# **Cell Reports**

# **Psychedelics Promote Structural and Functional Neural Plasticity**

# **Graphical Abstract**



# **Highlights**

- Serotonergic psychedelics increase neuritogenesis, spinogenesis, and synaptogenesis
- Psychedelics promote plasticity via an evolutionarily conserved mechanism
- TrkB, mTOR, and 5-HT2A signaling underlie psychedelicinduced plasticity
- Noribogaine, but not ibogaine, is capable of promoting structural neural plasticity

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# In Brief

Ly et al. demonstrate that psychedelic compounds such as LSD, DMT, and DOI increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation. These cellular effects are similar to those produced by the fast-acting antidepressant ketamine and highlight the potential of psychedelics for treating depression and related disorders.







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# *Banisteriopsis caapi*, a unique combination of MAO inhibitory and antioxidative constituents for the activities relevant to

# neurodegenerative disorders and Parkinson's disease

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# Abstract

**Aim of the study**—Parkinson's disease is a neurological disorder mostly effecting the elder population of the world. Currently there is no definitive treatment or cure for this disease. Therefore, in this study the composition and constituents of the aqueous extract of *B. caapi* for monoamine oxidases (MAO) inhibitory and antioxidant activities were assessed, which are relevant to the prevention of neurological disorders, including Parkinsonism.

**Materials and methods**—The aqueous extract of *B. caapi* stems was standardized and then fractionated using reversed-phase (RP) chromatography. Pure compounds were isolated either by reversed-phase (RP) chromatography or centrifugal preparative TLC, using a Chromatotron<sup>®</sup>. Structure elucidation was carried out by 1D and 2D NMR, Mass, IR and Circular Dichroism spectroscopy and chemical derivatization. Chemical profiling of the extract was carried out with RP-HPLC. The inhibitory activity of MAO-A, MAO-B, acetylcholinesterase, butyrylcholinesterase and catechol-*O*-methyl transferase enzymes, as well as antioxidant and cytotoxic activities of both *B. caapi* extract and isolated compounds were evaluated.

**Results**—An examination of the aqueous extracts of *B. caapi* cultivar Da Vine yielded two new alkaloidal glycosides, named banistenoside A (1) and banistenoside B (2), containing "azepino[1,2-a]tetrahydro- $\beta$ -carboline" unique carbon framework. One additional new natural tetrahydronorharmine (4), four known  $\beta$ -carbolines harmol (3), tetrahydroharmine (5), harmaline (6) and harmine (7), two known proanthocyanidines (–)-epicatechin (8) and (–)-procyanidin B2 (9), and a new disaccharide  $\beta$ -D-fructofuranosyl-(2 $\rightarrow$ 5)-fructopyranose (14) together with known sacharose (15) and  $\beta$ -D-glucose (16) were also isolated. In addition, the acetates of 1, 2, 8, 9, 14 and

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# Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey

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Abstract —Cluster headache is one of the most debilitating pain syndromes. A significant number of patients are refractory to conventional therapies. The Clusterbusters.org medication use survey sought to characterize the effects of both conventional and alternative medications used in cluster headache. Participants were recruited from cluster headache websites and headache clinics. The final analysis included responses from 496 participants. The survey was modeled after previously published surveys and was available online. Most responses were chosen from a list, though others were free-texted. Conventional abortive and preventative medications were identified and their efficacies agreed with those previously published. The indoleamine hallucinogens, psilocybin, lysergic acid diethylamide, and lysergic acid amide, were comparable to or more efficacious than most conventional medications. These agents were also perceived to shorten/abort a cluster period and bring chronic cluster headache into remission more so than conventional medications. Furthermore, infrequent and non-hallucinogenic doses were reported to be efficacious. Findings provide additional evidence that several indoleamine hallucinogens are rated as effective in treating cluster headache. These data reinforce the need for further investigation of the effects of these and related compounds in cluster headache under experimentally controlled settings.

