THE ADVERSE EFFECTS OF HALLUCINOGENS FROM INTRAMURAL PERSPECTIVE*

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A HALLUCINOGÉNEK KÁROS HATÁSAI TERÁPIÁS ALKALMAZÁSUK SZEMPONTJÁBÓL

Hosszan tartó moratórium után több kutatásban élenjáró ország nyit abba az irányba napjainkban, hogy vizsgálja a hallucinogén szerek élettani és terápiás hatásait. Jelen tanulmány célja annak áttekintése, hogy milyen káros hallucinogén hatással számolhat a kutató vizsgálati helyzetben és nem az ellenőrizetlen „utcai" használat következményeként. Az utóbbi 35 év prohibíciója miatt ennek felmérése nem egyszerű: a legtöbb publikáció az illegális „abúzus" folyamán felmerülő adverzív hatásokról számol be és így az adatok általánosítása körülményes a legitim 'úzus' vonatkozásában A megközelítés módja szükségszerűen széles, jórészt retrospektív, szemben a legális gyógyszerek jól kontrollált, összpontosított, prospektív jellegű premarketing vizsgálataival. Felmérésünk eredményét annak reményében összegezzük, hogy egyre több ésszerű lehetőség nyílik a hallucinogén szerek hatásainak vizsgálatára jól kontrollált, szigorúan felülvizsgált helyzetben.

KULCSSZAVAK: ayahuasca, hallucinogének, ibogain, lizergsav-dietilamid, mellékhatások, N,N-dimetiltriptamin, N-metil-3,4-metiléndioxiamfetamin, pszilocibin, terápiás alkalmazás

SUMMARY

Very recently, after a long-lasting, worldwide moratorium on research of hallucinogenic agents, a good number of advanced countries have been revising their position, and start to approve testing the physiological and therapeutic effects of hallucinogens in human subjects. The purpose of this article is to review safety information available in the literature on hallucinogen use, and sort out those data from the reported complications of their abuse. Because of prohibitory regulations of the last 35 years, there are difficulties in achieving this kind of evaluation. Our approach has to be broad, and at times retrospective, in contrast to the well-controlled, focused, prospective design of the premarketing trials of legal drugs. The article summarizes the analyses in anticipation of supportive regulatory changes for the use of hallucinogens in well controlled studies and strictly supervised clinical trials.

KEYWORDS: adverse effects, ayahuasca, N,N-dimethyltryptamine, hallucinogenic agents, ibogaine, lysergic acid diethylamide, N-methyl-3,4-methylenedioxyamphetamine, psilocybin, therapeutic use

Introduction

Certainly, and not without good reason, many readers' eyebrow gets raised by the message conveyed in the title. Therapeutic use of hallucinogens? What kind of nonsense is this? The title reflects an agenda that is different from the picture relayed by the media since the hippie movement and the countercultural upheaval of the sixties. The controversial fact is that for a long time the opinion of health care providers on hallucinogens has been

* The authors will expand the presented topic with more details in a book entitled Psychedelic Medicine, which is planned to be published by Praeger in 2007.

shaped by reports of journalists, policemen, legal representatives, artists, artisans, courtesans, and/or drug abuser subjects. Mostly laymen in clinical pharmacology. Exactly the above reaction facilitated the authors to approach the issue from a professional point of view. So much about the subjective side of the motivation. To understand the objective side one has to notice that the federal Food and Drug Administration (FDA) of the United States (US) has begun approving clinical trials for the investigation of classical hallucinogenic drugs in a good number of pathological conditions, ending a 35 years long moratorium. A modest psychedelic renaissance is on the rise returning in a cautious manner to the fifties when hundreds of publications were targeting the potential use of hallucinogenic compounds in clinical practice.

Thus far only a limited number of countries have lightened their regulations toward clinical studies with hallucinogens. The forerunner is Switzerland, where Franz Vollenweider's group has been running state of the art neuroimaging protocols (Gamma et al. 2000; Liechti & Vollenweider, 2000; Vollenweider et al., 1999) enjoying enlightened Swiss regulations, which permit enrollment of normal subjects. Germany is the next in lead, although with a limitation on the type of enrolled volunteers, who can only be health care providers as "normal" subjects in studies with hallucinogens. Brazil is also worth mentioning, where ayahuasca, a traditional Amazonian hallucinogenic beverage is permitted for use in ritual-religious settings.

