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Highlights...

This month's top story reports on an open-label study that found two administrations of psilocybin as part of a psychotherapy regimen resulted in rapid improvement of depressive symptoms in patients with depression. A majority of study participants met remission criteria at 4-week follow-up.

Inside

DEPRESSION TREATMENT

Study: Psilocybin enhances therapy in patients with major depression

Patients with major depressive disorder who received two administrations of the psychedelic psilocybin as part of a psychotherapy regimen saw a rapid and lasting improvement in depression symptoms, a randomized open-label trial has found. These findings extend results of research that have suggested antidepressant effects for psilocybin in patients with cancer and treatment-resistant depression, the researchers stated. Study results were published online Nov. 4, 2020, in *JAMA Psychiatry*.

An estimated 30 to 50% of patients with depression do not fully respond to conventional treatment, so the search for alternatives to antidepressant therapy remains a priority. Ketamine has demonstrated rapid and lasting effects on depression symptoms, but there are concerns about its abuse liability and physiological risks. Psilocybin has shown potential in producing antidepressant effects with a more favorable adverse effect profile.

précis

- Patients with moderate or severe episodes of depression and not using an antidepressant received two administrations of psilocybin in the context of 11 hours of supportive psychotherapy.
- Participants experienced rapid and lasting reductions in depressive symptoms after the psilocybin administrations, with 67% meeting response criteria after week 1 of treatment and 71% responding after week 4.
- Reported adverse events were minimal, with most involving the experience of challenging emotional and physical reactions during the psilocybin sessions.

PSILOCYBIN, *continued on page 5*

ADJUNCTIVE TREATMENT

Antipsychotic augmentation in depression linked with mortality risk, study suggests

précis

- A Medicaid cohort study compared mortality risk for adults ages 25 to 64 receiving augmented antidepressant treatment with either a newer antipsychotic or a second antidepressant.
- Patients who received antipsychotic augmentation had a 45% relative increase in mortality risk compared with patients receiving a second antidepressant.
- Olanzapine and risperidone were associated with the greatest risk of mortality among individual antipsychotics.

Antipsychotic augmentation in patients with depression who received an antidepressant for 90 days was associated with a higher risk of mortality than adding a second antidepressant, a cohort study involving nonelderly adults has found. Previous findings of mortality risk associated with use of newer antipsychotics in the elderly led to a black box warning on the medications from the Food and Drug Administration (FDA). Results of the latest study were published online Sept. 30, 2020, in *PloS One*.

The FDA has approved aripiprazole, quetiapine, and the combination of olanzapine and

ANTIPSYCHOTIC, *continued on page 6*

Psilocybin

continued from page 1

Researchers led by Alan K. Davis, Ph.D., of the Center for Psychedelic and Consciousness Research at the Johns Hopkins School of Medicine's Department of Psychiatry and Behavioral Sciences, conducted a randomized controlled trial that evaluated the effect of psilocybin in the context of approximately 11 hours of supportive psychotherapy in patients with depression.

Study methods

Adults ages 21 to 75 with moderate or severe episodes of major depressive disorder were eligible for enrollment. In order to avoid any potential confounding effects of antidepressant treatment, participants were not using any antidepressant therapy at screening and had to refrain from antidepressant use for up to 4 months after enrollment. Among those excluded were individuals with a past-year substance use disorder and those with substantial lifetime use or any recent use of ketamine or hallucinogens.

Twenty-seven participants were randomized to immediate treatment featuring two daylong open-label psilocybin administration sessions or the same treatment offered after an 8-week delay. Both groups received 8 weeks of treatment that included oral psilocybin doses of 20 mg/70 kg in the first administration and 30 mg/70 kg in the second administration, with the doses given an average of 1.6 weeks apart. The delayed treatment group was used so that the researchers could differentiate between the effect of psilocybin administration and spontaneous symptom improvement.

During the psilocybin administration sessions, participants were asked to lie down on a couch, and facilitators asked that they focus attention inward and "stay with" any experience that arose.

The primary outcome was score on the GRID-HAMD version of the Hamilton Depression Rating Scale, with assessments taken at baseline and follow-up weeks 1 and 4 in both treatment groups and at post-randomization weeks 5 and 8 in the delayed treatment group.

Depression response and remission rates were calculated. The researchers measured participants' blood pressure and heart rate before and during the psilocybin sessions.

Results

Twenty-seven participants were randomized to treatment, and 24 completed the intervention and the post-session assessments. Participants' mean age was 39.8 years, and two-thirds of the study completers were women.

Post-session depression scores in the immediate treatment group declined at the same time that they were increasing prior to psilocybin treatment in the delayed treatment group. Among all participants, 67% at week 1 and 71% at week 4 had a clinically significant response to the psilocybin intervention, while remission rates at weeks 1 and 4 were 58% and 54%, respectively.

"The effect sizes reported in this study were approximately 2.5 times greater than the effect sizes found in psychotherapy and more than 4 times greater than the effect sizes found in psychopharmacological depression treatment studies."

Alan K. Davis, Ph.D., et al.

After the first psilocybin session, participants experienced a rapid and large decrease in depression score on the Quick Inventory of Depressive Symptomatology—Self-Report, and the improvement persisted through week 4 after the second psilocybin session.

No serious adverse events were reported. Common nonserious events during the psilocybin sessions included challenging emotional experiences such as fear and sadness, and challenging physical experiences such as feeling one's body shake.

Implications

The researchers pointed out that these results from psilocybin administration compare favorably to those for ketamine in earlier studies, in that ketamine's effects on depressive symptoms appear to last for only a few days to 2 weeks and ketamine carries a greater risk of adverse effects.

"The present trial showed that psilocybin administered in the context of supportive psychotherapy (approximately 11 hours) produced large, rapid, and sustained antidepressant effects," the study's authors wrote. "The effect sizes reported in this study were approximately 2.5 times greater than the effect sizes found in psychotherapy and more than 4 times greater than the effect sizes found in psychopharmacological depression treatment studies." They added that because adverse effects from psilocybin administration were minimal, it is possible that patients might more eagerly accept this intervention over conventional antidepressant medications, which can be associated with more problematic effects.

In an editorial accompanying the journal article, Charles F. Reynolds III, M.D., of the University of Pittsburgh School of Medicine, wrote that while this research was a proof-of-concept study that requires further validation, it sheds further light on an intervention that is in some ways similar to complicated grief psychotherapy. Both interventions appear to work, Reynolds wrote, by disrupting brain circuits that encode depressive, maladaptive thoughts and behaviors.

Reynolds added that it will be important to investigate which patients might benefit most from psychedelic therapy, as he pointed out that this latest study did not include patients at high risk of suicide. ■

Study co-author Matthew W. Johnson, Ph.D., reported receiving a consulting fee from companies specializing in psychedelics.

Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: A randomized clinical trial. *JAMA Psychiatry* 2020; published online Nov 4; doi: 10.1001/jamapsychiatry.2020.3285. Correspondence to: Alan K. Davis, Ph.D., Center for Psychedelic and Consciousness Research, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224; Email: davis.5996@osu.edu.