American Journal of Therapeutics 31, e121–e132 (2024)

Psychedelic Therapy: A Primer for Primary Care Clinicians—Psilocybin

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Background: The primary psychoactive drug in magic mushrooms, psilocybin, induces profound alterations in consciousness through the 5-HT_{2A} receptor. This review consolidates current research findings to elucidate the pharmacology, safety profile, and clinical applications of psilocybin.

Areas of Uncertainty: Despite initial concerns that psilocybin could cause psychosis, contemporary research has demonstrated that psilocybin is generally safe. The most common adverse effects are nausea and headache, yet both tend to be transient. Serious adverse events can generally be avoided in controlled settings such as clinical trials. However, in the largest clinical trial to date, there were a total of 7 reported cases of suicidal ideation, up to 12 weeks after receiving a single 25 mg dose of psilocybin. That being said, all 7 cases did not respond to the treatment. Although selective serotonin reuptake inhibitors may blunt the hallucinogenic qualities of psilocybin, preliminary research suggests that they may enhance its antidepressant effects.

Therapeutic Advances: In clinical trials, psilocybin has shown promise for treating major depressive disorder and treatment-resistant depression. Initial studies indicated that 42%–57% of patients underwent remission after psilocybin-assisted therapy, which suggests that psilocybin is more effective than existing antidepressant medications. Clinical data have also demonstrated that psilocybin can manage substance use disorders and end-of-life anxiety with clinical outcomes that are sustained for months and sometimes years after 1 or 2 doses.

Limitations: However, larger Phase II trials with more than 100 depressed participants have shown a much smaller remission rate of 25%–29%, though these studies still observed that psilocybin causes a significant reduction in depressive symptoms.

Conclusions: Aside from ketamine, psilocybin is the most clinically well-researched psychedelic drug, with trials that have enrolled hundreds of participants and multiple therapeutic applications. Phase III trials will determine whether psilocybin lives up to the promise that it showed in previous clinical trials.

Keywords: psilocybin, psychedelics, psychosis, bipolar, depression, major depressive disorder, treatment-resistant depression, substance use disorder, tobacco addiction, alcohol use disorder, end-of-life anxiety, anxiety

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The authors have no conflicts of interest to declare.

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CLINICAL CASE

A 37-year-old woman with a medical history of tobacco use and a psychiatric history of major depressive disorder (MDD) presented after 13 years of treatment for her depression. She had persistent symptoms of MDD on initial evaluation. Her score on the Hamilton Depression Rating Scale (HAM-D) was 27, and her Personal Health Questionnaire-9 was 24. She had prior trials of fluoxetine up to 80 mg, sertraline up to 200 mg, and escitalopram up to 10 mg. Escitalopram dosing was limited by sexual side effects, including anorgasmia. During her trial of sertraline 1 year prior, augmentation with 2 mg of aripiprazole led to a weight gain of 8 kg before discontinuation. Her BMI is currently 29. Ten years ago, her primary care doctor's chart revealed a BMI of 24. She reports that her depression is "a little bit better" on her current regimen of desvenlafaxine 50 mg. However, her depression continues to be severe. She is currently on disability from her job as an insurance adjuster and has a 13-year-old child. Of note, on baseline assessment her hemoglobin A1C is 6.9. She is interested in treatments for depression that will not cause additional weight gain, and she is hopeful that the subsequent treatment might have fewer sexual side effects. She is not using recreational drugs, and she is not interested in ketamine therapy. Of note, she has a history of tinnitus and is wary of transcranial magnetic stimulation, given the potential adverse effect on her preexisting hearing damage.

BACKGROUND

History

Psilocybin is a naturally occurring tryptamine derivative found in certain species of mushrooms, such as *Psilocybe cubensis* and *Psilocybe mexicana*. Psilocybin mushrooms have a long history among indigenous cultures in Central and South America, which have traditionally consumed them in religious ceremonies.[1,2] Archaeological evidence suggests that the use of psilocybin-containing mushrooms dates back at least 3000 years. Artifacts such as mushroom stones have been found in ancient Mesoamerican sites.[3] The Aztecs had a reverence for these mushrooms and believed they were a gift from the gods.[4]

The modern scientific study of psilocybin began when it was isolated and synthesized by Swiss chemist Albert Hofmann in 1958. In the 1960s, psilocybin gained widespread attention as a potential treatment for psychiatric disorders. Researchers including Timothy Leary conducted studies exploring its effects on consciousness and behavior.[5] After its designation as a Schedule I substance in 1970, research was halted for decades.

Chemistry and mechanism of action

The chemical structure of psilocybin is a tryptamine with a phosphoryloxy substituent at the 4-position and a methyl group at the 2-position.[6] Psilocybin is a prodrug that is dephosphorylated by alkaline phosphatase to the active metabolite psilocin, which is the primary psychoactive compound responsible for the subjective effects of the drug.[6,7] Because dephosphorylation of psilocybin primarily takes place in the acidic environment of the stomach[8] and eating reduces gastric acidity,[9] most human studies on psilocin require participants to fast for an average of 2–4 hours (except for water) before administration.[8] To maximize the therapeutic effects, it may be advisable for participants to take psilocybin on an empty stomach in clinical settings.