Keywords — cluster headache, hallucinogens, Internet survey, lysergic acid amide, lysergic acid diethylamide, psilocybin

Cluster headache, often rated the most painful of all primary headache disorders, causes significant disability, with enormous personal, economic, and psychiatric burden (Robbins 2013; Rozen and Fishman 2012). The term "suicide headache" reflects the extraordinary intensity and relentless nature of these attacks (Horton 1952; Robbins 2013). In standard parlance, a *cluster attack* refers to the discrete paroxysm of pain—a unilateral stabbing that is primarily retro-orbital, lasting 15–180 minutes, occurring several times daily, usually at strikingly predictable times. A *cluster period* refers to the duration of time during which attacks occur regularly, ranging from weeks to years, often occurring at the same time each year. A *remission period* refers to a prolonged attack-free interval. In episodic cluster headache, periods are separated by months to years. In chronic cluster headache, the period lasts for over a year with no remission greater than one month. The etiology of cluster headache is incompletely

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# Hallucinogen use and intimate partner violence: Prospective evidence consistent with protective effects among men with histories of problematic substance use

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#### Abstract

Evidence suggests that hallucinogens may have therapeutic potential for addressing a variety of problem behaviors related to the externalizing spectrum of psychopathology, such as substance misuse and criminality. Intimate partner violence (IPV) is a prevalent form of criminal violence that is related to externalizing pathology. However, the association between hallucinogen use and IPV has not been comprehensively examined. In this prospective study, we examined the association between IPV and naturalistic hallucinogen use among 302 inmates at a US county jail. Cox regression analyses indicated that hallucinogen use predicted reduced arrest for IPV independently ( $\beta$ =-0.54, *SE*=0.20,  $\chi^2$ =7.19, exp(*B*)=0.58, *p*<0.01) and after accounting for covariates ( $\beta$ =-0.48, *SE*=0.23,  $\chi^2$ =4.44, exp(*B*)=0.62, *p*<0.05). These results add to a growing literature suggesting distinct therapeutic potential for hallucinogens to assist in the attenuation of problematic behavior.

#### Keywords

Hallucinogens, psychedelic, intimate partner violence, domestic violence

### Recidivism

The medical, spiritual, and social use of psychoactive substances generally classified as hallucinogens, also known as psychedelics and entheogens, can be traced to antiquity (Nichols, 2004). In the context of contemporary health science, preliminary studies suggest that hallucinogens may have therapeutic potential for addressing a variety of psychological and behavioral problems, including externalizing behaviors such as substance misuse (e.g., Bogenschutz et al., 2015; Johnson et al., 2014) and criminality (Hendricks et al., 2014). However, despite considerable interest in the therapeutic potential of hallucinogens, the extent to which hallucinogen use might influence risk for externalizing behavior has not been definitively determined.

Hallucinogens encompass a diverse group of substances that affect cognition and perception. The effects of hallucinogens are varied and can include the induction of transcendent and mystical experiences, altered states of self-awareness, and pseudohallucinations (Griffiths et al., 2006; Johnson et al., 2008; Vollenweider and Kometer, 2010). The most commonly used hallucinogens are the "classic psychedelics," which are serotonin 2A (5-HT2A) receptor agonists such as lysergic acid diethylamide (LSD), and psilocybin, but also include less widely used substances such as mescaline and dimethyltryptamine (DMT). However, the broad class of hallucinogens extends beyond these "classic psychedelics" to include substances with other primary modes of actions such as ketamine, phenylcyclidine (PCP), ibogaine, Salvia divinorum, and methylenedioxymethamphetamine (MDMA) (Bogenschutz and Pommy, 2012; Nichols, 2004; Vollenweider and Kometer, 2010).

Diverse cultural groups such as the Shipibo of Peru, the Huichol of Mexico, and the Bwiti of Gabon have long-standing and well-developed traditions of incorporating hallucinogens into the care of mental and physical health (Richards, 2014; Schultes et al., 2001). In contrast, the introduction of hallucinogens to Western medicine is relatively recent, and the determination of the therapeutic potential of these substances has been hampered by strict legal limitations on research (Nutt et al., 2013). As a result, most studies of hallucinogens and behavioral health were conducted prior to the tightening of restrictions in the late 1960s. One focus of this early research was on addressing concerns related to the externalizing spectrum of psychopathology, such as problematic substance use, and antisocial and impulsive behavior (Krueger

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# Hallucinogen use predicts reduced recidivism among substance-involved offenders under community corrections supervision

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#### Abstract

Hallucinogen-based interventions may benefit substance use populations, but contemporary data informing the impact of hallucinogens on addictive behavior are scarce. Given that many individuals in the criminal justice system engage in problematic patterns of substance use, hallucinogen treatments also may benefit criminal justice populations. However, the relationship between hallucinogen use and criminal recidivism is unknown. In this longitudinal study, we examined the relationship between naturalistic hallucinogen use and recidivism among individuals under community corrections supervision with a history of substance involvement (n=25,622). We found that hallucinogen use predicted a reduced likelihood of supervision failure (e.g. noncompliance with legal requirements including alcohol and other drug use) while controlling for an array of potential confounding factors (odds ratio (OR)=0.60 (0.46, 0.79)). Our results suggest that hallucinogens may promote alcohol and other drug abstinence and prosocial behavior in a population with high rates of recidivism.