In the US hallucinogenic studies are not permitted to enroll healthy volunteers, but are allowed to use subjects with compromised health in efficiency trials with potential improvement not attainable by alternative care. After a long-lasting moratorium on research into therapeutic uses of hallucinogenic drugs, the FDA is again approving testing with human subjects. Top researchers including psychiatrists, psychologists, and neurologists from medical schools of Harvard, University of California, and New York University study the potential uses for 'psychedelics' to treat disorders of mind and body. The following studies are on the way in the US: psilocybin treatment of obsessive-compulsive disorder by Francisco Moreno, the administration of Ecstasy (MDMA) in posttraumatic stress disorder by Michael Mithoefer, the use of marijuana in AIDS by Donald Abrams, psychedelics in treatment of migraine headaches by Andrew Sewell and John Halpern, application of ibogaine and LSD in substance abuse rehabilitation by Kenneth Alper and John Halpern, and employment of hallucinogens in hospice and oncology by Charles Grob. There are important clinical studies outside of the US as well, like Jacques Mabit's ayahuasca treatment of cocaine-paste addiction in Peru, and Evgeny Krupitsky's ketamine administration against alcoholism and drug addiction in Russia.

Hallucinogenic substances present in nature have been used by humans for hundreds of years (perhaps even for millennia) to produce changes in thought, mood and perception in order to facilitate healing in the broadest sense within a biopsycho-sociospiritual framework (Frecska & Luna, 2006). In the 1950s and 1960s professionals were studying practical medical and therapeutic uses for hallucinogens, including LSD and mescaline, supplied by pharmaceutical companies like Sandoz. However, the US government took steps to ban human consumption of hallucinogens, and thus the research. All human testing was stopped by 1970. Medical safety was not the main issue; the ban was moved by social concerns. The prohibition formulated in the Controlled Substances Act was not a scientific decision based on discouraging findings in clinical use, it was rather a political one due to irresponsible use promoted by some careless professionals like the legendary Harvard psychologist Timothy Leary, who advocated free use of hallucinogens by all who desired. „Turn on, tune in, drop out!" – was Leary's infamous slogan. The resulting prohibitory backlash effect was immense and keeps reverberating even 35 years later. The typical biphasic attitude change (initial enthusiasm followed by disappointment before sober approach) generally observed in the career of a pharmacological agent is especially deepened and protracted for hallucinogens.

There has been considerable excitement in the fifties for the clinical use of hallucinogens, for example in pharmacologically facilitated psychotherapy (so-called 'psychedelic psychotherapy'). The tide has turned in the sixties with widespread beliefs about the dangers of hallucinogenic drugs and frequent media reports attributing fatalities to hallucinogens. This media bias was typical in the early 1970s when much attention was focused on supposed chromosome damage and birth defects in children born to mothers who had taken LSD during pregnancy. Later on, negative results of

better controlled, rigorous investigations (Muneer 1978) refuted the earlier alarmist concerns but these received very little attention in the media. The controversial nature of the US drug policy and its influence on government sponsored research of illicit drugs has recently drawn media attention to investigational flaws of highly publicized research claiming harmful effects (Jennings, 2003).

Contrary to the preconceptions influencing public and professional media, hallucinogens actually do have a long history of safe administration in legal, controlled research settings (Strassman, 1984). The preconceptions, even when derived from unbiased publications, are related to illicit use (and abuse), rather than responsible clinical use (e.g., see Griffiths et al., 2006). Unfortunately a hallucinogenic drug's safety has been judged by its abuse and that has been applied to making decisions regarding its clinical use. In summary, the inconvenient truth is that the opinion of most of the health care providers and legislation makers on hallucinogenic agents is not well founded scientifically.

The purpose of this article is to review safety information available in the literature on hallucinogen use, and sort out those data from the reported complications of their abuse The article summarizes these analyses in anticipation of supportive regulatory changes for the use of hallucinogens in well controlled studies and strictly supervised clinical trials.

To preview these findings, the various hallucinogenic compounds are physically safe under controlled use, with the possible exception of the phenethylamine hallucinogens (such as Ecstasy), which have the risk of causing cardiovascular emergencies and liver failure. Nevertheless, there are limited records establishing death from overdoses directly attributable to their ingestion alone.

Classification, Chemical Structure, and Mechanism of Action

The conventional use of the term 'hallucinogen' disproportionately emphasizes perceptual effects, neglecting central actions on emotion and cognition as well. Psychopharmacologists define as hallucinogenic any agent that causes alterations in perception, cognition, and mood in the presence of an otherwise clear sensorium (lucid awareness). Most commonly this classification includes three major groups – indolealkylamines, ergolines, and phenethylamines – and excludes other substance that may induce hallucinations with profoundly altered orientation and vigilance. Excluded are the anticholinergic agents (i.e, plants such as Datura), the dissociative anesthetics such as phencyclidine (PCP), and psychostimulants such as amphetamine and cocaine.

The chemical structures of the classic hallucinogenic drugs are the basis for their classification into three groups: 1) simple indolealkylamine hallucinogens (e.g. N,N-dimethyltryptamine, DMT, and psilocybin), which have a common indolealkylamine structure with the neurotransmitter serotonin; 2) the ergolines, which share an indole group (e.g. lysergic acid diethylamide, LSD); and 3) the ring-substituted phenethylamine hallucinogens (e.g. mescaline, Ecstasy). The indole alkaloid ibogaine is a complex indolealkylamine compound, a beta-carboline derivative akin to harmaline and harmine. The latter is an active, although not the hallucinogenic component of the ayahuasca brew (see below).

