Psychedelic Treatment of Mental Illness

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https://hopkinspsychedelic.org
Email: mwj@jhu.edu
• Funded by Steven and Alexandra Cohen Foundation, and the Tim Ferriss Collaborative
• World’s largest center for psychedelic research
• Opioid addiction
• PTSD
• Anorexia
• fMRI study of alcoholism with comorbid depression
• Depression in Alzheimer’s disease
• Mood symptoms of post-treatment Lyme disease
• Microdosing
• Creativity
• Genetics, biomarkers
• Psilocybin in >200 mushroom species

• “Classic psychedelic”
  – Psilocybin
  – LSD
  – Mescaline (peyote)
  – DMT (ayahuasca)
Primary Role for 5-HT$_{2A}$

• Classic psychedelics produce discriminative stimulus effects
  – Hirschhorn & Winter (1971)
• Antagonists 5-HT$_{2A}$ antagonists block effects
  – e.g., Vollenweider et al. (1998); Winter et al. (2004)
• 5-HT$_{2A}$ affinity well correlated with human potency
  – Glennon (1984)
Ritualistic use dates back many millennia
1940s – 1970s

- Psychedelics were intensely investigated as research tools and therapeutics
- Promising findings for:
  - Cancer-related distress
  - Alcoholism
The Dark Ages

• Despite promising preliminary findings, human research with psychedelics became largely dormant.
• Dormancy largely a reaction to the association of LSD with the 1960s counterculture and casualties of reckless use outside of the clinic.
Abuse liability & Risks 2018

- Can cause harm in people with psychosis or predisposition
- For anybody, can cause fear, panic, confusion and potentially dangerous behavior
- Moderate elevations in pulse & blood pressure
- Headaches in day following use
Psilocybin Can Cause Temporary Headaches 2012

- Typically mild – moderate
- Might be a clue to understanding how psilocybin can treat cluster headaches

Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers

Matthew W. Johnson¹, R. Andrew Sewell²,³, Roland R. Griffiths⁴

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ABSTRACT

Background: Psilocybin is a well-characterized classic hallucinogen (psychedelic) with a long history of religious use by indigenous cultures and nonmedical use in modern societies. Although psilocybin is structurally related to migraine medications, and case studies suggest that psilocybin may be efficacious in treatment of cluster headache, little is known about the relationship between psilocybin and headache.

Methods: This double-blind study examined a broad range of psilocybin doses (0, 3, 10, 20, and 30 mg/70 kg) on headache in 18 healthy participants.

Results: Psilocybin frequently caused headache; the incidence, duration, and severity of which increased in a dose-dependent manner. All headaches had delayed onset, were transient, and lasted no more than a day after psilocybin administration.

Conclusions: Possible mechanisms for these observations are discussed, and include induction of delayed headache through nitric oxide release. These data suggest that headache is an adverse event to be expected with the nonmedical use of psilocybin-containing mushrooms as well as the administration of psilocybin in human research. Headaches were neither severe nor disabling, and should not present a barrier to future psilocybin research.
Abuse liability & Risks 2018

- Can cause harm in people with psychosis or predisposition
- For anybody, can cause fear, panic, confusion and potentially dangerous behavior
- Moderate elevations in pulse & blood pressure
- Headaches in day following use
- Persisting perceptual changes
- Data suggest no addiction
Safety Guidelines 2008

- Assisted in the approval of psychedelic studies by new scientists and universities

Original Papers

Human hallucinogen research: guidelines for safety

MW Johnson  Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.
WA Richards  Johns Hopkins Bayview Medical Center, Baltimore, MD, USA.
RR Griffiths  Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; Department of Neuroscience, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.