#### Keywords

Hallucinogen, psychedelic, psilocybin, lysergic acid diethylamide, recidivism, criminal justice, positive psychology

Hallucinogens, sometimes called psychedelics, psychotomimetics, or entheogens, are a class of psychoactive substances with low dependence potential that produce mystical-type experiences characterized by pseudo-hallucinations and feelings of bliss, unity, and transcendence of time and space (Griffiths et al., 2006; Johnson et al., 2008; Vollenweider and Kometer, 2010). Classic hallucinogens (dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), mescaline, and psilocybin) primarily act as agonists of serotonin 2A (5HT<sub>2A</sub>) receptors whereas non-classic hallucinogens (e.g. ketamine, ibogaine, methylenedioxymethamphetamine (MDMA)) have other primary modes of action (Bogenschutz and Pommy, 2012; Nichols, 2004; Vollenweider and Kometer, 2010). Nevertheless, classic and some non-classic hallucinogens may share a common indirect mechanism of modulating glutamatergic neurotransmission in prefrontal-limbic circuitries (Bogenschutz and Pommy, 2012; Nichols, 2004; Vollenweider and Kometer, 2010).

Hallucinogen research flourished in Western countries from the 1950s until the early 1970s, with several investigations suggesting that hallucinogen-based treatments held promise for a number of clinical applications including anxiety disorders, end of life issues, mood disorders, and sexual dysfunction (Bogenschutz and Pommy, 2012; Johnson et al., 2008; Malleson, 1971; Nichols, 2004; Pahnke et al., 1970; Sessa, 2005; Vollenweider and Kometer, 2010). Among the most promising findings was the indication that hallucinogens may have a beneficial effect on addictive behavior. Indeed, a 2012 meta-analysis of six randomized clinical trials conducted between 1966–1970 found that a single dose of

LSD administered in the context of treatment for alcoholism reduced alcohol misuse relative to comparison conditions (odds ratio (OR)=1.96; Krebs and Johansen, 2012).

A modern understanding of classic hallucinogen effects at both the biological and psychological levels suggests the plausibility of hallucinogens as therapeutic for engendering long-term behavior change. Potential biological mechanisms of persisting therapeutic effects may include increases in glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), down-regulation of  $5HT_{2A}$  receptors, changes in pyramidal cell dendritic spine organization (Bogenschutz and Pommy, 2012), and changes in default mode network functional connectivity (Carhart-Harris et al., 2012a), although more research is needed to determine if these effects are associated with therapeutic effects in humans. At the psychological level, research suggests that under interpersonally supportive

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# **Psychedelics as Medicines for Substance Abuse Rehabilitation: Evaluating Treatments with LSD, Peyote, Ibogaine and Ayahuasca**

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Abstract: Substances known as psychedelics, hallucinogens and entheogens have been employed in ethnomedical traditions for thousands of years, but after promising uses in the 1950's and 1960's they were largely prohibited in medical treatment and human research starting in the 1970's as part of the fallout from the war on drugs. Nonetheless, there are a number of studies which suggest that these substances have potential applications in the treatment of addictions. While these substances are generally classified as Schedule I, alleging no established medical uses and a high drug abuse potential, there is nonetheless evidence indicating they might be safe and effective tools for short term interventions in addictions treatment. Evidence suggests that the psychedelics have a much greater safety profile than the major addictive drugs, having extremely low levels of mortality, and producing little if any physical dependence. This paper reviews studies evaluating the use of LSD, peyote, ibogaine and ayahuasca in the treatment of dependencies and the possible mechanisms underlying the indications of effectiveness. Evidence suggests that these substances help assist recovery from drug dependency through a variety of therapeutic mechanisms, including a notable "after-glow" effect that in part reflects their action on the serotonin neurotransmitter system. Serotonin has been long recognized as central to the psychedelics' well-known phenomenological, physical, emotional and cognitive dynamics. These serotonin-based dynamics are directly relevant to treatment of addiction because of depressed serotonin levels found in addict populations, as well as the role of serotonin as a neuromodulators affecting many other neurotransmitter systems.

Keywords: Ayahuasca, entheogens, hallucinogens, ibogaine, LSD, peyote, psychedelics, psychointegrator.