Eighty percent of psychoactive psilocin is subsequently metabolized via glucuronidation by enzymes coded by UGT1A10 and UGT1A9 genes.[10] The metabolite psilocin-O-glucuronide is inactive and is subsequently eliminated via conjugation into stool. The remaining 20% of psilocin is eliminated through a variety of mechanisms (including MAO, ALDH, cytochrome oxidase, etc.) and subsequently excreted in stool.[7] The half-life of psilocin is 108 minutes.[11]

Along with all other classical psychedelics, psilocin is known to activate the serotonin-2A (5-HT_{2A}) receptor.[12] Blocking this receptor with 5-HT_{2A} antagonists such as ketanserin subdues or eliminates the subjective effects of psilocybin.[13–15] There is some evidence that the 5-HT_{1A} receptor may play a secondary role in modulating the hallucinogenic effects of psilocybin.[16]

While the neural mechanisms underlying the therapeutic effects of psilocybin are still unknown, a popular hypothesis is that psilocybin, like other classical psychedelics, enhances neuroplasticity in the prefrontal cortex.[17–19] In rodents, psilocybin elevates the expression of many genes (e.g., *c-Fos*) that encode processes related to synaptic plasticity.[20] For up to a month, just a single dose of psilocybin increases the size and density of dendritic spines in layer V pyramidal neurons in the mouse medial frontal cortex.[21] Another study found that, within 24 hours, psilocybin stimulates a marker of presynaptic density in the pig hippocampus.[22] Strengthening of excitatory synapses in both the mouse hippocampus and frontal cortex has been directly linked to the antidepressant effects of psilocybin.[21,23] A landmark study recently demonstrated that psilocin, as well as LSD, has 1000x higher affinity for

tropomyosin receptor kinase B (TrkB) than antidepressants.[24] TrkB is the receptor for brain-derived neurotrophic factor (BDNF), which plays a crucial role in neuroplasticity and is thought to be dysregulated in depression.[25,26] Intriguingly, the effects of psilocin on depression appear to be dependent on TrkB agonism but independent of 5-HT_{2A} activation.[24]

Psilocybin as an anti-inflammatory agent

It has been well-established that inflammation is associated with psychiatric disorders, with biochemical markers of inflammation noted in psychiatric populations.[27–29] However, the direction of causality between inflammation and psychiatric symptom is not clear.[27,28] Increased inflammation as a side effect of medical care has been linked to suicidality.[30] Conversely, anti-inflammatory agents have been explored as treatments for depression.[29] Of note, a "mega-analysis" of 18 randomized controlled trials (RCTs) found that immunomodulatory drugs targeting a range of mechanisms caused a modest but significant decrease in core depressive symptoms.[31] Animal models have observed a correlation between reduced inflammation and decreases in addictive behavior.[32] Taken together, these data suggest that a reduction of inflammation may contribute to perceived wellness and reduced psychopathology.

Psilocybin may exert its antidepressant effects by reducing inflammation.[32,33] The 5-HT_{2A} receptor is implicated in anti-inflammatory effects because of its expression in key components of the innate and adaptive immune response and its role in elevating production of inflammatory cytokines.[33–39] In vitro studies have demonstrated that psilocybin reduces the inflammatory response triggered by lipopolysaccharides, which are bacterial toxins; in particular, psilocybin diminishes the cytokine interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α).[40,41] A human study using ultra-high field magnetic resonance spectroscopy (MRS) to measure immune functioning observed a similar effect of psilocybin on TNF-α, but only for a week after treatment; however, psilocybin persistently reduced concentrations of IL-6 and C-reactive protein.[42]

Major depressive disorder

MDD is the leading cause of disability worldwide, according to the World Health Organization. Severe and treatment-resistant depression (TRD) is undertreated, with only 36.8% receiving treatment in any given year.[43] TRD, which is defined as any depressive episode not in remission after a first-line treatment, is the most common type of MDD, with 30.9%–70% of patients meeting TRD criteria.[44,45] The landmark STAR*D trial found that second-line, third-line, and fourth-line pharmacological agents do not provide reliable relief from depression symptoms. Remission rates drop from 37% to 31% with the second-line treatment, and they further decrease to 14% for the third-line treatment and 13% for the fourth-line treatment.[46] In addition, antidepressants are associated with a number of adverse effects. These include sexual dysfunction, fatigue, weight gain, liver toxicity, irregular heart rhythms (QTc prolongation), insomnia, tremor, and apathy.[47–50] Most concerningly, a recent meta-analysis showed that the antidepressant venlafaxine significantly increases risk of suicidal thoughts among children and adolescents,[51] although large-scale studies in adults have found no significant relationship between antidepressants and suicide.[52,53]

Traditional strategies for TRD have focused on switching to other pharmacological treatments until something works.[54] TRD treatment approaches have proven expensive and underwhelming and not all have been approved based on TRD efficacy. For example, in a phase III trial, the TRD-approved medication vortioxetine caused remission in 33% of patients with MDD, not TRD.[55] Alternative FDA-approved treatments for TRD include esketamine (see the Ketamine chapter in this special edition) and repetitive transcranial magnetic stimulation (TMS). However, the latter requires between 36 and 50 repeated treatments over multiple days.[56,57]

AREAS OF UNCERTAINTY

Psilocybin was made a Schedule I drug in 1970. It was thought to be unsafe because of its potential for triggering long-term mental health problems, such as psychosis.[58] However, the risk is much higher in individuals who have a personal or family history of psychotic disorders. In a recent case analysis of long-term negative psychological responses to psychedelics, all participants who received a psychiatric diagnosis after their psychedelic experience had already had some kind of preexisting mental illness.[59] There were also many other risk factors, such as an unsafe or stressful setting, polysubstance use, and questionable drug purity or quality. All these risks are mitigated or eliminated in clinical trials of psilocybin, where strict screening procedures and appropriate monitoring of patients during and after treatment are implemented to ensure safety and minimize risks.[60] Indeed, vulnerable populations, such as participants with a history of psychosis, are always excluded. A recent comprehensive review of clinical trials of psilocybin found no instances of severe adverse effects.[61] While anxiety

has been reported in these trials, it is typically transient.[60,62–66]