The indole structure found in serotonin is a common chemical characteristic of these compounds and suggests a specific mechanism of hallucinogenic effect exerted on the serotonergic system. Typical clinico-pharmacological features of classical hallucinogens involve alterations of all cortical functions including perception, mood, and cognition. They share common mechanisms in attaching to serotonin receptors through molecules that bind to the neurotransmitters sites for transferring the signal to the next neuron in the network. It is activation of the 5-HT2A and 5-HT2C receptors in the brain that primarily mediates their psychedelic effects.

Hallucinogen Acute Toxicity

The traditional measure of acute drug toxicity is 'therapeutic index': a ratio of the dose that kills 50% of subjects (LD50) to the dose that is effective in 50% of subjects (ED50). According to the Registry of Toxic Effects, the 'therapeutic index' for indolealkylamines and ergolines is above 600 (higher numbers indicate a better safety profile). For cannabis the index is even higher: it is on the order of 10,000s. Therefore these agents are relatively non-lethal in comparison to other substances. For example, the therapeutic index of aspirin is 199 and for nicotine 21, with the phenethylamine psychostimulants (such as methamphetamine) falling into this range.

There is no known recorded death due to marijuana intoxication at any time in US history. There are no documented toxic fatalities from LSD use either. There was a report (Klock et al., 1974) of accidental overdose of pure LSD that was mistaken for cocaine and snorted by eight individuals in quantities estimated at between 10,000 and 100,000 μg. In this case the subjects experienced mental status changes characterized by hallucinations, confusion, and suffered from hemorrhage, the latter possibly mediated by LSD antagonism of platelet serotonin function. All subjects have recovered. One ayahuasca related death was reported (Sklerov et al., 2005), an obscure case which needs further clarification (Callaway et al., 2006). All over the world up to the year 2006, only eight persons' death has been documented due to ibogaine intoxication. Ecstasy (MDMA) leads the group with an estimated annual fatality rate to be about three to four deaths in one million users. Fatal outcome of Ecstasy (MDMA) abuse is due to hyperpyrexia (heatstroke), rhabdomyolysis (muscle breakdown), liver failure, cardiac arrhythmias, strokes, coagulopathy, or drug-related accidents. These fatalities depend on mechanisms that are not specific to Ecstasy (MDMA) but common to all the amphetamines (Kalant 2001), and result from causes which most of the time cannot be separated from alcohol consumption and excessive physical exercise characteristic of rave dancing.

More casualties have been reported, when people abusing hallucinogens used them in combination with other, potentially more dangerous drugs and did irresponsible things under their influence. When used in improper settings – mostly outside medical or religious practices – hallucinogen intoxication can be disturbing and on occasions may temporarily increase the risk of suicidal behavior. After large doses of cocaine, amphetamines, LSD, and PCP, certain individuals may experience violent outbursts, probably because of preexisting psychopathology. Crimes or bizarre behavior associated with hallucinogen intoxication are regularly reported by the media. Sensationalization and exaggeration cannot be ruled out in the background, since many more morbidity and mortality cases related to common substances like alcohol are happening every day, and those have been less highlighted in the media. Of all psychoactive substances, alcohol is the only one whose consumption has been shown to commonly increase aggression.

Nonetheless, it is recognized that there is significant variability in the response to hallucinogenic agents both interindividually and intraindividually. In part, this is related to the set and setting (Faillace & Szara, 1968). In case of subjects who are unaware of the hallucinogen administration, the incidence of adverse effects is much higher. Generally, uninformed subjects show more anxiety, and cognitive disruption in contrast to the others who have an excess of euphoric responses. A second set of factors that influence hallucinogenic response are related to the personality of the subject. Acute psychedelic drug intoxication can manifest features of paranoia, confusion, and agitated behavior in a time-limited manner. This was one of the features supporting the proposition that psychedelic drugs were experimentally useful in producing a clinically relevant, discrete episode of psychosis in the 'psychotomimetic' (psychosis mimicking) model. Psychosis is the term used for denoting the distortion or disorganization of a person's capacity to recognize reality, think rationally, or communicate with others. The 'psychotomimetic' effects of hallucinogenic drugs (e.g. LSD, psilocybin, and mescaline) have been suggested to resemble the symptoms of acute schizophrenia.

