CHAPTER 25

Psychedelics in the Treatment of Addiction

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Introduction

In the original heyday of psychedelic research from the 1950s through the 1970s, when over 1,000 papers were published describing the treatment of over 40,000 patients with psychedelics (Grinspoon, 1981), one of the main therapeutic targets of interest was the treatment of addiction. Specifically, most of this research focused on using lysergic acid diethylamide (LSD) in the treatment of alcoholism, although in some cases the classic psychedelics mescaline (e.g., Smith, 1958, 1959) and dipropyltrypamine (Rhead et al., 1977) were also used to treat alcoholism. The initial hypothesis for using psychedelics for alcoholism was that they might serve to mimic delirium tremens, which sometimes prompted sobriety (Chwelos, Blewett, Smith, & Hoffer, 1959; Dyck, 2006; Smith, 1958). The logic was that classic psychedelics are relatively safe in the physiological domain, in contrast to delirium tremens, which could be fatal. However, rather than dysphoric reactions, these researchers often observed positive, mystical-type effects (i.e., involving distinct qualities including a strong sense of unity; closely related to, or perhaps synonymous with the concepts "peak experience" and "transcendental experience") and insightful effects that seemed to prompt sobriety in response to psychedelic drug administration. A number of studies investigated LSD in the treatment of alcoholism. These varied both in their methods and in their initially reported conclusions regarding efficacy, with some studies showing positive trends for LSD that did not reach statistical significance at relatively small sample sizes. These factors led reviewers to conclude that efficacy was undetermined (e.g., Abuzzahab & Anderson, 1971; Mangini, 1998). However, within the last decade, a meta-analysis of the only studies from the older era that randomly assigned patients to either an LSD or control condition (six original studies; a total of 536 patients) showed significant and substantial decreases in alcohol misuse at the first follow-up (at least 1 month after treatment) in the participants receiving LSD compared to the control participants (Krebs & Johansen, 2012). Renewed work along these lines, using the classic psychedelic psilocybin to treat alcohol use disorder,

has shown promising preliminary results in an open-label pilot study (Bogenschutz et al., 2015). For a far more detailed review of past and current research using psychedelics specifically to treat alcohol use disorder, see Chapter 24, this volume, coauthored by Michael P. Bogenschutz and Sarah E. Mennenga.

In early research examining psychedelics in the treatment of alcoholism, the observation that treatment outcomes depend on the nature of the subjective experience following psychedelic administration (Chwelos et al., 1959; Dyck, 2006; Smith, 1958) suggests something profound and possibly paradigm-shifting about this treatment model (Johnson, 2018b). It suggests that, unlike typical addiction medications, the efficacy of psychedelics in treating alcoholism might not rely on the ability of the medication to directly modify alcohol reinforcement, craving, or withdrawal at the neurobiological level governing alcohol effects. Rather, the psychedelic may occasion powerfully plastic biological, mental, and behavioral states during or after the period of drug action, in which heightened learning may occur, prompting persistent behavior change long after the biological effects of the medication have been resolved. This paradigm might afford some remarkable distinctions in comparison to traditional psychiatric medications. First, a single or a few administrations can be associated with persisting behavioral change, as shown in studies by colleagues and myself, which found that a single high dose of psilocybin led to lasting reductions in depression and anxiety among cancer patients, still persistent when examined at 6 months posttreatment in some studies (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). This differs strongly for the typical model necessitating regular (e.g., daily) administration of psychiatric medication as with typical antidepressants and anxiolytics. A second fundamental way in which the psychedelic therapy paradigm is distinguished may be in its generality. A powerful plastic state with enhanced potential for learning is one that may not only be applicable for the treatment of alcohol use disorders, but also applicable to behavioral change generally, including other substance use disorders, the focus of this chapter.

