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Psychedelics and a Return to the Concept of Recovery in Psychiatry

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Modern psychiatry plays an underdiscussed role in the observed epidemic of mental and brain health disorders. The prevailing model of psychopharmacology, and in medicine generally, suggests that a disease happens to reside inside of a person, and thus the disease should be the central focus of attention. That approach has its value, but it implies that treating the disease with better medicine is a sufficient objective. In CNS disorders, that has rarely proven to be the case.

To be sure, today’s medicines are lacking. Scientists have called the brain the “final frontier” of medical innovation. Most drugs presently in development are either reformulations of existing drugs or show only a marginal benefit over generics. SSRIs and their modern peers are as infamous for their side effects and their modern peers are as benefit over generics. SSRIs drugs or show only a marginal either reformulations of existing presently in development are medical innovation. Most drugs the brain the “final frontier” of

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This context is critical to the resurgence of interest in psychedelic-assisted therapy. As a profession, we should welcome and support further research into a new generation of medicines, built on decades of clinical data from human trials. But we should pursue just as adamantly a return to a psychiatric model aimed at recovery, one which requires building the digital scaffolding for a new generation of treatment.
Lysergic acid diethylamide (LSD) and psilocybin are serotonergic psychedelics that are candidates for the treatment of psychiatric disorders. Both agents stimulate serotonin 5-HT2A receptors; LSD also acts at dopamine D13-3 receptors, and the active metabolic of psilocybin (psilocin) inhibits the serotonin transporter. The similarities, acute effects, and dose equivalence of these agents in humans remains unclear.

The Current Study
Holze and colleagues directly compared the acute subjective, autonomic, and endocrine effects of LSD and psilocybin at 2 doses and placebo within the same participants. The acute subjective effects of these agents were assessed with validated psychometric instruments, and pharmacokinetic data were obtained over 24 hours. The investigators performed a double-blind, placebo-controlled crossover study with 5 experimental test sessions (placebo, LSD 100 µg, LSD 200 µg, psilocybin 15 mg, psilocybin 30 mg), with a washout period of at least 10 days between sessions.

The authors recruited 28 healthy participants; their mean age was 35 years and 50% were male. Exclusion criteria were: age less than 25 years or greater than 65 years, pregnancy, family history of major psychiatric disorders in first-degree relatives, current psychotropic medication use, acute or chronic physical illness, tobacco smoking of more than 10 cigarettes/day, lifetime illicit drug use exceeding 10 times (except use of tetrahydrocannabinol [THC], the principal psychoactive cannabinoid of cannabis), or illicit drug use in the past 2 months or during the study period. In terms of previous drug use, 11 participants had previously used LSD and 6 had previously used psilocybin; 13 had previously used a stimulant; and 10 participants had no history of noncannabis illicit drug use. LSD was administered as an oral solution and psilocybin as an oral capsule. A double-dummy method was used such that participants received 6 capsules and 2 solutions at each test session.

