The Potential of Psilocybin Administration in Terminal Cancer Patients

BY RICHARD SIMONEAUX

Psilocybin is a naturally occurring alkaloid found in more than 200 species of mushrooms. This compound, which was first isolated by the Swiss chemist Albert Hofman in 1959, is the active constituent of psychedelic mushrooms which are thought to have been utilized by humans since prehistoric times. *In vivo*, psilocybin is converted by the liver to psilocin, which is in fact the active pharmacological agent. Mechanistically, psilocin is thought to function as a partial agonist to several serotonin receptors.

In the 1960s, several different groups were performing research using psychedelic agents; however, these studies were drastically affected by the U.S. government's classification of both psilocybin and psilocin as Schedule I drugs in October 1970, though increasingly limited research continued at the Maryland Psychiatric Research Center until 1977 .

After a dormant period of 22 years, Roland Griffiths, PhD, and William Richards, PhD, successfully obtained federal and university clearances in 1999 to reinitiate human studies with psilocybin at the Johns Hopkins School of Medicine.

In October 2018, the FDA granted Breakthrough Therapy designation to psilocybin for treatment-resistant depression. "I am hopeful that the FDA's designation of psilocybin as a breakthrough therapy for treatment-resistant depression will allow greater exploration of psychedelic therapy in other patient populations," stated Richards, who is a psychologist in the Psychiatry Department of the Johns Hopkins University School of Medicine, Bayview Medical Center.

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Phase II Study in Cancer Patients

Many cancer patients experience psychological stress due to their diagnosis, which can result in clinically significant depression and/or anxiety. In a phase II clinical study (NCT00465595), supported by the Heffter Research Institute and performed at Johns Hopkins, researchers evaluated psilocybin in participants who had received a potentially life-threatening cancer diagnosis who also had anxiety and depressed mood (*J Psychopharm* 2016;30:1181-1197).

In this double-blind study, patients were randomized in a 1:1 ratio to two different psilocybin dosing regimens: high dose (22 or 30 mg/70 kg) first followed by a low dose (1 or 3 mg/70 kg) or low dose first followed by a high dose. Initially, the high dose was 30 mg/70 kg; however, this was reduced to 22 mg/70 kg after two of the first three patients receiving the high dose were discontinued by the study personnel.

The low dose of psilocybin was lowered to 1 mg/70 kg from 3 mg/70 kg after dosing 12 participants at the 3 mg level. This dose was altered because data from the same dose-effect study showed significant psilocybin effects at 5 mg/70 kg, and there was concern that 3 mg/70 kg might produce psychedelic effects in some research volunteers and not serve reliably as an inactive placebo.

There were two primary therapeutic outcome measures which were utilized: the widely used GRID-HAMD-17 for depression and HAM-A assessed with the SIGH-A for anxiety. These measurements were taken at baseline, 5 weeks after each session, and at 6 months. In clinician-rated measures, clinical significance was noted for those responses with a 50 percent or greater decrease in measure with respect to baseline, while symptom remission was defined as a 50 percent or greater decrease in measure relative to baseline and a score of seven or less on the GRID-HAMD or HAM-A.

This study, which included 51 patients (low/high–25; high/low–26), showed that, when administered in a psychologically supportive setting by properly trained personnel, a single dose of psilocybin can produce clinically significant responses, yielding substantial and enduring decreases in both depressed mood and anxiety. In addition, many of these cancer patients also reported increases in quality of life, as well as decreases in death anxiety. Enduring effects at 6 months were noted for the patients in assessments made by the patients, clinicians, and community observers.

> "I am hopeful that the results that have been obtained for cancer patients with psilocybin therapy and counseling may serve as a springboard to apply this treatment to others in need."

"At 6 months, the overall rate of clinical response for clinician-rated depression was 78 percent, while the figure for clinician-rated anxiety was 83 percent," Richards noted. Two similar studies conducted at UCLA and New York University also reported positive findings.

Pharmacokinetics Study

An open-label phase I dose-escalation study (NCT02163707) evaluated the safety and pharmacokinetics of psilocybin in 12 healthy adult participants in sequential doses of 0.3, 0.45, and 0.6 mg/kg (*Clin Pharmacokinet* 2017;56:1543-1554).

In preparation for receiving psilocybin, eligible healthy adults had between 6 and 8 hours of counseling prior to receiving their dosing. Psilocybin administration was performed at monthly intervals in a controlled environment with 24-hour monitoring.

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In some participants, an extended elimination phase was noted; this was postulated to be due to the hydrolysis of a key psilocin metabolite. An important observation was the fact that variability in psilocin clearance was not predicted by body weight. Importantly, no serious adverse events were noted during the course of this study.

Using the pharmacokinetic parameters obtained, a 25 mg oral dose of psilocybin would produce a drug exposure that approximated the 0.3 mg/kg oral dose utilized in this study. Importantly, no serious physical or psychological effects were noted during or up to 30 days after any dose, even at a dose of 0.6 mg/kg, which is roughly double that likely to be used in a clinical setting.