#### **INTRODUCTION**

The substances known as psychedelics, hallucinogens, entheogens, psychointegrators and sacred medicines have been employed in ethnopharmacologies for thousands of years [1, 2]. While there was a brief renaissance of their use in psychiatry in the 1950's and 1960's, these substances have been largely excluded from human research and treatment since their broad international prohibition in the 1970's. Nonetheless, there has emerged significant evidence that a number of these substances have important applications in the treatment of a variety of conditions, including addictions (see [3], Vol. 2 for review articles).

While it might seem somewhat incongruous to treat addicts with substances which are generally classified as Schedule I substances (alleging no medical uses and a high drug abuse potential), there are nonetheless many forms of evidence that suggest they are both reasonable and effective treatment for many conditions. First, the psychedelics have a much greater safety profile than the other major drugs, legal and illegal [4]. Even if we include the vast range of illicit use there is very little mortality associated with their use. Perhaps the greatest risk from the use of the psychedelics is from people thinking they can fly from the upper stories of buildings while under the influence [5]. Furthermore, the psychedelics produce little if any physical dependence [6]. And in contrast to the idea that these drugs might provoke additional addictive behaviors among susceptible populations, there is evidence that they reduce substance abuse, an "after-glow" effect that often appears to allow addicts to easily remain drug free for a period of several weeks to months after administration of psychedelics.

This afterglow effect appears to reflect action on the serotonin neurotransmitter system, which constitutes another significant reason for their use in addictions treatment. Since the 1960s the principal effects of the psychedelics have been recognized as derived from their effects on the serotonergic neurotransmitter system (see 7-10 for reviews). While psychedelics activate other neurotransmitter systems, it is the effects on serotonin neurotransmission that underlie psychedelics' well-known phenomenological, physical, emotional and cognitive dynamics. These serotonin-based dynamics are directly relevant to treatment of addiction because of depressed serotonin levels found in addict populations, as well as the role of serotonin as a neuromodulators affecting many other neurotransmitter systems.

A variety of forms of evidence indicate the possible effectiveness of psychedelics such as LSD, peyote, ibogaine and ayahuasca in the treatment of substance abuse. These four substances appear to constitute the bulk of the research on the use of psychedelics in addictions treatment, although there are some indications that psilocybin and ketamine also have useful applications<sup>1</sup>. This paper first reviews the evidence regarding their effects when used as drug abuse

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<sup>&</sup>lt;sup>1</sup>There is also some evidence which suggests that psilocybin [77], MDMA [78] and ketamine [73, 74, 79] might also have effectiveness in treating addictions.