Each test session lasted 25 hours and was conducted in a calm hospital room. Abstinence from illicit drugs was verified with a urine drug screen. Outcomes were repeatedly assessed for 24 hours. Standardized meals were served. An investigator was present in the room during the acute effect phase and remained in a room next to the participant for up to 24 hours. Subjective effects were assessed repeatedly using visual analogue scales (VAS), the Adjective Mood Rating Scale (AMRS), the 5 Dimensions of Altered States of Consciousness scale (5D-ASC), and the Mystical Effects Questionnaire (MEQ). Effect durations were assessed using the classic pharmacokinetic-pharmacodynamic link module. Blood pressure, heart rate, and temperature were repeatedly measured. Adverse effects were assessed 1 hour before and 12 and 24 hours after drug administration. Plasma LSD and psilocybin concentrations, and cortisol, prolactin, oxytocin, and brain-derived neurotrophic factor (BDNF) measurements were also obtained at multiple time points.
Both doses of LSD and the 30-mg psilocybin dose produced comparable subjective effects, based on VAS and 5D-ASC outcomes. There was significantly greater ego dissolution and a trend toward greater anxiety with 200 µg versus 100 µg LSD. Psilocybin 15 mg had significantly lower effects than psilocybin 30 mg and both LSD doses, based on VAS and 5D-ASC outcomes. Both LSD doses had significantly increased “emotional excitation” on the AMRS compared with psilocybin. There were no differences in subjective effects of LSD or psilocybin based on sex. Both LSD and psilocybin significantly increased systolic and diastolic blood pressure, temperature, and pupil diameter compared with placebo. Psilocybin 30 mg produced significantly greater increases in blood pressure and temperature compared with psilocybin 15 mg and both doses of LSD. By contrast, both LSD doses produced a greater increase in pulse compared with both psilocybin doses and placebo. Psilocybin produced greater impairments in pupil contraction compared with LSD. Both LSD and psilocybin increased the total acute (0-12 hours) adverse effect score compared with placebo. Subacute (12-24 hours) adverse effect scores were significantly greater with LSD 200 µg LSD and psilocybin 30 mg compared with placebo. The most common adverse effects were headaches. Five participants had 9 flashback episodes within 72 hours. No severe adverse events were observed.

Both LSD doses had significantly longer effect durations (10-11 versus 6-7 hours) and earlier onset of effects (0.4-0.6 versus 0.8 hours) compared with both psilocybin doses. The elimination half-life values were about 4 hours for LSD and 2.5 hours for psilocybin. Both LSD and psilocybin significantly increased plasma cortisol, prolactin, and oxytocin levels, but neither affected BDNF levels. Both LSD and psilocybin showed linear pharmacokinetics, which were not influenced by body weight.

In terms of blinding, no clear distinction between LSD and psilocybin could be made after the session or at study end point. Participants correctly identified the psychedelic and dose in about 60% of sessions, compared with 96% for placebo.

**Study Conclusions**

The authors investigated and directly compared the acute effects of LSD and psilocybin in healthy participants in a well-blinded study. They concluded that psilocybin 15 mg exerted clearly weaker subjective effects, and both agents had dose-dependent effect durations (significantly longer for LSD), stimulant autonomic effects, and increased endocrine parameters. Body weight had no influence on blood concentrations. The investigators noted the data further supported the notion that states of consciousness alteration induced by LSD and psilocybin are more likely dose-dependent rather than substance-dependent. In addition, they concluded the differences in the pharmacological profiles of LSD and psilocybin do not relevantly influence subjectively experienced effects of both psychedelics.

Study strengths included the within-subjects design and the use of well-characterized, fixed dosing. The primary study limitations were the use of a highly controlled setting and the participation of healthy participants only.

**The Bottom Line**

This study supports dose finding for research and psychedelic-assisted therapy. Psilocybin 20 mg is likely equivalent to LSD 100 µg. There was no evidence for qualitative differences in altered states of consciousness, except for a shorter duration of action for psilocybin.

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Interest Grows in Treatment of Mood Disorders by Classic Psychedelics

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There is a buzz surrounding the potential use of psychedelic drugs as novel treatments in mental health—both for the public and within the scientific community. Although this buzz may be akin to a similar, less regulated boom that occurred in the 1950s and 1960s, psychedelic drugs have been used for spiritual and folk healing rituals for thousands of years. In particular, the use of naturally occurring compounds such as N,N-dimethyltryptamine (DMT), ibogaine, psilocybin (“magic mushrooms”), and mescaline have dated to 10,500 BP or earlier, in various locations throughout the world. These compounds share similarities in their pharmacologic and psychotropic properties, namely due to their agonistic effects on postsynaptic serotoninergic (5-HT) receptors and consequent hallucinogenic properties. Evidence suggests that the 5-HT2A receptor mediates drug effects, as there is a very strong correlation between receptor affinity and human hallucinogenic potency. Together with other synthetically manufactured drugs such as lysergic acid diethylamide (LSD), these substances make up a family of compounds known as classic psychedelics.