Abstract

There has recently been a renewal of human research with classical hallucinogens (psychedelics). This paper first briefly discusses the unique history of human hallucinogen research, and then reviews the risks of hallucinogen administration and safeguards for minimizing these risks. Although hallucinogens are relatively safe physiologically and are not considered drugs of dependence, their administration involves unique psychological risks. The most likely risk is overwhelming distress during drug action ("bad trip"). This could lead to potentially dangerous behaviour such as leaving the study site. Less common are prolonged psychoses triggered by hallucinogens. Safeguards against these risks include the exclusion of volunteers with personal or family history of psychiatric disorders or other severe psychiatric disorders, establishing trust and rapport between session monitors and volunteer before the session, careful volunteer preparation, a safe physical session environment and interpersonal support from at least two study monitors during the session. Investigators should probe for the relatively rare hallucinogen persisting perception disorder in follow-up contact. Persisting adverse reactions are rare when research is conducted along these guidelines. Incautious research may jeopardize participant safety and future research. However, carefully conducted research may inform the treatment of psychiatric disorders, and may lead to advances in basic science.

Key words
5-HT₂A agonists; adverse reactions; DMT; entheogens; hallucinogens; human research; LSD; mescaline; psilocybin; psychotics; safety guidelines
Mystical Experiences & Lasting Benefit 2006 & 2008

- Safe in this structured setting
- Among the 5 most meaningful life experiences for majority of people
- Improvements in mood and quality of life >1 year after sessions

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

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 14-month follow-up and examines the relationship of the follow-up results to data satisfaction; 58% met criteria for having had a ‘complete’ mystical experience. Correlation and regression analysis 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 vitality assessed across the
Psilocybin Dose Effects 2011

- Increasing psilocybin dose has an orderly effect on mystical experience, challenging experience, and long term positive attribution.
Mystical Experience

- About 60% of participants in both studies met criteria for a “complete” mystical experience
  - Unity
  - Noetic quality
  - Sacredness
  - Sense of transcending time and space
  - Positive mood
  - Ineffability
Mystical Experience Scale “MEQ30” 2012 & 2015

- First validated scale to assess mystical experiences from drugs or other specific experiences
- Factors: unity, positive mood, transcendence of time/space, ineffability

Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin

Frederick S Barrett¹, Matthew W Johnson¹ and Roland R Griffiths¹,²

Abstract
The 30-item revised Mystical Experience Questionnaire (MEQ30) was previously developed within an online survey of mystical-type experiences occasioned by psilocybin-containing mushrooms. The rated experiences occurred on average eight years before completion of the questionnaire. The current paper validates the MEQ30 using data from experimental studies with controlled doses of psilocybin. Data were pooled and analyzed from five laboratory experiments in which participants (n=184) received a moderate to high oral dose of psilocybin (at least 20 mg/70 kg). Results of confirmatory factor analysis demonstrate the reliability and internal validity of the MEQ30. Structural equation models demonstrate the external and convergent validity of the MEQ30 by showing that latent variable scores on the MEQ30 positively predict persisting change in attitudes, behavior, and well-being attributed to experiences with psilocybin while controlling for the contribution of the participant-rated intensity of drug effects. These findings support the use of the MEQ30 as an efficient measure of individual mystical experiences. A method to score a “complete mystical experience” that was used in previous versions of the mystical experience questionnaire is validated in the MEQ30, and a stand-alone version of the MEQ30 is provided for use in future research.

Keywords
Psilocybin, hallucinogens, entheogen, psychedelic, spiritual, mystical experience, factor analysis, structural equation modeling, psychometrics
Psilocybin Increases Openness 2011

- First experimental study to change a personality dimension
- Driven by mystical experience

Original Paper

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

Katherine A MacLean¹, Matthew W Johnson¹ and Roland R Griffiths¹,²

Abstract

A large body of evidence, including longitudinal analyses of personality change, suggests that core personality traits are predominately 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 on 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
Driven by Mystical Experience

- Complete Mystical Experience
- Incomplete or No Mystical Experience

Openness (T score)

Pre | Post
---|---

*
Cancer Existential Distress 2016

- 51 patients
- Life threatening cancer
- Depression and/or anxiety disorder

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths¹,², Matthew W Johnson¹, Michael A Carducci³, Annie Umbricht¹, William A Richards¹, Brian D Richards⁴, Mary P Cosimano¹ and Margaret A Klinedinst¹

Abstract
Cancer patients often develop chronic, clinically significant symptoms of depression and anxiety. Previous studies suggest that psilocybin may decrease depression and anxiety in cancer patients. The effects of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. This randomized, double-blind, cross-over trial investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg) vs. a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. Instructions to participants and staff minimized expectancy effects. Participants, staff, and community observers rated participant moods, attitudes, and behaviors throughout the study. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, those changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with >80% endorsing moderately or greater increased well-being/life satisfaction. Community observer ratings showed corresponding changes. Mystical-type psilocybin experience on session day mediated the effect of psilocybin dose on therapeutic outcomes.