References	Design/setting	Subjects	Dose	Main results	Safety
Sheppard (1994) <sup>a</sup>	Open-label Non-medical Amsterdam, The Netherland	7 (heroin, methadone, codeine, and ethanol) 5 men, mean age 29.28 vears	Single doses 11.7–25 mg/kg	Absence of withdrawal symptoms after 24–38 hr for all subjects, two relapsed within 48 hr, two after several weeks, one reverted to intermittent heroin use. and three remained drug-free >14 weeks	No medical screening or monitoring No serious adverse reactions
Luciano (1998	) Open-label Setting (?)	3 (cocaine, opiates/ opioids, and ethanol) Gender age (?)	Single doses 20–25 mg/kg	Abstinence (?)	Medical screening and monitoring No serious adverse reactions
Alper et al. (1999) <sup>a</sup>	Open-label Non-medical United States and The Netherlands	33 (heroin. methadone, and cocaine) 22 men, mean age 27.3 years	Single doses 6–29 mg/kg	Absence of withdrawal symptoms and drug use for $25 (76\%)$ subjects after 72 hr, four did not report symptoms but used drugs in $<72$ hr, two reported attenuated symptoms and no drug use in $<72$ hr, and	Medical screening and monitoring one fatality, probably caused by concomitant heroin use
Mash et al. (2000) <sup>b</sup>	Open-label Private clinic St. Kitts, West Indies	27 (heroin, methadone [?] and cocaine) 23 men, mean age 34.6 (opiates/opioids) and 25.6 (control) toome	Single doses 500, 600, and 800 mg	Significant ( $p < .005$ ) reductions in all HCQN-29 subscales <sup>6</sup> and in two CCQN-45 subscales <sup>4</sup> after 36 hr and 14 days, and significant ( $p < .0005$ ) reductions in BDI scores after one month	Medical screening and monitoring No serious adverse reactions
Mash et al. (2001) <sup>b</sup>	Open-label Private clinic St. Kitts, West Indies	37.5 (Ocanie) years 32 (heroin and methadone) 23 men, mean age 33.6 years	Single dose 800 mg	Significant ( $p < .05$ ) reductions in OOWS scores after 12–24 hr and in OP-SCL scores after <72 hr and 6–9 days, and months of abstinence in many subjects (althouch data were not necented)	Medical screening and monitoring No serious adverse reactions
Alper (2001) <sup>a</sup>	Open-label Non-medical United States and The Netherlands	41 (heroin. methadone, cocaine, sedatives, ethanol) Gendar and (?)	Single doses 6–29 mg/kg	15 (29%) subjects reported abstinence for <2 months, 15 (29%) subjects reported abstinence for <2 months, 15 (29%) for $\geq 2$ months/<6 months, 7 (13%) for $\geq 6$ months/<1 year, 10 (19%) for >1 year, and 5 (10%) the outcomes could not be determined	Medical screening and monitoring No serious adverse reactions
Schenberg et al. (2014)	Open-label Private hospital Santa Cruz do Rio Pardo, Brazil	75 (ethanol, cannabis, cocaine, and crack- cocaine) 67 men and 8 women, mean age 34.16 (men) and	Single and multiple doses; mean number of sessions 3.83 (men) and 5.40 (women)	Significant ( $p < .001$ ) increases in abstinence duration, and 61% of subjects were abstinent after single (median 5.5 months) and multiple (median 8.4 months) doses	Medical screening and monitoring No serious adverse reactions
Glue, Cape, Tunnicliff, Lockhart, Lam, Gray, et al. (2016)	Randomized, double-blind, placebo-controlled, single ascending-dose clinical trial Research unit Dunedin, New Zealand	29.50 (women) years 27 (methadone) 21 men, mean age 41.2 years	1/-20 mg/kg Single doses (noribogaine) 60, 120, and 180 mg	Non-significant effects on SOWS, OOWS, COWS, and time to resumption of MST	Medical screening and monitoring No serious adverse reactions Significant QT interval prolongation
Note. BDI, Beck	Depression Inventory; CCON-45, C	Cocaine Craving Questionnair	e; COWS, Clinical Op	ioid Withdrawal Scale; HCQN-29, Heroin Craving Qu	estionnaire; OOWS, Objective Opiate

Table 1. Open-label case series and clinical trials describing the antiaddictive effects of ibogaine

Withdrawal Scale; OP-SCL, Opiate-Symptom Checklist; MST, methadone substitution treatment; SOWS, Subjective Opioid Withdrawal Scale. Interrogation: not informed. <sup>a</sup>Included subjects from the same sample.

<sup>b</sup>Included subjects from the same sample.

<sup>°</sup>Desire to Use, Intention to Use, Anticipation of Positive Outcomes, Relief of Negative States, and Lack of Control. <sup>d</sup>Relief of Negative States and Lack of Control.

# RESEARCH



**Open Access** 

# Traditional medicine applied by the Saraguro yachakkuna: a preliminary approach to the use of sacred and psychoactive plant species in the southern region of Ecuador

Chabaco Armijos<sup>\*</sup>, Iuliana Cota and Silvia González

## Abstract

**Background:** During the colonial period, the indigenous saraguros maintained their traditions, knowledge, and practices to restore and preserve the health of their members. Unfortunately, many of their practices and medicinal resources have not been documented. In this study, we sought to document the traditional healers' (*yachakkuna* saraguros) knowledge about medicinal and psychoactive plants used in the *mesas* and in magical-religious rituals. The study was conducted under a technical and scientific cooperation agreement between the Universidad Técnica Particular de Loja (UTPL), the Dirección Provincial de Salud de Loja (DPSL), and the Saraguro Healers Council (Consejo de Sanadores de Saraguro).

**Methods:** For the present study, the DPSL and Saraguro Healers Council selected the 10 *yachakkuna* most recognized for their knowledge and their use of sacred and psychoactive species. Ten interviews with the selected *yachakkuna* were conducted between 2010 and 2011 to ascertain how the Saraguro traditional healing system is structured and to obtain a record of the sacred and medicinal plant species used to treat supernatural diseases and for psychoactive purposes.