Originally hallucinogens carried the misnomer of 'psychotogenic' (psychosis generating) agents, but the hallucinogenic effect is distinct from psychosis on several accounts; essentially the two experiences are fundamentally different. Reality control is well maintained after minimal experience with hallucinogens, and the psychedelic effect is actively sought by users. Psychosis is neither voluntary nor desired. It is a disordered mental state over which the subject has no control. Hallucinogenic agents, when taken in appropriate settings in a responsible manner, induce a coherent mental state with feeling of increased internal order and personal growth. An experienced hallucinogen user may be regarded as a competent navigator or a „co-dancer" with the drug (Shanon, 2002). No such statement applies to a psychotic. Sporadic anecdotal observations noticed a relationship between the onset of schizophrenia and hallucinogen use in a vulnerable population. However, when schizophrenic symptoms did persist beyond 24 hours, it appeared that the particular syndrome was a hallucinogen-precipitated event in schizophrenia-prone individuals (e.g., those with relatives with psychiatric problems), rather

than a specific and genuine hallucinogen-induced persistent psychosis.

Recent reports (Caspi et al., 2005; Henquet et al., 2006) indicate that people with a certain gene variant (Val allele) of the catecholamine-O-methyltransferase enzyme are more vulnerable to a schizophrenia-like psychosis after cannabis abuse, and regular use of cannabis is a risk factor of schizophrenia. Carriers of the Val allele were most sensitive to cannabis-induced psychotic experiences, but this was conditional on the presence of pre-existing psychosis liability. Cannabis abuse had no such adverse influence on individuals with two copies of the Met allele. These findings underline the importance of thorough screening before enrollment into a hallucinogen trial, and explain why such precaution is so helpful for minimizing the risk of adverse outcomes.

Acute Clinical Effects

Common psychedelic experiences include a profound change of perception which can include visual, auditory, olfactory, gustatory and somatic illusions or hallucinations, and synesthesias. At the onset of hallucinogen action there may be a feeling of energy in the body, and the sense that things are different than usual. As the effects intensify, a wide variety of profound mental changes may occur. The full blown psychedelic experience is usually accompanied by intensified mood, or exaggeration of the emotional state existing at the time of ingestion of the drug. This can include euphoria or elation, depression, anxiety, and panic feelings. Increased visual imagery with closed eyes is the most common perceptual change. Open-eye visual hallucinations are more likely to occur at higher doses, and may affect the behavior of inexperienced or unattended subjects. High dose effects may also include extreme time-dilation, with seconds or minutes feeling like hours or days. Cognition can be altered to the extent that the experience takes on a mystical quality, and past memories may be re-experienced with picture-like intensity. Advanced users may experience expanded spiritual awareness or a sense of universal understanding through their use of hallucinogens, and report religious revelations, spiritual awakening, dissolution of the ego, near death experiences, and encounters with seemingly autonomous entities. While these experiences are described by many people as pleasant (good trips), and serve basis for hallucinogen abuse, to some they may be confusing and frightening (bad trips).

Acute Side Effects

When hallucinogens are used in moderate psychedelic doses, these compounds may cause common adverse reactions (harmless with minimal care), such as nausea, vomiting, dizziness, headaches, insignificant elevation in pulse and blood pressure, dilated pupils, slightly elevated temperature, raising of skin-hair, impaired coordination, and increased reflexes. These symptoms usually begin within one hour after taking the drug and can last up to several hours (depending on the rate of absorption and metabolism of the drug). Various blood hormones and liver enzymes can also show clinically insignificant, temporary elevation.

Emergency Care of Hallucinogen Induced Adverse Effects

The current chapter is about the risks of hallucinogenic agents used in a clinical, well-controlled, secure setting. After proper and thorough screening of enrolled subjects, fewer complications are expected than from uncontrolled street abuse. Nevertheless, the hospital environment provides less than ideal atmosphere for the psychedelic experience (Strassman, 2000). Symptoms of acute hallucinogen drug intoxication may develop, which can manifest in paranoia, confusion, fear of death, and disordered self-control.

The focus of care is to prevent subjects from harming themselves or others, and reducing complications related to acute effects until these time-limited phenomena resolve. The toxic psychosis generally resolves in 2-6 hours. At times after-effects, such as mild depersonalization-derealization may linger for a couple of days. Calm, reassuring, and non-threatening behavior can be useful in „talking down“ patients to allow necessary treatment to be applied and interventions to proceed. Subjects need to be reassured, that they are not “crazy”, what they sense is “just” the result of a chemical, and will go away soon without a trace, with the eventual return of ordinary reality. The optimal placement of sufferers is under one-to-one supervision (one trained staff person attending the patient), in a quiet room with diminished lighting and other stimuli. Both stimulus deprivation and overstimulation have to be avoided. Bed rest in supine position is not necessary, and is dis-

advantageous in patients with nausea and vomiting.