Aside from anxiety, nausea and headache are common adverse effects of psilocybin. A 10 mg/70 kg dose of psilocybin causes headache in roughly 40% of participants, whereas doubling the dose increases the proportion of headaches to 70% of participants, and tripling it further elevates the rate to around 90%.[67] However, all headaches subsided within a day of receiving psilocybin. Although significantly greater than that of placebo, the intensity of the nausea induced by psilocybin has been rated on average less than 1 out of a maximum of 4.[68] The most concerning adverse effect is an increase in suicidal ideation, which has only been reported in 1 clinical trial.[69] Of 79 participants, there were 4 cases of suicidal ideation between Day 2 and Week 3 after treatment with a single 25-mg dose, as well as 3 cases between Week 3 and Week 12. In the 10-mg group, which included 75 participants, there were 5 total cases between Day 2 and Week 12. However, all 3 did not respond to the psilocybin treatment, so the suicidal behavior may have arisen from disappointment that was intensified by expectancy effects.

It was initially thought that participants receiving psilocybin for treating depression should withdraw from existing antidepressant medications because antidepressants either subdue or eliminate the subjective effects of psychedelics.[62,70] In most of the clinical trials on psilocybin for depression, participants were required to discontinue antidepressants, primarily to remove any confounding influences.[69,71–74] However, as discussed below, the combination of selective serotonin reuptake inhibitors (SSRIs) and psilocybin was recently associated with a higher remission rate (42%) than psilocybin alone (29%), although the latter group had a much larger sample size.[75] Furthermore, psilocybin induced strong hallucinogenic effects in participants who received psilocybin treatment while concurrently taking SSRIs.[75]

Aside from history or family history of psychosis, one potential contraindication for psilocybin treatment is cardiovascular disease because psilocybin is known to moderately elevate heart rate and blood pressure.[76,77] Psilocin is an agonist at the 5-HT_{2B} receptor,[10] which, when activated with pharmacological interventions, can cause cardiac valvulopathy.[78] However, a recent report suggested that psilocybin may be not only safe but also beneficial for users suffering from cardiovascular conditions because psilocybin protected against cell death and hypertrophy when cardiomyocytes (excitable heart cells) were treated with a vasoconstrictor peptide.[79] Psilocybin's safety profile is also favorable to existing treatments such as antipsychotic medications, which carry more severe cardiometabolic risks.[80,81]

Overall, psilocybin appears to be safe for clinical use, as long as it is not administered to people who have a history or family history of psychosis. Clinicians must ensure that psilocybin treatment is given in a safe, well-controlled, and well-monitored setting to mitigate the risk of psychosis, which is already very low to begin with.

THERAPEUTIC ADVANCES

Psilocybin as a novel antidepressant

In the contemporary era of psychedelic research, there have been at least 8 published studies on the antidepressant efficacy of psilocybin, including 4 trials in patients with MDD, 3 trials in patients with TRD, and 1 in bipolar type II patients experiencing major depressive episodes (Table 1). Among the MDD trials, the first to be published was a waiting list-controlled trial, in which 15 patients were randomized to immediate treatment, and the remaining 12 were randomized to delayed treatment.[72] The effects of 2 psilocybin sessions in conjunction with psychological support were compared with spontaneous improvement from MDD based on GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores. Four weeks after treatment, 54% of participants across both groups were in remission (GRID-HAMD $\leq$7). A follow-up on the study showed that remission was sustained among 58% of participants at 12 months.[82] A subsequent phase II trial compared scores on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) between 30 patients with MDD who received 2 sessions of psilocybin treatment and 29 patients with MDD who received 6 weeks of daily escitalopram, an SSRI.[71] Six weeks after the treatments finished, 57% of participants in the psilocybin group were in remission (QIDS-SR-16 $\leq$ 5), compared with only 28% of participants in the escitalopram group. However, the mean difference in QIDS-SR-16 scores, which was the primary outcome measure, was not significant (-2.0, $P = 0.17$). That being said, at 6 weeks, there were pronounced differences in ratings on 3 other scales of depression symptoms—Hamilton Depression Rating Scale, 17-item (HAM-D-17), Montgomery-Åsberg Depression Rating Scale (MADRS), and Beck Depression Inventory (BDI)—although these secondary outcomes were not corrected for multiple comparisons. The remaining 2 MDD trials were both placebo-controlled and administered a single, moderate dose of psilocybin in conjunction with psychological support. One enrolled 52 patients with

Table 1. Contemporary (21st century) clinical trials on psilocybin.