**Results:** The present study describes the traditional health system in the Saraguro indigenous community located in southern Ecuador. It also describes the main empirical methods used to diagnose diseases: direct physical examination of the patient, observation of the patient's urine, documentation of the patient's pulse, *limpia*, palpation and visionary methods, including supernatural diseases (*susto, vaho de agua, mal aire, mal hecho, shuka*) and reports of the use of sacred and medicinal psychoactive plants, such as the San Pedro cactus (*Echinopsis pachanoi*), *wandug (Brugmansia spp.)*, and tobacco (*Nicotiana spp.)*. This study also describes the rituals (*limpia, soplada*) employed by the Saraguro *yachakkuna* to treat supernatural diseases. Finally, we report on the main plants used during *limpia* in the Saraguro community.

**Conclusion:** The current traditional health system in the Saraguro community is the cultural expression of the Saraguros' presence as an Andean group in southern Ecuador: it represents their character as indigenous group, their ability to survive as a community despite strong external pressure, and the desire to maintain their ancient healing heritage.

Keywords: San Pedro cactus, Medicinal plants, Saraguro, Psychoactive plants, Yachakkuna, Healing rituals

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# Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

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#### Abstract

Background: Clinically significant anxiety and depression are common in patients with cancer, and are associated with poor psychiatric and medical outcomes. Historical and recent research suggests a role for psilocybin to treat cancer-related anxiety and depression.

**Methods:** In this double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and received treatment with single-dose psilocybin (0.3 mg/kg) or niacin, both in conjunction with psychotherapy. The primary outcomes were anxiety and depression assessed between groups prior to the crossover at 7 weeks.

**Results:** Prior to the crossover, psilocybin produced immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related demoralization and hopelessness, improved spiritual wellbeing, and increased quality of life. At the 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects (approximately 60–80% of participants continued with clinically significant reductions in depression or anxiety), sustained benefits in existential distress and quality of life, as well as improved attitudes towards death. The psilocybin-induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression.

**Conclusions:** In conjunction with psychotherapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant effects in patients with cancer-related psychological distress.

Trial Registration: ClinicalTrials.gov Identifier: NCT00957359

#### Keywords

Psilocybin, psychedelic, cancer, depression, anxiety, mystical experience

### Introduction

Enduring clinically significant anxiety and/or depressive symptoms are common in patients with cancer, present in 30–40% of patients in hospital settings (Mitchell et al., 2011). These symptoms are associated with a variety of poor outcomes, including medication non-adherence, increased health care utilization, adverse medical outcomes, decreased quality of life, decreased social function, increased disability, hopelessness, increased pain, increased desire for hastened death, increased rates of suicide, and decreased survival rates (Arrieta et al., 2013; Brown et al., 2003; Jaiswal et al., 2014).

Although pharmacotherapeutic and psychosocial interventions are commonly used to treat anxiety and depression in cancer patients, their efficacy is mixed and limited (Grassi et al., 2014; NCCN, 2014). There are no US Food and Drug Administration approved pharmacotherapies for cancer-related psychological distress, the onset of clinical improvement with anti-depressants is delayed, relapse rates are high, and significant side effects compromise treatment adherence (Freedman, 2010; Li et al., 2012). <sup>1</sup>Department of Psychiatry, New York University School of Medicine, New York, NY, USA

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# **Drugs and Mysticism**

# Walter N. Pahnke

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The claim has been made that the experience facilitated by psychedelic drugs, such as LSD, psilocybin, and mescaline, can be similar or identical to the experience described by the mystics of all ages, cultures, and religions. This paper will attempt to examine and explain this possibility.

There is a long and continuing history of the religious use of plants that contain psychedelic substances. Scholars such as Osmond (1957b), Schultes (1963), and Wasson (1961) have made valuable contributions to this intriguing field. In some instances, such natural products were ingested by a priest, shaman, or witch doctor to induce a trance for revelatory purposes; sometimes they were taken by groups of people who participated in sacred ceremonies. For example, the dried heads of the peyote cactus, whose chief active ingredient is mescaline, were used by the Aztecs at least as early as 300 B.C. and are currently being employed by over fifty thousand Indians of the Native American Church as a vital part of their religious ceremonies. Both ololiuqui, a variety of morning-glory seed, and certain kinds of Mexican mushrooms (called *teonanacatl*, "flesh of the gods") were also used for divinatory and religious purposes by the Aztecs. These practices have continued to the present among remote Indian tribes in the mountains of the state of Oaxaca, in Mexico. Modern psychopharmacological research has shown the active chemicals to be psilocybin in the case of the mushrooms, and several compounds closely related to LSD in the case of ololiuqui. Amanita muscaria, the mushroom that has been used for unknown centuries by Siberian shamans to induce religious trances, does not contain psilocybin. The most important psychologically active compound from this mushroom has not yet been isolated, but promising work is in progress. Other naturally occurring plants, which are used by various South American Indian tribes in a religious manner for prophecy, divination, clairvoyance, tribal initiation of male adolescents, or sacred feasts are: cohoba snuff, made from the pulverized seeds of *Piptadenia*; the drink vinho de Jurumens, made from the seeds of Mimosa hostilis; and the drink caapi, made from Banisteriopsis. These last three products contain various indolic compounds that are all closely related to psilocybin, both structurally and in their psychic effects (bufotenine, dimethyl-tryptamine, and harmine, respectively). Both LSD and psilocybin contain the indolic ring, and mescaline may be metabolized to an indole in the body.