Appropriate use of chemical or physical restraints may be required if verbal reassurance is not working. Physical restraints are seldom needed, and must be the last resort. Benzodiazepines are probably the safest sedatives and can be effective for calming most subjects. For fast response these agents are best administered intravenously. More severe reactions of anxiety or dangerous levels of agitation may require antipsychotic medication. First generation antipsychotics (such as haloperidol or droperidol) must be avoided due to narrow receptor profile (lack of serotonin blockade) and cardiac side effects. Second generation antipsychotics with 5-HT2A antagonism and parenteral formulation are safer and more effective.

Tolerance

While hallucinogenic agents are classified as drugs causing dependence, they are physiologically non-addictive. There is no evidence that these drugs produce physical withdrawal symptoms when chronic use is stopped (American Psychiatric Association, 1994). On the other hand, the tolerance phenomenon is well-known. Psilocybin, LSD, and mescaline users quickly develop a high degree of tolerance for the drug effect: after repeated use, they need increasingly larger doses to produce similar responses. Cross-tolerance is built up for other serotonergic hallucinogenic drugs such as psilocybin and mescaline, but not to drugs such as marijuana, amphetamines, and PCP, which do not act directly on the serotonin receptors. LSD given daily becomes less effective at the same dose (Isbell et al. 1956). This tolerance is short-lived, lasting only for several days; in humans tolerance to gross behavioral changes develops in 4 to 7 days of daily administration and lasts approximately 3 days. Schizophrenic patients may develop tolerance sooner, in 2 to 3 days (for review see Abraham et al., 1996). Dimethyltryptamine is unique in this respect: given frequently does not elicit tolerance neither in animal (Kovacic & Domino, 1976) nor in human (Strassman et al. 1996) experiments. Although DMT acts on the same receptors as LSD, its cross-tolerance with LSD and other serotonergic hallucinogens is limited.

Long-Term Effects

The widely publicized "flashbacks" associated with the hallucinogenic drugs attest to their long-term effects. A number of chronic clinical syndromes due to hallucinogenic drugs have been recognized, including Hallucinogen-Induced Persistent Psychosis and Hallucinogen Persisting Perception Disorder (formerly Post Hallucinogen Perception Disorder).

Hallucinogen-Induced Persistent Psychosis. The overwhelming nature of a full-blown psychedelic experience can lead to significant psychological disturbances after the acute drug effects have worn off. Under some hallucinogens, especially LSD, users may experience devastating mental effects that persist longer than one month after the trip has ended. These long-lasting psychosis-like effects of the drug are labeled as a 'Hallucinogen-Induced Persistent Psychosis', and distinguished from the 'Hallucinogen Persisting Perception Disorder' described subsequently. Hallucinogen-Induced Persistent Psychosis commonly include a dramatic affective component with mood swings from mania to profound depression, religious thought contents, vivid visual disturbances, and hallucinations not typical in schizophrenia (i.e, not auditory hallucinations of conversing, commenting, or commanding voices). The clinical picture of the Hallucinogen-Induced Persistent Psychosis appears to resemble schizoaffective disorders with the not-infrequent addition of visual disturbances. It was noted in an early LSD experiment (Fink et al., 1966) with persistent psychotic patients that, „the hazard of LSD administration appears not to be in the precipitation of a schizophrenic-like state but rather in decreasing emotional and affective controls and inducing a persistent state of altered consciousness."

This type of adverse hallucinogen drug effect may also be akin to the pathological sequelea of psychological traumas such as: rape, natural disaster, or combat experience. These effects may last for years and can affect people who have no history or other symptoms of psychiatric disorder. Nevertheless, investigators have found early on that it was very uncommon to diagnose Hallucinogen-Induced Persistent Psychosis after hallucinogen use in secure, professional settings. The incidence of LSD related psychosis was estimated to

be about 0.8/1000 in experimental subjects, and 1 case was reported in 247 LSD users surveyed (Cohen, 1960; McGlothlin & Arnold, 1971). The low incidence of such unfavorable outcomes was the result of carefully screening volunteers, closely monitoring their sessions, and providing supportive follow-up as indicated (Strassman, 1995).

Hallucinogen Persisting Perception Disorder. One of the most common adverse effects of hallucinogens is known colloquially as "flashbacks", and in its severe form called 'Hallucinogen Persisting Perception Disorder' by physicians (American Psychiatric Association, 1994). "Flashbacks" are spontaneous, repeated, and at times continuous recurrences of one or more of the sensory, cognitive, or emotional symptoms of the hallucinogenic experience after an intervening drug-free period. In earlier decades, "flashbacks" got media attention and were highlighted as a deterrent to recreational use. Most subjects having these experiences find them interesting, enjoyable, and time-limited. Only when such incidences cause distress and interfere with ordinary function do people turn to clinicians. Therefore, it is not well established how often "flashbacks" occur. In addition, because the term "flashback" has been used in many different ways, determining the true incidence of the disorder is even more difficult to determine. Reports from early studies on LSD users (McGlothlin & Arnold, 1971) suggested that subjects with less than 10 exposures report "flashbacks" at a rate of 12%, and they were less common in medically controlled settings as compared to street users. This early observation was recently reinforced by Halpern and Pope (2003), who also pointed out that when LSD was used in a therapeutic or research setting, the Hallucinogen Persisting Perception Disorder appeared less frequently than when it was used recreationally.