Classic psychedelics induce altered states of consciousness that are experienced through visual effects, changes in perception, and distortions in sense of time and space. They can produce a sense of awe and connectedness, as well as personal insights and strong emotions. Research into classic serotonergic psychedelics began in the late 1930s when Albert Hofmann synthesized LSD for use as a cardiorespiratory stimulant only to accidentally ingest it and realize its psychotropic properties. This event, coupled with an article by R. Gordon Wasson in Life in 1957 entitled “Seeking the Magic Mushrooms,” catapulted psychedelics into public and scientific awareness. Numerous research studies were carried out over a decade in various patient cohorts including alcohol use disorder, schizophrenia, and depression before the work was abruptly halted. Growing concerns over the mainstream use of psychedelics, their impact on individuals’ health, and the enactment of the Controlled Substances Act in the United States led to an embargo on research. Although this initial wave of psychedelic research would not hold up to the rigorous scientific methods and ethical policies of today, it has helped inform the development of present-day trials, both positively and negatively. Current protocols involve intensive screening procedures followed by several hours of psychological support provided before, during, and after the dosing session(s). Psychedelic research has increased exponentially over the past 10 years (Figure), with the market value projected to grow from $2 billion in 2020 to $10.75 billion by 2027. Besides 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), classic psychedelics—especially psilocybin—are at the forefront of this growth with increasing interest in their therapeutic potential as fast-acting antidepressants.

Depression
Depression is one of the most common psychiatric illnesses throughout the world, affecting more than 290 million individuals. In 2010, it was reported that depressive disorders alone were the second-leading cause of years lived with disability, and the rates of diagnosis are expected to increase as the repercussions from the COVID-19 pandemic become more apparent. The current standard of care involves antidepressants and/or second-generation antipsychotics along with structured psychotherapy. Unfortunately, for some individuals, these options are sometimes ineffective; current medication options can come with undesirable adverse effects and high rates of relapse, in addition to delays in therapeutic effects. More recently, several clinical trials have demonstrated positive response and remission rates for intravenous and intranasal ketamine, which are thought to produce their antidepressant effects through NMDA receptor antagonism. Larger-scale studies with longer follow-up periods and larger, representative...
sample sizes are needed before any concrete conclusions can be made.9 Finally, neurostimulation treatments including repetitive transcranial magnetic stimulation have emerged with promising results; however, optimal treatment parameters have yet to be determined and accessibility remains a barrier. Thus, psychedelic drugs have experienced a resurgence in interest as a potential treatment for mood disorders.

Mechanism of Action
Depression is characterized by negativity bias, rigid thought patterns, rumination, and cognitive inflexibility. The brain’s default mode network (DMN)—made up of the ventromedial prefrontal cortex, the perigenual anterior cingulate cortex, and the posterior cingulate cortex—is involved in introspection and self-referential thinking. Altered activity, specifically overactivity, of the DMN has been demonstrated in depression in addition to hypoconnectivity with other higher-order cognitive networks such as the executive network and the salience network.14,15 Although there is some debate in the field, it is believed that classic psychedelics may exert their effects—at least in part—by disrupting activity in these networks.14,15 Evidence from ayahuasca and psilocybin imaging studies has demonstrated decreases in activity in key regions of the DMN.16-18 Connectivity alterations may also be strengthened by the promotion of structural and functional neuronal plasticity.19 Taken together, it is theorized that classic psychedelics exert their effects through differential changes in connectivity, which can result in increased cognitive flexibility and disruptions to maladaptive patterns of thoughts and behavior.

Clinical Trials
Several trials investigating the use of psilocybin for major depression have been conducted using open-label or wait-list controlled designs.20-22 Results were promising, with rapid and significant antidepressant effects 1 week post treatment that were largely sustained at follow-up periods of 3, 6, 12, and 24 months: a study found that 58% of participants maintained remission at 12 months.23 Likewise, trials have been conducted in patients in end-of-life care who are experiencing depression/anxiety, with similar beneficial outcomes.14,15 Most AEs reported in the trials were mild and transient, with the most common being a headache following the dosing session.