Heroin

The idea that psychedelics held clinical potential for substances of abuse beyond alcohol goes back to the earlier era of research. One early study tested whether LSD might have therapeutic potential in the treatment of opioid dependence (Savage & McCabe, 1973). This study was with 78 heroin-using individuals who were inmates under parole/probation supervision by the State of Maryland. Participants were randomized to either a psychedelic therapy condition involving a single administration of LSD (300–450 μg) during a 6-week residential stay at a "halfway house" or a comparison condition involving attendance at an outpatient clinic, daily urine testing for opiates, and weekly group therapy sessions. The LSD group showed significantly lower urinalysis-confirmed heroin use at every time point examined, including the 12-month posttreatment assessment, at which continuous abstinence rates were 25% in the LSD group versus 5% in the comparison group. A fascinating component of the report consisted of participant comparisons of LSD effects with heroin effects. One participant stated, "Heroin has a numbing-like effect on you. It tends to relax you and somewhat takes you out and away from your surroundings and yourself. LSD makes you more aware of yourself and puts you right into whatever has been troubling you." Echoing a similar theme, another participant stated, "Comparing LSD to heroin is like comparing a speck of dust with a mountain. The difference is that heroin helps you to turn from yourself and LSD show you how to face yourself." A third stated, "The two experiences of heroin and LSD are like night and day. Heroin is night, a time to sleep and with sleep, nothing comes but a dream. But with LSD, it is like dawn, a new awakening, it expands your mind, it gives you a brand-new outlook on life."

A major caveat in interpreting the results of this study, as acknowledged by the study's authors, is that the groups differed on other aspects of treatment aside from LSD treatment, including a 6-week residential stay for the LSD group. However, these preliminary data were promising, and it is a shame that 45 years have passed since their publication,

with no follow-up studies. With the United States now facing an epidemic of opioid dependence and associated fatalities (Kolodny et al., 2015), the present is an ideal time for revisiting the use of psychedelics in the treatment of opioid use disorders.

Tobacco

Based on these early data suggesting antiaddiction efficacy of classic psychedelics across multiple target drugs of abuse, my colleagues and I embarked on a study using the classic psychedelic psilocybin as a smoking cessation medication. Tobacco addiction seemed an intriguing target for a number of reasons. Although there was preliminary evidence of antiaddiction efficacy of classic psychedelics for alcoholism and opioid dependence, those are addictions to drugs that are extremely intoxicating. Tobacco addiction is similar in that it is unquestionably a drug addiction, with all of the hallmark features present to one degree or another in other forms of drug addiction, including drug-mediated reinforcement, craving, withdrawal, preference for immediate drug reward over delayed but arguably more highly valued consequences such as improved health, and high rates of relapse among those attempting to quit (Bickel, Johnson, Koffarnus, MacKillop, & Murphy, 2014; Hughes, 2006; Johnson, Bickel, & Baker, 2007). However, tobacco addiction differs from alcohol, opioids, and many other drugs of abuse, in that it is not associated with substantial behavioral intoxication and associated current quality-of-life destruction, at least as typically consumed in the form of modern cigarettes (Hughes, 2006). This begs an interesting question: Are psychedelics potentially effective in addiction treatment because they somehow allow the person to reevaluate the life disintegration that often comes with highly impairing drugs? Put another way, do they prompt something like a "rock bottom" experience, with accompanying realization about the harms one has done to him- or herself and loved ones? If so, perhaps tobacco addiction would not be sensitive to psychedelic treatment. Rarely does one lose a job, ruin a career, or lose a spouse due to his or her tobacco addiction, as is known to happen with highly intoxicating drugs such as alcohol and opioids. In some sense, one might consider tobacco addiction a "purer" form of addiction, in that it constitutes more of a straightforward competition between short- versus long-term interests. Life is relatively unimpaired for the vast majority of years of a smoking career, but then an increased probability of serious illness and premature death typically come after decades of smoking. Could psychedelic sessions be efficacious in helping individuals resolve such competing motivations at play in addiction, in the absence of severe current life destruction? Cigarette smoking seemed a fascinating test case.

