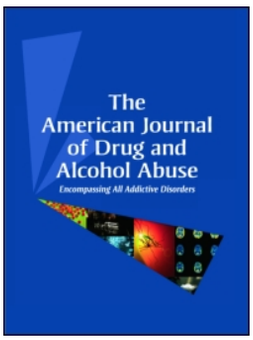

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COMMENTARY

It's time to take psilocybin seriously as a possible treatment for substance use disorders

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In the current issue of the *American Journal of Drug and Alcohol Abuse*, Johnson et al. (1) provide long-term outcome data from a smoking cessation pilot study of a treatment model using 2–3 doses of psilocybin in combination with cognitive behavioral therapy (CBT) for smoking cessation. The short-term results of this study were remarkable: 12/15 participants (80%) were abstinent at 6-month follow-up, based on the self-report validated by urinary cotinine and breath carbon monoxide levels (2). The long-term results reported in the current are even more impressive: 10/15 remained abstinent at 12 months, and 9/12 remained abstinent at long-term follow-up (ranging from 16 to 57 months). Such results are unheard of in smoking cessation treatment. In addition, subjects reported no persisting adverse effects from treatment.

These results are consistent with results of a proof-of-concept study (n = 10) of psilocybin-assisted treatment of alcohol dependence conducted by my research team, which showed robust decreases in drinking, with a pre-post effect size of $d > 1$ persisting at the final 9-month follow-up visit (3). Additional support for this line of research is found in results of a meta-analysis of the results of randomized trials conducted with lysergic acid diethylamide (LSD) in the treatment of alcoholism in the 1960s to early 1970s, where LSD approximately doubled the odds of abstinence or clinical recovery at initial follow-up (4). Randomized-controlled trials are now in progress testing the efficacy of psilocybin-assisted treatment of tobacco, alcohol, and cocaine use disorders.

Initial findings from studies of psilocybin-assisted treatment of mood and anxiety disorders are also very promising. Following up on a pilot study published by Grob et al. in 2011 (5), Phase 2 trials were recently completed at Johns Hopkins University and New York University testing the effects of psilocybin in the treatment of symptoms of anxiety and depression in the context of a life-threatening cancer diagnosis. Although the results have not yet been published in full, preliminary findings from the Hopkins study presented at the American College of Neuropsychopharmacology (ACNP) conference in 2015 included medium to large effects at a 5-week follow-up on symptoms of depression and anxiety in patients treated with a moderate to high dose of psilocybin, relative to a low-dose psilocybin control condition (6). The improvement was sustained at 6-month follow-up. Very recently, results were reported from a pilot study in which 12 patients with treatment-resistant depression received psilocybin-assisted treatment including a low dose session followed one week later by a high-dose session (7). Depressive symptoms were markedly reduced following the high-dose session, and remained so at the final follow-up, with an effect size of g = 2 at three months. There were no serious or unexpected adverse events.

Although the limitations of these small studies are obvious and not to be ignored, there are striking consistencies across the studies that enhance their credibility. The first consistent finding is robust and persistent long-term change in outcome measures following discrete exposure(s) to the drug, in the context of psychosocial treatment platform that both addresses the problematic behaviors/symptoms and provides a safe container for the experience. The second is the lack of harmful effects among study participants. Although the total number of study participants in the recent clinical studies is small, the safety profile of psilocybin in nonclinical samples has also been excellent. The third finding of interest in both the smoking and alcohol pilot studies was that aspects of the psilocybin experience were predictive of outcome. In particular, the degree to which participants reported mystical-type experiences with psilocybin related to greater

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improvement in smoking or drinking behavior. In the alcohol study other measures of experience intensity were also predictive of benefit. These findings were statistically significant in spite of very small sample size in both studies. These findings are consistent with what was generally assumed to be the mechanism of LSD-assisted treatment of alcoholism (i.e., the "peak-psychedelic" experience) in the 1950s and 1960s.

It is worth pausing to note just how impressive these findings are. There are no currently available medications in psychiatry that produce such long-lasting effects on the basis of one or a few discrete exposures. Ketamine has rightly received a great deal of attention because it rapidly produces rapid antidepressant effects after a single infusion. However, the effects of ketamine treatment on depressive symptoms usually last no more than two weeks, whereas the evidence suggests that psilocybin treatment produces effects that can last for months or even years. The importance of these findings, if substantiated by data from larger controlled trials, is extraordinary, both in terms of medication development and in terms of understanding neurobiological mechanisms of change, and the role of conscious experience in producing and maintaining these changes.

Given the steady accumulation of promising findings, the limited efficacy of existing treatments for addictions and other psychiatric disorders, and the general failure in producing new effective treatments in spite of the tremendous advances in brain science, it is puzzling that the field has been so slow to commit resources to evaluating the efficacy of classic hallucinogens such as psilocybin. There are several possible reasons for this.

1. *Limitations of existing data*. The recent studies are all small, often uncontrolled, and mostly lacking replication. However, the lack of definitive studies could just as well be seen as a reason to prioritize such research, based on the impressive results of the small studies conducted to date.
2. *Bad reputation of the drugs*. Many people, particularly in the addiction field, see classic hallucinogens only as dangerous drugs of abuse. While these drugs certainly are misused and have significant risks when they are misused, it is important to keep these risks in context. The harms associated with illicit use of classic hallucinogens are modest relative to most other illicit substances (7).To make a concrete comparison, psilocybin is much safer in terms of addiction, medical, and psychiatric risks than ketamine, even though the latter happens to be a schedule III drug and psilocybin is schedule I. Diversion of clinical material for illicit use would be almost impossible with current treatment models because the drugs are always administered on site at the time of supervised drug administration sessions. A related concern is that medicalization of classic hallucinogens could lead to decreased perception of use, and increased illicit use. This is a real possibility, and it is important for researchers in the field to be very clear that research findings concerning safety and efficacy do not extend beyond the highly controlled conditions under which the drugs are being used in clinical protocols.
3. *Suspiciousness of drug-induced experiences as a mediator of change*. Behavioral science has taken great pains to establish itself as a legitimate objective scientific discipline. It is not surprising that a treatment model that may rely on induction of unusual, non-rational, and ineffable experiences should be greeted with skepticism. However, these experiences are epistemologically no different from other experiences (such as feeling depressed or anxious) that are experienced subjectively and measured indirectly through self-report. Such experiences are correlated with measurable changes in brain activity. It would be very interesting if these experiences were shown to mediate persisting therapeutic changes in brain and behavior, analogous to the detrimental changes that can be produced by traumatic experiences. However, efficacy can be evaluated independent of any assumptions about the underlying mechanisms of therapeutic effects.
4. *Relative lack of commercial potential*. It is hard to see how anyone could make a great deal of money by marketing psilocybin or other well-known classic hallucinogens. Psilocybin, psilocin, mescaline, dimethyltryptamine, and LSD were all characterized over half a century ago, and all but LSD are naturally occurring. Furthermore, the treatment models currently under investigation involve administration of no more than a few doses of the drug. The lack of industry funding likely also decreases the enthusiasm of federal funding agencies, which rely on industry to cover the vast majority of drug development costs.

In the absence of other sources of funding, philanthropists and private nonprofit organizations such as the Heffter Research Institute, the Beckley Foundation, and the Usona Institute have scraped together funding for almost all of the clinical research that has been conducted with classic hallucinogens in the past 15 years. Progress in the field continues to be hampered by the lack of

government support for clinical research with classic hallucinogens such as psilocybin. It seems reasonable to hope that the steady stream of data demonstrating the clinical relevance and scientific importance of these compounds will soon convince rational minds that research in this area should be a high priority.

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