Trial Registration
ClinicalTrials.gov Identifier: NCT00465595

Keywords
Psilocybin, hallucinogen, cancer, anxiety, depression, symptom remission, mystical experience
Study Design

- Two psilocybin sessions 5 weeks apart
- 1 (or 3) mg/70 kg versus 22 (or 30) mg/70 kg
Serious adverse events

• No serious adverse events attributable to psilocybin
Lasting Antidepressant & Anti-Anxiety

HAM-D (Depression)

- Cohen’s $d = 1.30$
- Cohen’s $d = 3.08$

HAM-A (Anxiety)

- Cohen’s $d = 1.22$
- Cohen’s $d = 3.71$
Mystical Experience Correlated with Therapeutic Effects

**HAM-A Anxiety**

$\begin{align*}
\text{r} &= -0.59 \\
p &< 0.0001
\end{align*}$

**HADS Depression**

$\begin{align*}
\text{r} &= -0.36 \\
p &< 0.01
\end{align*}$
Consistent findings

• Cancer patients:
  – Grob et al., 2011
  – Ross et al., 2016

• Outside of cancer:
  – Carhart-Harris et al., 2016
Depression Pilot

- Wait-list control study
- Current n=12
Addiction Treatment

- Classic psychedelics can be misused but are not addictive
Krebs & Johansen (2012)
Across studies, LSD nearly doubled the odds that alcoholic patients would be improved at the 1st follow up (N=536)
Ceremonial psychedelic use linked with addiction recovery

— Peyote and the Native American Church
  • Albaugh & Anderson, 1974; Bergman, 1971; Blum et al., 1977; Calabrese, 1997; Garrity, 2000; Menninger, 1971; Pascarosa et al., 1976; Roy, 1973

— Ayahuasca ceremonies in South America and South American Religions
  • Dobkin de Rios et al., 2002; Halpern et al., 2008
Pilot study of the 5-HT2A-R agonist psilocybin in the treatment of tobacco addiction

Matthew W. Johnson, Albert Garcia-Romeu, Mary P. Cosimano, and Roland R. Griffiths

Original Article

Long-term follow-up of psilocybin-facilitated smoking cessation

Matthew W. Johnson, PhD\textsuperscript{a}, Albert Garcia-Romeu, PhD\textsuperscript{a}, and Roland R. Griffiths, PhD\textsuperscript{ab}

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ABSTRACT

Background: A recent open-label pilot study (N = 15) found that two to three moderate to high doses (20 and 30 mg/70 kg) of the serotonin 2A receptor agonist psilocybin, in combination with cognitive behavioral therapy (CBT) for smoking cessation, resulted in substantially higher 6-month smoking abstinence rates than are typically observed with other medications or CBT alone. Objectives: To assess long-term effects of a psilocybin-facilitated smoking cessation program at ≥12 months after psilocybin administration. Methods: The present report describes biologically verified smoking abstinence outcomes of the previous pilot study at ≥12 months, and related data on subjective effects of psilocybin. Results: All 15 participants completed a 12-month follow-up, and 12 (80\%) returned for a long-term (≥16 months) follow-up, with a mean interval of 30 months (range = 16–57 months) between target-quit date (i.e., first psilocybin session) and long-term follow-up. At 12-month follow-up, 10 participants (67\%) were confirmed as smoking abstenent. At long-term follow-up, nine participants (60\%) were confirmed as smoking abstinence. At 12-month follow-up 13 participants (86.7\%) rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives. Conclusion: These results suggest that in the context of a structured treatment program, psilocybin holds considerable promise in promoting long-term smoking cessation.
• ~5 millions deaths per year world wide (WHO, 2009)
• ~69% of U.S. smokers want to quit (CDC, 2011)
• Even effective medications (Chantix, Zyban, NRT) fail to help ~70-80% of patients remain smoke free for a year
Kick Your Smoking Habit With...Magic Mushrooms?