Study	Type	Dosing	Sample	Findings
[62]	Open-label	Two doses of 10 mg and 25 mg, 7 d apart	12 patients with TRD	At 3 mo: Significant reduction in QIDS-SR-16 scores (MD: −9.2, P = 0.003); 42% in remission.
[72,82]	Waiting-list controlled RCT	Two doses of 20 mg/70 kg and 30 mg/70 kg, 7 d apart	27 patients with MDD	At 4 wks: Significant reduction in GRID-HAMD scores (MD: −15.8, $P <$ 0.001, d = 2.5); 54% were in remission. At 12 mo: 58% were in remission.
[71]	Double-blind, placebo-controlled RCT (phase II)	Two doses of 25 mg, 3 wks apart, + 6 wks daily placebo, versus two doses of 1 mg, 3 wks apart, + 6 wks daily escitalopram	59 patients with MDD	At 6 wks: Insignificant between-group difference in QIDS-SR-16 scores (MD −2.0, P = 0.17); in the psilocybin group; 57% were in remission, compared with 28% in the escitalopram group; all secondary measures favored psilocybin over escitalopram.
[69]	Double-blind, dose-response RCT (phase II)	One dose of 25, 10, or 1 mg (control)	233 patients with TRD	At 3 wks: Significant difference in MADRS scores between 25 and 1 mg (MD: −6.6, $P <$ 0.001); insignificant difference between 10 mg and 1 mg (MD: −2.5, P = 0.18); 29% remission rate in the 25-mg group versus 9% remission rate in the 10-mg group and 8% in the 1-mg group.
[73]	Double-blind, placebo-controlled RCT (phase II)	One dose of 0.215 mg/kg versus mannitol	52 patients with MDD	At 2 wks: Significant difference in MADRS scores between psilocybin and placebo (MD: ∼−10, d = 0.97, P = 0.0011); in the psilocybin group, 54% were in remission.
[75]	Open-label	One dose of 25 mg, with concurrent SSRI use	19 patients with TRD	At 3 wks: Reduction in MADRS scores (MD: −14.9); 42% were in remission.
[74]	Double-blind, placebo-controlled RCT (phase II)	One dose of 25 mg versus niacin	104 patients with MDD	At 43 d: Significant difference in MADRS scores between psilocybin and placebo (MD: −12.3, $P <$ 0.001); insignificant 25% remission rate.

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Table 1. (*Continued*) Contemporary (21st century) clinical trials on psilocybin.

Study	Type	Dosing	Sample	Findings
[83]	Open-label	One dose of 25 mg	15 patients with BDII and a current depressive episode	At 3 wks: Significant reduction in MADRS scores (MD: −24, $d = 4.08$, $P < 0.001$); 73% were in remission.
[84]	Double-blind, placebo-controlled RCT	One dose of 0.2 mg/kg versus niacin	12 people with advanced-stage cancer and anxiety	At 1 mo: Significant reduction in STAI trait anxiety ($P = 0.001$), which was sustained at 3 mo ($P = 0.03$).
				At 6 mo: Significant reduction in BDI scores ($P = 0.03$).
[60]	Double-blind, placebo-controlled RCT with crossover	Two doses (control: 1 or 3 mg/70 kg; high: 22 or 30 mg/70 kg), 5 wks apart. CD1 refers to group that received control first; HD1 refers to group that received high dose first	51 people with life-threatening cancer and depression and/or anxiety	At 5 wks after high-dose session: Significant reduction in GRID-HAMD-17 scores (MD for CD1: −15.82, $P < 0.001$; MD for HD1: −16.32; $P < 0.001$); significant reduction in HAM-A scores (MD for CD1: −16.76, $P < 0.001$; MD for HD1: −17.25, $P < 0.001$).
				At 6 mo: 59% and 71% in remission from depression in CD1 and HD1, respectively; 50% and 63% in remission from anxiety in CD1 and HD1.
[65,85]	Double-blind, placebo-controlled RCT with crossover	One dose of 0.3 mg/kg versus niacin. Crossover at 7 wks	29 people with life-threatening cancer and depression and anxiety	At 7 wks, before crossover: Significant decreases in STAI-trait ($d = 1.29$, $P < 0.001$), STAI-state ($d = 1.18$, $P < 0.01$), BDI ($d = 0.82$, $P < 0.05$), HADS-D ($d = 0.98$, $P < 0.01$), HADS-A ($d = 1.07$, $P < 0.01$), HADS total ($d = 1.36$, $P < 0.001$); ∼80% in remission from depression, according to BDI scores. At 4.5 yrs: 79% in remission from depression, according to HADS-D scores
[66]	Open-label	One dose of 0.3–0.36 mg/kg	18 older men with AIDS, suffering from demoralization	Decrease in DS-II scores at 3 wks (MD: −6.67) and at 3 mo (MD: −5.78).
[64,86]	Open-label	Two doses of 20 mg/70 kg and 30 mg/70 kg, 2 wks apart and an optional 30 mg/70 kg dose 6 wks after second session	15 nicotine-dependent smokers	At 6 mo: 80% were abstinent from smoking, according to self-report and carbon monoxide and urinary cotinine levels.

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Table 1. (*Continued*) Contemporary (21st century) clinical trials on psilocybin.

Study	Type	Dosing	Sample	Findings
				At long-term follow-up (mean interval: 30 mo): 60% were abstinent from smoking.
[87]	Open-label	Two doses of 0.3 mg/kg and 0.4 mg/kg, 4 wks apart	10 people with alcohol dependence	At wks 5–12: Significant reduction in percentage of heavy drinking days (mean difference: −26.0; P = 0.008). Decrease remained significant up to wk 36.
[63]	Double-blind, placebo-controlled RCT	Two doses of 25 mg/70 kg and 25–40 mg/70 kg, 4 wks apart, versus diphenhydramine	95 people with alcohol dependence	Across 32 wks: Significant difference in percentage of heavy drinking days between psilocybin and placebo groups (mean: −13.9%, P = 0.01).

BDII, bipolar II disorder; BDI, Beck Depression Inventory; DS-II, Demoralization Scale-II; GRID-HAMD, GRID-Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; HADS-D, Hospital Anxiety and Depression Scale, Depression Subscale; HADS-A, Hospital Anxiety and Depression Scale, Anxiety Subscale; MADRS, Montgomery-Åsberg Depression Rating Scale; MD, mean difference; MDD, major depressive disorder; QIDS-SR-16, Quick Inventory of Depressive Symptomatology, self-reported, 16-item; STAI, State-Trait Anxiety Inventory; TRD, treatment-resistant depression.

