MDMA, CSF 5-HIAA, a metabolite of serotonin, is reduced.<sup>45</sup>

Clinical disorders reported in conjunction with acute MDMA use include panic disorder, psychoses, hyperthermia, and death when the drug supervened on a pre-existing medical disorder. Dantrolene has been reported helpful in hyperthermia with rhabdomyolysis.

It is paradoxical that while designer drugs of the phenylethylamine type interest both neuroscientists and psychotherapists, data from the former would appear to obviate use by the latter. Such a rush to judgment is premature. While designer drugs are neurotoxic at high doses in animals, adequate human studies at lesser doses have not been done because of ethical concerns and legal constraints. The application of the existing standards for the conduct of scientifically and ethically credible research in humans is useful for the adjudication of this controversy. That is, if studies are contemplated, they should have measurable outcomes, random assignments, blinded observations, and adequate controls. Consent must be informed, and the benefits should outweigh the risks. In the absence of such data, claims for the safety and efficacy of these agents in the treatment of psychiatric disorders must be treated with skepticism.

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