## An Experimental Examination of the Claim that Psychedelic Drug Experience May Resemble Mystical Experience

Some of the researchers who have experimented with synthesized mescaline, LSD, or psilocybin have remarked upon the similarity between drug-induced and spontaneous mystical experiences because of the frequency with which some of their subjects have used mystical and religious language to describe their experiences. These data interested the author in a careful examination and evaluation of such claims. An empirical study, designed to

#### ORIGINAL INVESTIGATION

# Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance

R. R. Griffiths · W. A. Richards · U. McCann · R. Jesse

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#### Abstract

*Rationale* Although psilocybin has been used for centuries for religious purposes, little is known scientifically about its acute and persisting effects.

*Objectives* This double-blind study evaluated the acute and longer-term psychological effects of a high dose of psilocybin relative to a comparison compound administered under comfortable, supportive conditions.

*Materials and methods* The participants were hallucinogennaïve adults reporting regular participation in religious or spiritual activities. Two or three sessions were conducted at 2-month intervals. Thirty volunteers received orally administered psilocybin (30 mg/70 kg) and methylphenidate hydrochloride (40 mg/70 kg) in counterbalanced order. To

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W. A. Richards · R. Jesse Council on Spiritual Practices, Box 460220, San Francisco, CA 94146-0220, USA obscure the study design, six additional volunteers received methylphenidate in the first two sessions and unblinded psilocybin in a third session. The 8-h sessions were conducted individually. Volunteers were encouraged to close their eyes and direct their attention inward. Study monitors rated volunteers' behavior during sessions. Volunteers completed questionnaires assessing drug effects and mystical experience immediately after and 2 months after sessions. Community observers rated changes in the volunteer's attitudes and behavior.

*Results* Psilocybin produced a range of acute perceptual changes, subjective experiences, and labile moods including anxiety. Psilocybin also increased measures of mystical experience. At 2 months, the volunteers rated the psilocybin experience as having substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers.

*Conclusions* When administered under supportive conditions, psilocybin occasioned experiences similar to spontaneously occurring mystical experiences. The ability to occasion such experiences prospectively will allow rigorous scientific investigations of their causes and consequences.

**Keywords** Psilocybin · Methylphenidate · Hallucinogen · Entheogen · Mystical experience · Spiritual · Religion · Anxiety · Humans

#### Introduction

Psilocybin, a naturally occurring tryptamine alkaloid with actions mediated primarily at serotonin 5-HT<sub>2A/C</sub> receptor sites, is the principal psychoactive component of a genus of

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# Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14

# months later

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## Abstract

Psilocybin has been used for centuries for religious purposes; however little is known scientifically about its long-term effects. We previously reported the effects of a double-blind study evaluating the psychological effects of a high psilocybin dose. This report presents the 14month follow-up and examines the relationship of the follow-up results to data obtained at screening and on drug session days. Participants were 36 hallucinogen-naïve adults reporting regular participation in religious/spiritual activities. Oral psilocybin (30 mg/70kg) was administered on one of two or three sessions, with methylphenidate (40 mg/70kg) administered on the other session(s). During sessions, volunteers were encouraged to close their eves and direct their attention inward. At the 14-month follow-up, 58% and 67%, respectively, of volunteers rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives; 64% indicated the experience increased well-being or life satisfaction; 58% met criteria for having had a "complete" mystical experience. Correlation and regression analyses indicated a central role of the mystical experience assessed on the session day in the high ratings of personal meaning and spiritual significance at follow-up. Of the measures of personality, affect, quality of life, and spirituality assessed across the study, only a scale measuring mystical experience showed a difference from screening. When administered under supportive conditions, psilocybin occasioned experiences similar to spontaneously-occurring mystical experiences that, at 14-month follow-up, were considered by volunteers to be among the most personally meaningful and spiritually significant of their lives.