Aside from serving an intriguing model system of addiction, cigarette smoking is, of course, of interest because it is responsible for far more deaths than any other drug. In the United States, smoking is responsible for approximately five to seven times more deaths than alcohol, and approximately 26 times more deaths than all illicit drugs combined (Danaei et al., 2009; Mokdad, Marks, Stroup, & Gerberding, 2004). Although smoking cessation medications are approved by the U.S. Food and Drug Administration (FDA) and show greater efficacy than placebo, the large majority of individuals fail to maintain abstinence in the long term for any given quit attempt with these medications (e.g., Hughes, Shiffman, Callas, & Zhang, 2003; Jorenby et al., 2006). Therefore, there is a dire unmet need for more effective medications, particularly given the overwhelming mortality associated with smoking.

In order to evaluate safety and test the waters for feasibility and potential efficacy of the approach, we conducted an open-label pilot study in 15 nicotine-dependent, treatment-resistant tobacco cigarette smokers (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014). Participants (10 men and five women) with a mean age of 51 years, had been smoking for a mean of 31 years. They reported a mean of six previous serious quit attempts using a variety of methods, and currently smoked an average of 19 cigarettes per day. They provided breath and urine samples that showed carbon monoxide and cotinine levels, respectively, that confirmed their status as smokers. Participants underwent a 15-week program including manual-

ized cognitive-behavioral therapy (CBT) for smoking cessation and up to three psilocybin sessions. After four preparatory sessions in which CBT content and specific preparation for receiving psilocybin were provided, the first psilocybin session occurred on the participant's predesignated target quit date. This session involved the administration of a moderately high dose (20 mg/70 kg) of psilocybin. Additional psilocybin sessions were provided at 2 and 8 weeks after the target quit date. For these last two sessions, the default plan was to administer a high dose (30 mg/70 kg) unless the moderately high dose seemed of sufficient strength in the judgment of the participant (only one participant deviated from the default plan). Between and after these psilocybin session days, volunteers visited the laboratory on a weekly basis. During these visits, CBT content was provided.

No serious adverse events attributable to psilocybin occurred during the study. At the 6-month posttarget quit date, 12 out of 15 participants (80%) were biologically verified (via breath carbon monoxide and urine cotinine analysis) as smoking abstinent. Nine of the 15 participants (60%) met the threshold criteria to qualify as having had a "complete" mystical-type experience (a subjective experience sensitive to psychedelic effects, as described in the Introduction) on the States of Consciousness Questionnaire in at least one of their multiple sessions (Garcia-Romeu, Griffiths, & Johnson, 2014). Those who were smoking abstinent at 6 months had significantly higher mystical-type experience scores as measured by the States of Consciousness Questionnaire on their session days. Moreover, a significant negative relationship was shown between mystical-type experience score on the States of Consciousness Questionnaire on their session days, and the degree of cigarette craving reduction at study intake to the 6-month follow-up. At a very long-term follow-up 2.5 years after the target quit date, 12 of the original 15 participants were qualitatively interviewed regarding their experience in the study (Noorani, Garcia-Romeu, Swift, Griffiths, & Johnson, 2018). Participants described the psilocybin sessions as leading to insights into self-identity and reasons for smoking, and a lasting sense of interconnectedness, awe, and curiosity. These psilocybin effects were reported to have overshadowed tobacco withdrawal symptoms. Moreover, aside from smoking, participants reported increases in prosocial behavior and aesthetic appreciation.

Volunteers were reassessed with breath and urine samples at their 12-month follow-up and at the very long-term follow-up, which was on average 2.5 years after the target quit date. Biologically confirmed abstinence rates were 67 and 60% at these two time points, respectively. Although the open-label and nonrandomized nature of the design precludes any definitive conclusions regarding the efficacy of psilocybin per se, these results were very promising. Consider that at approximately 6 months posttarget quit date, over-the-counter nicotine replacement therapy is associated with an approximately 7% abstinence rate (Hughes et al., 2003), sustained-release bupropion is associated with an approximately 20% abstinence rate (Jorenby et al., 2006), and varenicline is associated with an approximately 30% abstinence rate (Jorenby et al., 2006). So, if the question was whether the approach was promising enough to warrant the time and resources for conducting a more rigorous follow-up, the answer was a resounding "yes."