Future Studies

A randomized, double-blind phase II clinical study (NCT03866174), which is being sponsored by the Usona Institute, is planned to include 80 participants from 21 to 65 years old who meet the criteria for major depressive disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Stratification will be performed according to study site, with participants being randomized in a 1:1 ratio to a single oral dose of either 25 mg psilocybin or placebo (100 mg niacin).

"The GMP quality psilocybin that will be used in this study was synthesized in a laboratory and does not come from mushrooms," Richards noted.

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The primary outcome in this study is the difference in the centrally rated Montgomery-Asberg Depression Rating Scale (MADRS) total score between baseline and day 8 post-dose. This clinican-rated scale is designed to measure depression severity and to detect changes resulting from antidepressant therapy. The MADRS consists of 10 items, each being scored from 0 (if the item is not present or normal) to 6 (severe or continuous presence of the symptoms); with this scale, a higher score represents a more severe condition.

Among the MADRS-derived secondary outcomes in this study were change in a centrally rated MADRS score from baseline to day 43 post-dose; sustained depressive symptom response, which is defined as a 50 percent or greater reduction from baseline in the centrally rated MADRS score at all post-dose assessments (at days 8, 15, 29, and 43 post-dose); and sustained depressive symptom remission, which is defined as a centrally rated MADRS score 10 or less at all post-dose assessments (at days 8, 15, 29, and 43 post-dose).

An additional secondary outcome is the difference in the local investigator-assessed Sheehan Disability Scale (SDS) scores between baseline and day 43 post-dose. The SDS, which consists of three self-rated items, is designed to gauge the degree to which a patient's life is affected by psychiatric symptoms, including depression.

The study is estimated to start in September 2019 and expected to be completed by February 2021.

In another phase IIb clinical study (NCT03775200), the safety and efficacy of psilocybin is being evaluated in patients diagnosed with treatment-resistant depression. This trial, which is being conducted at treatment centers in North America and Europe, is planned to include 216 patients from 18 to 55 years of age.

This study, which is quadruple-masked (patient, care provider, investigator, and outcomes assessor), includes three different treatment arms: low-dose psilocybin, medium-dose psilocybin, and high-dose psilocybin. The primary outcome measure in this trial is the MADRS, measured up to 12 weeks after dosing.

Discussion

When asked about his background with psilocybin therapy for cancer patients, Richards replied, "I treated my first cancer patient with psilocybin in 1967. Over the years, the responses that I have noted in cancer patients who have received psilocybin-based psychedelic therapy combined with counseling have been remarkably transformative."

Richards explained the procedure for prospective candidates receiving psychedelic therapy. "First, potential candidates for this therapy are screened to determine if this therapy would be appropriate for them. Next, the patient undergoes a total of 6-8 hours of counseling prior to being dosed with psilocybin. This counseling is extremely important, as it develops a sense of trust with the staff that will be present with the patient when they are under the influence of psilocybin, as well as prepare the participants for what they may experience during the dosing session.

"It is essential that the patient establish a significant level of trust with the individuals who will be with them during the action of psilocybin, as that will put them at ease and allow them to be more open to their unfolding inner experiences; the ability to be at ease and open to the alternative states of consciousness is of paramount importance for the patient to derive the most benefit from the agent. Many [bad experiences] are often the result of the patient trying to be in control of the psychedelic experiences instead of allowing them to follow their own course."

Regarding the results he has personally observed, Richards stated, "The outcomes observed in our studies have been significantly transformative, with many patients showing positive effects many months after a single dose of psilocybin. In many instances, not only does the terminal cancer patient lose their fear of death, but they will actually take on the role of a counselor and help those grieving in their families to cope with their impending mortality.

"The main thing that I would like to convey to clinicians is that the transformation that psilocybin ushers forth, which is often several months in length, is drawn from the patient's long-term memory, not the result of any lingering compound present in their system or continuing drug administration.

When asked why psilocybin was still listed as a Schedule I substance, Richards replied rhetorically, "Now that is a very profound question, isn't it? The University of Wisconsin study showed that, in healthy adults, no serious psychological or physical effects were observed up to 30 days after dosing, even at supratherapeutic levels.

"In terms of abuse potential, psilocybin is absolutely not habit-forming, does not result in physical dependence even with repeated use, and in my opinion has much less risk for overuse than the opioids which are routinely prescribed for pain management. That having been said, it is crucial that when someone takes psilocybin that they are in a safe environment in the company of appropriately trained professionals who can ensure their personal safety."

Summarizing, Richards stated, "Now is a very exciting time to be doing psychedelic research using psilocybin; the FDA's granting of Breakthrough Therapy designation for psilocybin for treatment-resistant depression is a noteworthy milestone which may eventually lead to the removal of its Schedule I classification.

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Richard Simoneaux is a contributing writer.

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Analyze outcomes observed in various studies that used psilocybin for patients with terminal cancer. 2.Outline the goals of future research that will treat terminal cancer patients with psilocybin.

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