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#### MYSTICAL GROUND OF RELIGION

Entheogenic approaches to religious studies largely build on the assumption (some would say "observation") that mystical experiences—primary religious experiences (PREs)—were an experiential, historical origin of religion and a constant though uncommon source of nourishment through the ages.<sup>1</sup> Today, entheogens make PREs more accessible. Entheogens can—but do not always—produce mystical experiences, and by providing a useful mindset in the subjects and a supportive environment, researchers can increase the likelihood of such intense spiritual experiences.

From a mystical perspective, primary religious experiences are the ground religion springs from, thus today's theology and other beliefs, liturgy and rites, social concerns and moral action, and religious organizations all have some of their roots (not all of their roots) in primary religious experience.



With both natural, plant-derived entheogens and laboratory synthesized entheogens, it is possible to develop what Huston Smith called "experimental mysticism." These leads provide opportunities in the sciences, in the humanities, and — most interesting of all — experimental procedures for linking these two.

#### SCIENCES

In the sciences much (though not all) research on religion is descriptive. Activities in the nervous system during religious experiences are described. Relationships among religious activities, denominational membership, demographic variables, social values and morals, and political positions are correlated. Frequency of prayer and other religious activities are associated with health, mental adjustment, or other supposed outcomes. Psychoactive plants and chemicals used in a spiritual context can extend descriptive scientific studies and add treatment variables for the experimental study of religion, for example:

# Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness

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#### Abstract

A large body of evidence, including longitudinal analyses of personality change, suggests that core personality traits are predominantly stable after age 30. To our knowledge, no study has demonstrated changes in personality in healthy adults after an experimentally manipulated discrete event. Intriguingly, double-blind controlled studies have shown that the classic hallucinogen psilocybin occasions personally and spiritually significant mystical experiences that predict long-term changes in behaviors, attitudes and values. In the present report we assessed the effect of psilocybin or changes in the five broad domains of personality – Neuroticism, Extroversion, Openness, Agreeableness, and Conscientiousness. Consistent with participant claims of hallucinogen-occasioned increases in aesthetic appreciation, imagination, and creativity, we found significant increases in Openness following a high-dose psilocybin session. In participants who had mystical experiences during their psilocybin session, Openness remained significantly higher than baseline more than 1 year after the session. The findings suggest a specific role for psilocybin and mystical-type experiences in adult personality change.

#### Keywords

Hallucinogen, mystical experience, openness, personality, psilocybin, psychedelic

## Introduction

Psilocybin and other classic hallucinogens with actions mediated at the 5-HT<sub>2A</sub> receptor site (Glennon et al., 1984; Nichols, 2004) produce a unique profile of subjective effects including robust changes in perception, cognition, affect, volition, and somaesthesia (Isbell, 1959; Rosenberg et al., 1964; Wolbach et al., 1962). In early trials of hallucinogens administered under supportive conditions, 50-80% of participants claimed lasting beneficial changes in personality, values, attitudes and behavior (McGlothlin and Arnold, 1971; Metzner and Editors, 1963). Some of the most frequent subjective reports included greater appreciation of music, art and nature, greater tolerance of others, and increased creativity and imagination (McGlothlin et al., 1967). Consistent with these findings, Studerus et al. (2011) recently reported that nearly 40% of participants in several laboratory studies of psilocybin claimed positive long-term changes in aesthetic experience and in their relationship with the environment (i.e. nature) following their psilocybin sessions.

The long-term positive impact of hallucinogens may depend on their ability to occasion profound insights and mystical-type experiences (Doblin, 1991; Pahnke, 1963). The core features of *mystical experience*, as defined by Stace (1960) and Hood (2003), are feelings of unity and interconnectedness with all people and things, a sense of sacredness, feelings of peace and joy, a sense of transcending normal time and space, ineffability, and an intuitive belief that the experience is a source of objective truth about the nature of reality. Because such experiences appear to enable individuals to transcend their usual patterns of thinking, feeling, and acting, it is plausible that they could occasion changes in core dimensions of personality. In support of this, a doubleblind controlled study by Griffiths et al. (2006, 2008) demonstrated that a single psilocybin session occasioned mystical experiences associated with positive changes in behaviors, attitudes and values more than a year later. Moreover, independent ratings from participants' romantic partners, coworkers, and friends corroborated the first-person reports. These findings suggest fundamental changes in personal concerns, goals, and identity, which are considered to be important dimensions of personality (e.g. in the framework described in McAdams, 1995). However, the impact

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