We are now conducting a comparative efficacy trial that randomizes treatment-resistant smokers to a single psilocybin session (concurrent with the target quit date) or the transdermal nicotine patch (per FDA guidelines, beginning 24 hours after their target quit date). Both treatment arms are run in combination with a 13-week program of the same manualized CBT used in our pilot study. Before their target quit date, and after 24 hours of nicotine abstinence, participants undergo functional magnetic resonance imaging (fMRI), during which they complete a variety of tasks including the Multi-Source Interference Task (MSIT), a measure of cognitive control. Participants complete the task again, 24 hours after their target quit date. Interim results were presented at the 80th Annual Scientific Meeting of the College on Problems of Drug Dependence (Johnson, 2018a) and the 2018 meeting of the Society

of Biological Psychiatry (McKenna et al., 2018). Interim results show substantially higher cotinine-verified 12-month abstinence rates in the psilocybin group (50%, *n* = 10) compared to the nicotine patch group (*n* = 9, 20%), continuing to suggest promising results for psilocybin in smoking cessation. MSIT results showed significant pre- versus post-target quit date reductions in the reaction time congruency effect in psilocybin participants (*n* = 9), but there was no change in the nicotine patch group (*n* = 7). For psilocybin participants, MSIT congruency effect reaction time was significantly and positively correlated with superior parietal cortex activation during the task for the prepsilocybin scan, but not for the postpsilocybin scan. These preliminary neurocognitive analyses suggest significantly improved cognitive control and a reduction of fMRI response in the superior parietal cortex the day after quitting for the psilocybin group, suggesting psilocybin may improve smoking cessation outcomes by enhancing cognitive control. This study is ongoing. If results continue to suggest promise in using psilocybin in smoking cessation, the approach should be tested in additional, rigorous studies.

Cocaine

Cocaine use disorder is a clinical target of psychedelic therapy under investigation by Peter Hendricks (2018) at the University of Alabama at Birmingham. Although dozens of compounds have been tested over the last few decades, no medication has been approved by the FDA for the treatment of cocaine use disorder. This ongoing double-blind study plans to randomize 40 individuals with cocaine use disorder to receive either 25 mg/70 kg psilocybin or a psychoactive comparison compound (100 mg diphenhydramine) on a single session day. Like the aforementioned cigarette smoking cessation research, in the weeks preceding the drug administration session, preparatory meetings take place involving both CBT content for the treatment of cocaine use disorder and specific preparation for a high-dose psilocybin session. Also, like the current smoking cessation trial, fMRI is conducted both before the psilocybin session day and the day after psilocybin in order to determine potential neurobiological correlates of treatment success that might underlie potential psilocybin efficacy for cocaine abstinence. Weekly CBT-based sessions continue for 4 weeks following the psilocybin. A final follow-up session is conducted about 6 months after the end of active treatment (i.e., the last CBT-based session).

Interim results from the cocaine use disorder trial were recently presented at the 80th annual scientific meeting of the College on Problems of Drug Dependence (Hendricks, 2018). Although very preliminary, with 10 participants thus far (six randomized to psilocybin, and four randomized to diphenhydramine; relatively well matched on demographics at this preliminary stage), results were promising regarding both safety and potential efficacy for cocaine abstinence. No serious adverse events were attributable to study medication. Although the groups were statistically indistinguishable in their urinalysis-confirmed cocaine abstinence at baseline assessment, the psilocybin group had a mean of 100% cocaine-abstinent days during the final 90- to 180-day assessment period, while the control group had a mean of approximately 86% cocaine-abstinent days during the same time period, which was a statistically significant difference. Urinalysis was performed at the 180-day follow-up, providing confirmation regarding abstinence during the several days preceding the follow-up visit. To be clear, results for both groups thus far are better than one would expect for cocaine use disorder treatment. Perhaps the careful preparation, rapport building, and willingness to take a bold step such as psychedelic therapy might be part of the mix for both groups that may account for promising preliminary results.