MDD and found that psilocybin caused remission in 54% of participants, where remission is defined as a score of less than 10 on the MADRS scale.[73] The most recent study, a phase II clinical trial that enrolled 104 patients with MDD, determined that psilocybin was associated with a remission rate of 25% (MADRS <10) at 6 weeks after the treatment, although this effect was insignificant.[74] Nevertheless, a significant proportion of participants (41.7%) exhibited a sustained antidepressant response to psilocybin.

The first trial on psilocybin for TRD was an open-label feasibility study with only 12 patients, in which 2 sessions of psilocybin were administered together with psychological support.[62] Three months after the treatment, 42% of patients were in remission, as defined by scores of less than 10 on the BDI. A much larger phase II trial with 233 TRD patients found that a single 25-mg dose of psilocybin was associated with a 29% remission rate (MADRS <10) 3 weeks after the treatment.[69] In addition, a 25-mg dose, but not a 10-mg dose, yielded a significant decrease in depression symptoms relative to the control (1-mg dose); at 3 weeks, the mean difference in MADRS scores between the 25-mg and 1-mg groups was −6.6 (P < 0.001), but the mean between-group difference for the 10-mg dose was only −2.5 (P = 0.18). However, the study did not directly compare psilocybin with antidepressant treatments. In a subsequent study, which included participants from the previous study who were unable or unwilling to withdraw from antidepressants, 25 mg of psilocybin was administered as an adjunct to concurrent antidepressant medication, this time alongside psychological support.[75] Of a total sample size of 19 participants, 8 (42%) achieved remission (MADRS ≤10) 3 weeks after the treatment.

Finally, the most recently published clinical trial on psilocybin was an open-label study on 15 participants who had bipolar type II disorder and were undergoing a major depressive episode.[83] Eleven (73%) of the participants were in remission (MADRS <10) 3 weeks after receiving a single dose of psilocybin. Psilocybin also insignificantly decreased the severity of mania symptoms, as evaluated with the Young Mania Rating Scale. The study raises the intriguing possibility that psilocybin may be safe in some populations that could have a predisposition for psychosis.

Three general patterns emerge from these findings. First, in trials with fewer than 60 participants, psilocybin's remission rate is superior to that of antidepressants, which is approximately 30%.[88] In 3 small trials of psilocybin for MDD, the remission rate was 54%–57%. However, when the sample size expands to >100 patients, the remission rate declines to 25%–29%. Thus, the initial trials may have overestimated the therapeutic efficacy of psilocybin because of their small sample sizes. Second, although psilocybin's remission rate for TRD (29%) is nearly twice as high as that of third-line (14%) and fourth-line (13%) antidepressants, it is about

the same as the remission rate of second-line antidepressants (30%).[88] Therefore, psilocybin may be most helpful for people who have had more than 2 failed antidepressant treatments. Third, psilocybin together with antidepressants appears to be more effective at treating depression than psilocybin alone,[75] although studies with larger sample sizes are needed to confirm this result.

Remission rates notwithstanding, there are reasons to prefer psilocybin over existing antidepressants. First, psilocybin may have fewer side effects. No serious adverse events were recorded except in one of the studies,[69] which was addressed in the section above ("Areas of Uncertainty"). Generally speaking, adverse events are mild and transient, such as headache and nausea. Many of the worst side effects of antidepressants, such as insomnia, sexual dysfunction, and weight gain,[89] have not been reported in psilocybin therapy. Furthermore, although adverse events from psilocybin sessions generally subside within a week,[74] adverse effects of antidepressants often last for the entire duration of the treatment, which can often be several months.[90] For this reason, psilocybin may be tolerated better than antidepressants. In the clinical trial that directly compared psilocybin with escitalopram, 4 of 29 participants in the escitalopram group stopped taking their medication because of adverse effects, whereas only 2 of 30 participants did not show up for the second session of psilocybin treatment, which may not have been the result of adverse effects.[71] Third, current treatment modalities require continued adherence in Medicaid populations, whose time on a health plan is an average of 10 months.[91] Because, psilocybin displays sustained effects after a small number of dosing regimens, it may be much more cost-effective than existing treatments. However, as the current Schedule I status of traditional psilocybin makes clear, overcoming regulatory concerns will require a robust commitment from study sponsors and providers to implement risk evaluation and mitigation strategies.

End-of-life anxiety

Studies investigating psilocybin have provided valuable insights into its therapeutic potential for a range of other mental health conditions. In the contemporary era of psychedelic research, the first clinical use case of psilocybin was for treating end-of-life anxiety in patients with terminal cancer. To date, there have been at least 4 completed studies, including 1 pilot study on 12 patients[84]; 2 subsequent RCTs on 51 and 29 patients, respectively,[60,65] including a 4.5-year follow-up on the former study[85]; and 1 open-label feasibility study on 18 AIDS survivors.[66] Among the 2 studies that measured remission from depressive symptoms, there was a roughly 80% remission rate (Hospital Anxiety and Depression Scale—Depression score ≤7) in 1 study at 6 months and 4.5 years after treatment[65,85] and either a 59% or 71% remission rate at 6 months in the other trial, depending on whether participants received a low dose or a high dose first in the 2 psilocybin sessions.[60] In addition to diminishing anxiety, psilocybin caused a clinically meaningful reduction (−5.78) in scores on the Demoralization Scale-II within AIDS survivors.[66] A recent meta-analysis of all 4 studies showed that psilocybin was associated with a significant effect size (Hedges' g) of −1.03 for treating state anxiety and −1.08 for treating trait anxiety at 2 weeks.[92] Notably, the aforementioned open-label study on psilocybin for TRD found that psilocybin-assisted therapy reduced symptoms of not only depression but also anxiety.[62]