The symptoms of Hallucinogen Persisting Perception Disorder are better defined: they most commonly consists of visual disturbances such as: simple geometric pseudo-hallucinations (dots, grids, zigzags, spirals, etc.); seeing halos, bright, colorful flashes, or trails attached to moving objects; and perceiving false motion on the edges of the field of vision. There appears to be no strict relationship between the frequency of hallucinogen use and the rate of occurrence: a single dose of LSD can cause the disorder. Stress, fatigue, sleep deprivation, dark environment, marijuana use, depression and anxiety are known precipitating or augmenting factors. This condition is typically persistent, and in some cases remains unchanged for years after individuals have stopped using the hallucinogen (Abraham, 1983). Given that millions of people have taken hallucinogens, the incidence of Hallucinogen Persisting Perception Disorder appears to be very small, and there is presently no fully effective treatment.

The characteristics of the Hallucinogen Persisting Perception Disorder suggest that hallucinogens may exert long-lasting physiological changes in the brain with hyperexcitability of the visual system. Psychological studies found abnormalities in visual function, supporting the hypothesis that imagery continued to be processed although the test stimulus had been removed. This dysfunction may arise from a destruction of inhibitory interneurons of the visual pathways that receive serotonergic input and were over-stimulated by LSD, with subsequent excitotoxic degeneration. Preclinical research (Gewirtz et al., 2002) showed that the phenethylamine hallucinogen 2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) increased the expression of the brain-derived neurotrophic factor, which can provide another clue to the mechanism by which hallucinogens might exert long-lasting changes in synaptic connections of the nervous system.

Personality Changes. The psychedelic impact a hallucinogen may have on its users need not be confined to the period of the acute drug effects. Having experienced the extraordinary effects induced by the hallucinogen, many partakers feel that they undergo deep personal changes. It is common to hear hallucinogen users testify that they underwent major transformations and their lives were no longer the same. The changes mentioned pertain to new psychological understandings and personal insights; modifications of belief systems, world-views, and perspectives on life; and religious conversion and adherence to a spiritual life-style. Not infrequently, these effects may result in radical decisions and actions, sometimes at variance with family members' conventional expectations (Grob, 2002a; Shanon, 2002; Walsh & Vaughan, 1993).

Neurotoxic Effects

There has been an extensive debate in the literature (see Grob, 2002b) on the neurotoxic effects of hallucinogenic compounds with more focus on the members of the phenethylamine group, especially

on Ecstasy (MDMA). The debate culminated in Science's retraction of an erroneous publication (Ricaurte et al., 2002) purporting to show that even one-time use of Ecstasy (MDMA) causes damage to the dopamine system that creates a risk of developing Parkinson's disease later in life. Twenty percent of the studied monkeys died quickly, and another twenty percent became sick with severe brain damage after their second or third dose of the investigational drug, which later turned out to be methamphetamine. Critics blamed the researchers' and Science reviewers' biased mind set for overlooking the extreme fatality rates unusual in recreational Ecstasy (MDMA) users.

MDMA. At variance with the retracted report on dopamine neurotoxicity, extensive studies in animals indicate that high or repeated dose Ecstasy (MDMA) exposure can damage serotonergic nerve fibers as result of metabolic stress (Baggott & Mendelson, 2001, Green et al., 1995). The toxic effect is increased under prolonged physical exertion and high ambient temperature (conditions frequently encountered in rave dancing). Similar changes can be induced by methamphetamine and some other phenethylamine agents (Miller & O'Callaghan, 1996; Seiden & Sabol, 1996). However, there is controversy over the extent to which analogous changes occur in humans. Ecstasy (MDMA) toxicity has not been documented in controlled research experiments with human subjects, but it has been alleged to occur in settings outside of clinical research. When considering the millions of users taking Ecstasy of unknown origin, purity, and potency (Gore, 1999; Henry & Rella, 2001), serious toxicity appears to rarely happen (less than four deaths in one million users are estimated). Such users routinely consume estimated Ecstasy (MDMA) doses much higher than those administered in therapeutic protocols. Before the drug was placed into Schedule I, psychiatrists in the US and Europe reported using Ecstasy (MDMA) in a large number of patients, and these therapists did not report any severe adverse effects occurring during or after MDMA-assisted psychotherapy sessions (Gasser, 1994; Greer & Tolbert, 1986, 1998). There is now a considerable body of information indicating that the likelihood of significant toxicity is very low from the doses of Ecstasy (MDMA) used in study protocols. To date, Ecstasy (MDMA) has been administered to over 230 people in controlled and uncontrolled trials in clinical settings and have failed to demonstrate toxicity (De La Torre et al., 2000; Gamma et al., 2000; Grob et al., 1996; Liechti et al., 2000; Vollenweider et al., 1999). There may nonetheless be legitimate concerns about complications arising as a consequence of polydrug abuse, and the interactions of prescription drugs and food substances with MDMA.