Regarding long-term changes other than cocaine abstinence, the psilocybin group, compared to the control group, showed substantial increases in ratings of life satisfaction at each of the follow-up visits and reported substantially reduced stress at the majority of follow-up visits. It is possible that such changes are related to addiction recovery, either as a cause or a consequence. Regarding the nature of their session day

experiences, the psilocybin group showed substantially higher ratings on all factors of mystical-type experience, a construct of subjective experience known to be sensitive to psilocybin effects, as discussed earlier in regard to smoking cessation. In this study, mystical-type experience was assessed on session days (after psilocybin effects had largely resolved) using the validated 30-item Mystical Experience Questionnaire (MEQ-30; Barrett, Johnson, & Griffiths, 2015). These psychometrically distinct factors include (1) unity, noetic quality, and sacredness; (2) positive mood; (3) transcendence of time and space; and (4) ineffability. The psilocybin group also showed substantially higher ratings on all factors of the Challenging Experience Questionnaire, a measure validated to assess subjectively difficult reactions to psilocybin, sometimes colloquially referred to as "bad trips" but often valued as learning experiences within supervised psychedelic therapy sessions (Barrett, Bradstreet, Leoutsakos, Johnson, & Griffiths, 2016). These psychometrically distinct factors include grief, fear, death, insanity, isolation, physical distress, and paranoia. Therefore, session content very much appeared to be in line with expectations regarding the administration of a high dose of psilocybin within a psychedelic therapy context. Moreover, every patient in the psilocybin group indicated that the session was among either the single most meaningful experience of his or her lifetime (two volunteers) or among the five most meaningful experience of his or her lifetime (four volunteers). One of the four volunteers in the control group indicated that the session was among the meaningful experience of his or her lifetime (none in the other category). This response from a control group participant clearly suggests that placebo effects and/or the nonpharmacological aspects of the intervention can play a powerful role in shaping the experience. Although very preliminary, study results thus far suggest that examining psychedelic therapy for cocaine use disorder is a credible and promising line of research. Given the incredible amount of resources over the last few decades devoted to finding an effective medication for the treatment of cocaine use disorder, and the fact that no medication has been approved by the FDA, continued promising results would be exciting and might address a critical unmet need.

Conclusions

While we await more definitive results for the lines of research using psilocybin to treat tobacco and cocaine use disorders, the emerging possibility of an approach with cross-addiction generality is looking more realistic. On the short list of research that needs to be conducted is to revisit the use of psychedelics in the treatment of opioid use disorder, particularly given the modern opioid epidemic (Kolodny et al., 2015). One could also test the treatment on a whole host of target drugs of abuse, including methamphetamine. Moreover, it is plausible that antiaddiction effects are not limited to drugs of abuse. Credibility for this argument is lent by the finding discussed in the Introduction regarding persisting reductions in depression and anxiety in cancer patients (Griffith et al., 2016; Grob et al., 2011; Ross et al., 2016). As I have postulated previously (Johnson, 2018b; Pollan, 2018), it may be that depression, anxiety, and other psychiatric disorders that are not nominally considered addictions may in fact constitute addictions as broadly defined; that is, they involve a narrowed mental and behavioral repertoire in which one is stuck in a certain pattern, focused on a certain activity to the suboptimal exclusion of other aspects of the environment and life. Whether that pattern of behavior is in the self-administration of tobacco, alcohol, cocaine, opioids, or other drugs, or whether it is the cyclical, self-perpetuating thoughts of self-hatred, inevitable failure, or worry that can come with mood and anxiety disorders, it may be that psychedelics have the ability to at least temporarily allow one to see outside of those narrow patterns, to recognize the suboptimality of these patterns, and therefore become motivated and learn to adopt more optimal patterns of living. This broad view of psychedelics as behavior-change agents may constitute a paradigm shift in psychiatry (Johnson, 2018b; Kuhn, 1962). Although each disorder needs to be empirically tested, and more research is needed at the psychological and biological levels to understand the mechanisms of this

broad behavior-change potential, it already seems justified to test the ability of psychedelic therapy to treat disorders including anorexia, obesity, gambling disorder, and sexual impulse control disorders. I hope that the field of psychedelic research will sufficiently expand, both in terms of attracting qualified scientists and acquiring federal funding, in order to fully test the potential of psychedelics as behavior-change agents.

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