Substance use disorders

Psilocybin may also be beneficial for treating substance use disorders. In contemporary psychedelic research, there have been 3 trials on psilocybin for tobacco and alcohol addiction. Among these, 1 open-label pilot study on 15 nicotine-dependent participants found that 80% were abstinent after 6 months.[64] Sixty percent remained abstinent in a long-term follow-up in which the mean interval was 30 months.[86] By comparison, a recent meta-analysis showed that existing behavioral and pharmacological interventions for smoking addiction, such as bupropion, nicotine replacement theory, and varenicline, were associated with a roughly 25% abstinence rate 6 months after the treatment.[93]

In an open-label pilot study on 10 alcohol-dependent participants, psilocybin-assisted therapy significantly reduced the percentage of heavy drinking days by 26%.[87] A subsequent double-blind RCT on 95 alcohol-dependent participants showed that psilocybin-assisted therapy significantly decreased the percentage of heavy drinking days by 13.9% more than therapy in conjunction with placebo.[63] Psilocybin outperforms all but one of the 19 existing treatments for alcohol use disorder that are examined in a recent meta-analysis. Psilocybin has a rate ratio (incidence of heavy drinking days in participants who received the psilocybin treatment over the incidence in participants who got placebo) of 0.36, whereas the median rate ratio among the existing treatments is 0.82.[94] The only treatment that performed better than psilocybin was disulfiram.

CONCLUSIONS

This comprehensive review consolidates a diverse array of research findings to underscore the therapeutic

benefits of psilocybin, a naturally occurring psychedelic compound found in various species of mushrooms. Clinical trials demonstrating the safety and efficacy of psilocybin-assisted therapy in ameliorating mental health conditions mark a paradigm shift in psychiatric care. Double-blind RCTs have indicated that psilocybin shows promise for treating depression, including in treatment-resistant populations, end-of-life anxiety in patients with terminal diseases, and substance use disorders. However, RCTs with larger sample sizes need to be conducted, especially since the only 2 RCTs with more than 100 participants did not observe a remission rate as high as that of the smaller trials.

REFERENCES

1. Carod-Artal FJ. Hallucinogenic drugs in pre-Columbian Mesoamerican cultures. *Neurol Barc Spain*. 2015;30:42–49.
2. Klein CF, Guzmán E, Mandell EC, et al. The role of shamanism in mesoamerican art: a reassessment. *Curr Anthropol*. 2002;43:383–419.
3. Guzmán G. Hallucinogenic mushrooms in Mexico: an overview. *Econ Bot*. 2008;62:404–412.
4. Nichols DE. Psilocybin: from ancient magic to modern medicine. *J Antibiot (Tokyo)*. 2020;73:679–686,
5. Leary T, Litwin GH, Metzner R. Reactions to psilocybin administered in a supportive environment. *J Nerv Ment Dis*. 1963;137:561–573.
6. Glatfelter GC, Pottie E, Partilla JS, et al. Structure–activity relationships for psilocybin, baeocystin, aeruginascin, and related analogues to produce pharmacological effects in mice. *ACS Pharmacol Transl Sci*. 2022;5:1181–1196.
7. Dinis-Oliveira RJ. Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. *Drug Metab Rev*. 2017;49:84–91.
8. MacCallum CA, Lo LA, Pistawka CA, et al. Therapeutic use of psilocybin: practical considerations for dosing and administration. *Front Psychiatry*. 2022;13:1040217.
9. Lanzon-Miller S, Pounder RE. The effect of fasting on 24-hour intragastric acidity and plasma gastrin concentration. *Am J Gastroenterol*. 1991;86:165–167.
10. Ling S, Ceban F, Lui LMW, et al. Molecular mechanisms of psilocybin and implications for the treatment of depression. *CNS Drugs*. 2022;36:17–30.
11. Becker AM, Holze F, Grandinetti T, et al. Acute effects of psilocybin after escitalopram or placebo pretreatment in a randomized, double-blind, placebo-controlled, crossover study in healthy subjects. *Clin Pharmacol Ther*. 2022;111:886–895.
12. Nichols DE. Psychedelics. *Pharmacol Rev*. 2016;68;264–355.
13. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, et al. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*. 1998;9:3897–3902
14. Kometer M, Schmidt A, Jäncke L, et al. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. *J Neurosci*. 2013;33:10544–10551.
15. Quednow BB, Kometer M, Geyer MA, et al. Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology*. 2012;37:630–640.
16. Pokorny T, Preller KH, Kraehenmann R, et al. Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience. *Eur Neuropsychopharmacol*. 2016;26:756–766.
17. Calder AE, Hasler G. Towards an understanding of psychedelic-induced neuroplasticity. *Neuropsychopharmacology*. 2023;48:104–112.
18. Aleksandrova LR, Phillips AG. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. *Trends Pharmacol Sci*. 2021;42:929–942.
19. Olson DE. Biochemical mechanisms underlying psychedelic-induced neuroplasticity. *Biochemistry*. 2022;61:127–136.
20. Jefsen OH, Elfving B, Wegener G, et al. Transcriptional regulation in the rat prefrontal cortex and hippocampus after a single administration of psilocybin. *J Psychopharmacol (Oxf.)*, 2021;35:483–493.
21. Shao L-X, Liao C, Gregg I, et al. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*. 2021;109:2535–2544.e4.
22. Raval NR, Johansen A, Donovan LL, et al. A single dose of psilocybin increases synaptic density and decreases 5-ht2a receptor density in the pig brain. *Int J Mol Sci*. 2021;22:835.
23. Hesselgrave N, Troppoli TA, Wulff AB, et al. Harnessing psilocybin: antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. *Proc Natl Acad Sci USA*. 2021;118:e2022489118.
24. Moliner R, Girych M, Brunello CA, et al. Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nat Neurosci*. 2023;26:1032–1041.
25. Miranda M, Morici JF, Zanoni MB, et al. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. *Front Cell Neurosci*. 2019;13:363.
26. Yang T, Nie Z, Shu H, et al. The role of BDNF on neural plasticity in depression. *Front Cell Neurosci.* 2020;14. Available at: https://www.frontiersin.org/articles/10.3389/fncel.2020.00082. Accessed May 25, 2023.
27. Hong H, Kim BS, Im H-I. Pathophysiological role of neuroinflammation in neurodegenerative diseases and psychiatric disorders. *Int Neurourol J*. 2016;20(suppl 1):S2–S7.
28. Radtke FA, Chapman G, Hall J, et al. Modulating neuroinflammation to treat neuropsychiatric disorders. *Biomed Res Int*. 2017;2017:5071786–5071821.
29. Vasiliu O. Investigational drugs for the treatment of depression (Part 1): monoaminergic, orexinergic,