Ibogaine. Several studies have reported cerebellar (Purkinje) cell degeneration in rats after ibogaine administration at doses of 100mg/kg. However, the neurotoxic effect of ibogaine appears to occur at levels higher than those used for opioid withdrawal or recreational purpose. Moreover, rats appear to be more sensitive to potential ibogaine neurotoxicity than other species (including primates). Contrary to expectations from an allegedly abusive drug, since ibogaine has a broad receptor profile with glutamate antagonistic activity at NMDA specific sites, that feature suggests neuroprotective potential in stroke patients. Ibogaine was reported to protect against methamphetamine neurotoxicity (for review see Alper, 2001).

Indolealkylamines. Very little is known about the neurotoxicity of the indolealkylamine group; in part because they represent the lowest frequency of use, and no controlled studies are available. Conclusions from observational reports of sacramental use, that contrary to expectations, the DMT and beta-carboline containing ayahuasca may have protective effects (Grob et al., 1996). Some other conjectural evidence supports the notion that this group of hallucinogens may exert neuroprotection. The receptor profile of the indolealkylamines hallucinogens is unique among the classical hallucinogens for their significant 5-HT1A agonist property, and neuroprotective action from 5-HT1A agonists have been demonstrated in different species (De Vry, 1995).

Ergolines. An intermediary position is represented by the ergoline group (e.g., such as LSD), where the relatively strong flashback inducing effect may be related to their neurotoxicity within the visual system (Abraham & Mamen, 1996). On the other hand, there are circumstances where LSD and other 5-HT2A receptor agonists were found to be neuroprotective (Farber et al., 1998).

Chemical Interactions

Since the final common pathway of the classical hallucinogenic drugs is the serotonin system, the main concern about drug interactions is primarily in terms of the possibility of an alarming increase

in serotonergic effects. A set of symptoms known as the 'serotonin syndrome', which is characterized by excessive levels of the neurotransmitter serotonin both in the brain and in the bodily organs. Symptoms are typically initial excitement, nausea and confusion, followed by tremors, vomiting, convulsions, and loss of consciousness (Isbister & Buckley, 2005). The incidence of the 'serotonin syndrome' is not known, since most of the cases are mild and resolve undiagnosed. In its severe form if emergency treatment is instituted (which is essentially supportive care for lack of specific antidotes) the syndrome typically resolves within 24 hours. Confusion can last for days, and death has been reported in extreme cases due to circulatory collapse, malignant hyperthermia, or prolonged convulsions (Settle, 1998).

Several different drug combinations can lead to this potentially fatal condition. The most common and most dangerous is the mixture of serotonergic agents with MAOIs (monoamine-oxidase-inhibitors) of the irreversible type. Monoamine-oxidase enzymes (MAO-A and MAO-B) are found in the brain, the lung, the liver, as well in the gastrointestinal system and provide a multiple defense line against invasions of the body from dietary monoamines, particularly tyramine, a food component which can cause extreme high blood pressure. While inhibition of the MAO's action is not intrinsically life threatening – if some dietary constrains are maintained – fatalities from combinations of MAOIs with specific serotonin reuptake inhibitors (SSRIs) have been reported. A mixture of a MAOI with an SSRI results in blockages of the serotonin metabolism by monoamine-oxidation and serotonin reuptake into nerve terminals. The production of serotonin continues unaffected while its important pathways of elimination are shut down, causing serotonin accumulation which can increase to toxic levels.

Among hallucinogenic compounds the Amazonian decoctum *ayahuasca* has the greatest potential for a variety of chemical interactions (Callaway & Grob, 1998). *Ayahuasca* is a hallucinogenic beverage derived by boiling parts of two or more plants. The brew contains beta-carbolines, which are extremely effective MAOIs, and the potent indolealkylamine hallucinogen DMT. The beta-carbolines, however, are reversible MAOIs, which means they are readily displaced by dietary monoamines or endogenous serotonin, allowing them to be metabolized and thereby avoiding accumulation of these substances to toxic levels. The clinical consequence of the reversible property of beta-carbolines is that strict dietary restrictions may not be required when *ayahuasca* is used in its traditional formulation. There are other features of beta-carbolines which may explain why reports of hypertensive crises following the ingestion of *ayahuasca* have not been documented: beta-carbolines are highly selective inhibitors of MAO-A, a variant of the enzyme which prefers tryptamines (including serotonin) over the pressor agent tyramine as substrates (Yasuhara, 1974), and their affinity is lower for liver MAO compared to brain MAO. This complex mechanism would explain the lack of any reports of peripheral autonomic stimulation associated with the ingestion of *ayahuasca* in combination with sympathomimetic drugs or foods containing tyramine (McKenna et al., 1998).