BY PAULA MEJIA 9/11/14 AT 5:42 PM
Table 1. Demographic and smoking characteristics, N=15.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>10 M, 5 F</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (10.5)</td>
<td>26-65</td>
</tr>
<tr>
<td>Education b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>7 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Cigarette dependence (FTCD) c</td>
<td>5.3 (1.3)</td>
<td>3-8</td>
</tr>
<tr>
<td>Years smoking</td>
<td>31 (9.9)</td>
<td>10-49</td>
</tr>
<tr>
<td>Previous quit attempts</td>
<td>6 (3.6)</td>
<td>2-12</td>
</tr>
<tr>
<td>Cigarettes/day at intake</td>
<td>19 (2.9)</td>
<td>15-25</td>
</tr>
<tr>
<td>Breath CO at intake</td>
<td>30 (9.9)</td>
<td>13-53</td>
</tr>
<tr>
<td>Urine cotinine at intake</td>
<td>1676 (594)</td>
<td>841-3212</td>
</tr>
</tbody>
</table>
Pilot Study Timeline

• 15 week protocol with weekly meetings
• Cognitive behavioral therapy
• 3 psilocybin sessions over 8 weeks (20-30 mg/70 kg)
• 1\textsuperscript{st} Psilocybin session on target quit date
Serious adverse events

- No serious adverse events attributable to psilocybin
7-day Point Prevalence Abstinence (N = 15)
Success Rates Substantially Higher than Typical

(Hughes et al., 2003; Jorenby et al., 2006; Sykes & Marks, 2001)
Mystical Experience in Smoking Cessation 2015

- Greater success in those who had mystical experience
- Mystical experience associated with craving reduction
Qualitative analysis: Smoking Cessation, 2018

- Persisting sense of interconnectedness, awe, curiosity

- Reduced smoking withdrawal symptoms compared with previous quit attempts

- Other positive changes: Altruism, appreciation for aesthetics

- Insights: self-identity, smoking reasons
Randomized Comparative Efficacy Trial

- 80 treatment-resistant smokers
- Randomized to psilocybin or nicotine patch
- Same cognitive behavior therapy
- 1 psilocybin session
7 Day Point Prevalence Biologically Confirmed
% Abstinent – Completing Treatment Sample

Psilocybin

NRT

3 Months (n=46) 6 Months (n=37) 12 Months (n=28)
Psilocybin improves cognitive control and downregulates parietal cortex in treatment-seeking smokers

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Neuroimaging Research Branch, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, MD³
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Preliminary Cognitive and fMRI Results (17 Psilocybin, 10 NRT)

- Multi-Source Interference Task (MSIT) (Bush & Shin, 2006)
  - Cognitive interference
  - Congruency effect:
    - Reaction time of incongruent – congruent trials

![Diagram showing reaction times for congruent and interference trials](image-url)
Psilocybin group shows less “cognitive interference” the day after quitting
Alcohol Dependence Pilot

- 10 alcohol-dependent participants
- Motivational Enhancement Therapy
- 2 sessions of .3 mg/kg and .4 mg/kg psilocybin
Understanding Psychedelic Behavior Change

Common Mechanisms?
• Narrowing of behavioral and mental repertoire
  – Addiction broadly defined
  – Supported by overly rigid brain networks

Endogenous role for 5-HT2A receptors in modulating meaning and mental/behavioral plasticity?
The Dope Slap Effect

“Matt Johnson believes that psychedelics can be used to change all sorts of behaviors, not just addiction. The key, in his view, is their power to occasion a sufficiently dramatic experience to ‘dope-slap people out of their story...’ Psychedelics open a window of mental flexibility in which people can let go of the mental models we use to organize reality.”
Acknowledgments

Roland Griffiths, Ph.D.  Theresa Carbonaro, Ph.D.  Nora Belblidia
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