GABA-ergic, and anti-inflammatory agents. *Front Pharmacol*. 2022;13:884143.
30. Schiweck C, Aichholzer M, Reif A, et al. Targeting IL-17A signaling in suicidality, promise or the long arm of coincidence? Evidence in psychiatric populations revisited. *J Affective Disord Rep*. 2023;11:100454.
31. Wittenberg GM, Stylianou A, Zhang Y, et al. Effects of immunomodulatory drugs on depressive symptoms: a mega-analysis of randomized, placebo-controlled clinical trials in inflammatory disorders. *Mol Psychiatry*. 2020;25:1275–1285.
32. Nichols D, Johnson M, Nichols C. Psychedelics as medicines: an emerging new paradigm. *Clin Pharmacol Ther*. 2017;101:209–219.
33. Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents. *Int Rev Psychiatry*. 2018;30:363–375.
34. Cloëz-Tayarani I, Petit-Bertron A-F, Venters HD, et al. Differential effect of serotonin on cytokine production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells: involvement of 5-hydroxytryptamine2A receptors. *Int Immunol*. 2003;15:233–240.
35. Kang BN, Ha SG, Bahaie NS, et al. Regulation of serotonin-induced trafficking and migration of eosinophils. *PLoS One*. 2013;8:e54840.
36. Aune TM, Kelley KA, Ranges GE, et al. Serotonin-activated signal transduction via serotonin receptors on Jurkat cells. *J Immunol*. 1990;145:1826–1831.
37. Herr N, Bode C, Duerschmied D. The effects of serotonin in immune cells. *Front Cardiovasc Med*. 2017;4:48.
38. Ito T, Ikeda U, Shimpo M, et al. Serotonin increases interleukin-6 synthesis in human vascular smooth muscle cells. *Circulation*. 2000;102:2522–2527.
39. De Bie JJ, Henricks PA, Cruikshank WW, et al. Modulation of airway hyperresponsiveness and eosinophilia by selective histamine and 5-HT receptor antagonists in a mouse model of allergic asthma. *Br J Pharmacol*. 1998;124:857–864.
40. Nkadimeng SM, Steinmann CML, Eloff JN. Anti-inflammatory effects of four psilocybin-containing magic mushroom water extracts in vitro on 15-lipoxygenase activity and on lipopolysaccharide-induced cyclooxygenase-2 and inflammatory cytokines in human U937 macrophage cells. *J Inflamm Res*. 2021;14:3729–3738.
41. Smedfors G, et al. Psilocybin combines rapid synaptogenic and anti-inflammatory effects in vitro. In Review, preprint; 2022. 10.21203/rs.3.rs-1321542/v1
42. Mason NL, Szabo A, Kuypers KPC. Psilocybin induces acute and persisting alterations in immune status in healthy volunteers: an experimental, placebo-controlled study. *Brain Behav Immun*. 2023;114:299–310.
43. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health (WMH) surveys. *Psychol Med*. 2018;48:1560–1571.
44. Pigott HE, Kim T, Xu C, et al. What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR*D study's patient-level data with fidelity to the original research protocol. *BMJ Open*. 2023;13:e063095.
45. Zhdanava M, Pilon D, Ghelerter I, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. *J Clin Psychiatry*. 2021;82:20m13699.
46. Warden D, Rush A, Trivedi M, et al. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep*. 2007;9:449–459.
47. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. *Dialogues Clin Neurosci*. 2008;10:409–418.
48. Oliva V, Lippi M, Paci R, et al. Gastrointestinal side effects associated with antidepressant treatments in patients with major depressive disorder: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;109:110266.
49. Wang S-M, Han C, Bahk WM, et al. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. *Chonnam Med J*. 2018;54:101–112.
50. Zhou S, Li P, Lv X, et al. Adverse effects of 21 antidepressants on sleep during acute-phase treatment in major depressive disorder: a systemic review and dose-effect network meta-analysis. *Sleep*. 2023;46:zsad177.
51. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet (London, England)*. 2018;391:1357–1366.
52. Seemüller F, Riedel M, Obermeier M, et al. The controversial link between antidepressants and suicidality risks in adults: data from a naturalistic study on a large sample of in-patients with a major depressive episode. *Int J Neuropsychopharmacol*. 2009;12:181–189.
53. Stübner S, Grohmann R, Greil W, et al. Suicidal ideation and suicidal behavior as rare adverse events of antidepressant medication: current report from the AMSP multicenter drug safety surveillance project. *Int J Neuropsychopharmacol*. 2018;21:814–821.
54. Reif A, Bitter I, Buyze J, et al. Esketamine nasal spray versus quetiapine for treatment-resistant depression. *N Engl J Med*. 2023;389:1298–1309.
55. Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012;73:953–959.
56. Cole EJ, Phillips AL, Bentzley BS, et al. Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry*. 2022;179:132–141.
57. Horvath JC, Mathews J, Demitrack MA, et al. The NeuroStar TMS device: conducting the FDA approved protocol for treatment of depression. *J Vis Exp*. 2010;45:2345.
58. Friesen P. Psychosis and psychedelics: historical entanglements and contemporary contrasts. *Transcult Psychiatry*. 2022;59:592–609.