Whilst *ayahuasca* is less likely to induce hypertensive crises with the concomitant administration of sympathomimetic drugs or with tyramine-rich foodstuffs, it still seems wise to advocate care in combining it with potentially interacting medications and to advise a degree of caution with regard to the dietary intake of foodstuffs likely to contain high tyramine content. These typically include fermented or processed food, (since bacteria and fungi turn the amino acid tyrosine to tyramine), such as aged cheese, smoked or cured meat, liver products, concentrated yeast or protein extracts, soy foods, fava bean pods, sauerkraut, tap beer, and some brands of red wine. Any protein containing food or beverage improperly stored or handled should be avoided (Gardner et al., 1996).

Directions for Future Research

We are limited in our ability to address all possible complicating factors in the use of hallucinogens as therapies or research medications because of the limited research designs which have thus far been employed. Ascribing adverse effects to a particular hallucinogenic agent (or any kind of drug) is not simple, if one is bound to scientific scrutiny. A causal relationship implies a fixed temporal sequence between drug and effect and conclusions based on well-established evidence linking the two. In pharmacological research different study levels with increasing scientific rigor are instituted for evaluation of a drug.

Double blind, randomized, placebo controlled (RPCT) trials represent the highest level of valid-

ity with the random and blind assignment of subjects to a drug cohort or a placebo control group. This golden standard, designed for medication development (double blind, randomized, rigorous trials) is rarely accomplished in hallucinogenic research. Since the end of the long moratorium on human experimentation with hallucinogens, a series of new studies has emerged utilizing careful attention to experimental design. One remarkable example is the replication of the preeminent Good Friday Experiment (Pahnke, 1963) by a group from the Johns Hopkins Hospital (Griffiths et al., 2006) for psilocybin's effect in occasioning mystical experiences. Griffiths' group advanced the methodology of the pioneering study, and improved the set and settings as well. Both studies were double blind, active placebo controlled trials, but the blind in the Good Friday Experiment was easily broken during the session by the participants' psychedelic experience. Another limitation of the Pahnke study was that it was conducted in a group setting. The Johns Hopkins study used better blinding and comparison control procedures, applied empirically validated measures of mystical experience, and assessed effects in individual participants undisturbed by group interactions. Besides a successful replication of the Good Friday Experiment (its results were even better), an important finding of the Griffiths study was, that with careful volunteer screening and preparation, and when sessions are conducted in a comfortable, well-supervised setting, a high dose of psilocybin can be administered safely.

This renaissance is promising, but has not yet produced an abundance of well-controlled trials on the putative dangers of hallucinogenic drugs. In order to adequately answer safety concerns related to these compounds one may need Phase II and III clinical trials.

Today we are witnessing the entrance of hallucinogens (ibogaine, marijuana, MDMA, and psilocybin) into the Phase II stage of well-controlled trials. As an FDA approved anesthetic, ketamine has already passed these phases, and off-label trials are under way (Zarate et al., 2006). The cost of a Phase III study is so expensive, that usually industry sponsored trials can afford that investment. Appropriate information can also be gained in a cost-effective manner via post-marketing (post-approval) trials (not necessarily RPCT), representing the IVth phase in the development of a therapeutic agent.

Conclusions

It is apparent that more and better controlled research (at least Phase II) is needed to clarify the adverse effects of hallucinogens. That kind of research would need enrollment of healthy human volunteers. While rigid administrative regulations in the US are loosening up for the therapeutic use of hallucinogens in severely ill patients, the US is lagging behind Switzerland and Germany where hallucinogen research is not restricted to sick people. Drug safety can not be reliably evaluated only on individuals with compromised health.

In summary of our current knowledge, when hallucinogens are ingested outside of controlled medical, ceremonial, or research settings, these agents have a relatively low potential to be harmful. Nonetheless, ill-conceived hallucinogen experimentation may induce unstable affect and even precipitate psychotic breaks, especially in individuals with dormant or pre-existing psychopathology. What follows is that the recreational use of hallucinogens has not been proven to be 'safe'.

The situation is not alarming under controlled settings, where careful screening of participants, close monitoring of the sessions, and providing follow-up minimizes the incidence of serious adverse events to a very low level, below the reasonably accepted threshold. Certainly, one should not judge a drug from its misuse since that way of evaluation is scientifically incorrect, and there is a possibility of well-conducted studies of both therapeutic and socially acceptable use. With the FDA approving several hallucinogen treatment trials and the US Supreme Court siding with the Uniao do Vegetal in the *ayahuasca* case that possibility is on a cautious path of realization.

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