59. Bremler R, Katati N, Shergill P, et al. Case analysis of long-term negative psychological responses to psychedelics. *Sci Rep*. 2023;13:15998.
60. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol (Oxford, England)*. 2016;30:1181–1197.
61. Roscoe J, Lozy O. Can psilocybin be safely administered under medical supervision? A systematic review of adverse event reporting in clinical trials. *Drug Sci Policy L*. 2022;8:205032452210852.
62. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry*. 2016;3:619–627.
63. Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry*. 2022;79:953–962.
64. Johnson MW, Garcia-Romeu A, Cosimano MP, et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol (Oxford, England)*. 2014;28:983–992.
65. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol (Oxford, England)*. 2016;30:1165–1180.
66. Anderson BT, Danforth A, Daroff PR, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. *eClinicalMedicine*. 2020;27:100538.
67. Johnson MW, Sewell RA, Griffiths RR. Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug Alcohol Depend*. 2012;123:132–140.
68. Carbonaro TM, Johnson MW, Hurwitz E, et al. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. *Psychopharmacology (Berl.)*. 2018;235:521–534.
69. Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N Engl J Med*. 2022;387:1637–1648.
70. Bonson KR, Buckholtz JW, Murphy DL. Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. *Neuropsychopharmacology*. 1996;14:425–436.
71. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med*. 2021;384:1402–1411.
72. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2021;78:481–489.
73. Von Rotz R, Schindowski EM, Jungwirth J, et al. Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomised clinical trial. *eClinicalMedicine*. 2023;56:101809.
74. Raison CL, Sanacora G, Woolley J, et al. Single-dose psilocybin treatment for major depressive disorder: a randomized clinical trial. *JAMA*. 2023;330:843–853.
75. Goodwin GM, Croal M, Feifel D, et al. Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication. *Neuropsychopharmacology*. 2023;48:1492–1499.
76. Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, et al. Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d--methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. *Neuropsychopharmacology*. 1999;20:565–581.
77. Hasler F, Grimberg U, Benz MA, et al. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berl.)*. 2004;172:145–156.
78. Cavero I, Guillon J-M. Safety Pharmacology assessment of drugs with biased 5-HT2B receptor agonism mediating cardiac valvulopathy. *J Pharmacol Toxicol Methods*. 2014;69:150–161.
79. Nkadimeng SM, Steinmann CML, Eloff JN. Effects and safety of Psilocybe cubensis and Panaeolus cyanescens magic mushroom extracts on endothelin-1-induced hypertrophy and cell injury in cardiomyocytes. *Sci Rep*. 2020;10:22314.
80. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302:1765–1773.
81. Thomas K, Malcolm B, Lastra D. Psilocybin-assisted therapy: a review of a novel treatment for psychiatric disorders. *J Psychoactive Drugs*. 2017;49:446–455.
82. Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: prospective 12-month follow-up. *J Psychopharmacol (Oxf.)*. 2022;36:151–158.
83. Aaronson ST, van der Vaart A, Miller T, et al. Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: a non-randomized controlled trial. *JAMA Psychiatry*. 2023;e234685.
84. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry*. 2011;68:71–78.
85. Agin-Liebes GI, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *J Psychopharmacol*. 2020;34:155–166.
86. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse*. 2017;43:55–60.

87. Bogenschutz MP, Forcehimes AA, Pommy JA, et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol (Oxf.)*. 2015;29: 289–299.
88. Gaynes BN, Rush AJ, Trivedi MH, et al. The STAR*D study: treating depression in the real world. *Cleve Clin J Med*. 2008:75:57–66.
89. Kearns B, Cooper K, Orr M, et al. The incidence and costs of adverse events associated with antidepressants: results from a systematic review, network meta-analysis and multi-country economic model. *Neuropsychiatric Dis Treat*. 2022;18:1133–1143.
90. Bet PM, Hugtenburg JG, Penninx BWJH, et al. Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol*. 2013;23:1443–1451.
91. Sugar S, Peters C, Lew ND, et al. *Medicaid Churning and Continuity of Care: Evidence and Policy Considerations before and after the COVID-19 Pandemic*. USA: Assistant Secretary for Planning and Evaluation: Issue Brief; 2021.
92. Yu C-L, Yang F-C, Yang S-N, et al. Psilocybin for end-of-life anxiety symptoms: a systematic review and meta-analysis. *Psychiatry Investig*. 2021;18:958–967.
93. Rosen LJ, Galili T, Kott J, et al. Diminishing benefit of smoking cessation medications during the first year: a meta-analysis of randomized controlled trials. *Addict Abingdon Engl*. 2018;113:805–816.
94. Bahji A, Bach P, Danilewitz M, et al. Pharmacotherapies for adults with alcohol use disorders: a systematic review and network meta-analysis. *J Addict Med*. 2022; 16:630–638.