More recently, a phase 2, double-blind, randomized, controlled trial of escitalopram vs psilocybin-assisted therapy for major depressive disorder (MDD) was conducted.24 Participants randomized to the psilocybin group had 2 dosing sessions separated by 3 weeks, where they received 1 dose of 25 mg of psilocybin at each session and were given placebo pills to take between treatments. Participants in the escitalopram group received 10 to 20 mg of escitalopram administered over 6 weeks. All participants had moderate to severe depression at baseline (mean scores of 14.5 in the psilocybin group and 16.4 in the escitalopram group, as determined by the Quick Inventory of Depressive Symptomatology Self-Report [QIDS-SR-16]).

At the 6-week follow-up, participants in both groups had lower QIDS-SR scores compared with baseline, but the scores did not significantly differ between the escitalopram and psilocybin groups (difference, −2.0; 95% CI, −5.0 to 0.9; P = .17). Similar results between the groups were seen for response (decrease in score of ≥50% from baseline) and remission (score of 0-4 using the QIDS-SR-16) rates. Secondary measures of depression (Beck Depression Inventory, Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale [MADRS]) favored psilocybin over escitalopram. However, the authors did not correct for multiple comparisons, so these results must be interpreted with caution.24 Psilocybin is not the only serotonergic psychedelic being investigated as a potential treatment for depression. The “vine of the souls” plant traditionally found in South America and commonly known as ayahuasca has also demonstrated antidepressant properties in clinical and nonclinical trials.25-27 In one randomized, controlled trial, patients with treatment-resistant depression who were given a single dose of ayahuasca had significantly lower MADRS scores compared with the placebo group at day 1 (P = .04), day 2 (P = .004), and day 7 (P = .0001) post dose.28 Likewise, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), a potent, short-acting psychedelic, and LSD, a serotonergic and dopaminergic partial agonist, have ongoing or completed clinical trials investigating their therapeutic benefits for depression (Table).

Although this evidence demonstrates positive results, the data on efficacy and safety of psychedelics in the treatment of MDD are preliminary and should be considered in the context of several challenges facing the field.29

Ethical Considerations
It appears that research into the therapeutic effects of serotonergic psychedelics will grow in the coming years. As more data become available, establishing clear guidelines for psilocybin-assisted psychotherapy (PAP)
will be important. Discussions regarding therapist training, burden of cost, accessibility, and participant safety are needed. Psychedelic therapy is resource intensive and necessitates several hours of specialized therapy. Innovative study protocols aimed at reducing cost and resource burdens will be important in facilitating this research into clinical practice, especially in underresourced communities.

Recent studies have found serious AEs to be rare if proper screening, monitoring, and safety protocols are in place. However, increasing attention to these drugs suggests that investigators need to be cautiously aware of how results of clinical trials are communicated to the public. Transparency regarding AEs, rigorous reviews of study data, and critiques from the scientific community should not be overshadowed by positive results.

Expectancy effects also require consideration—previous experience using psychedelics and enthusiasm in the media may predispose study participants to expect positive treatment outcomes. This issue is further confounded by difficulties in blinding for both participants and therapists. Blinding helps prevent bias and ensures an equal distribution of placebo effects. Current protocols have tried to mitigate these challenges through active placebos or drug comparisons using standard-of-care treatment, but more work is required.

Investigators should also pay special attention to informed consent. It can be difficult to fully prepare someone for a psychedelic experience; it necessitates a thorough consent and preparatory process in which participant boundaries (eg, hand-holding when feeling distressed during the dosing sessions) are established in advance of treatment.

Finally, more research needs to be conducted in participants with diverse ethnic and socioeconomic backgrounds. To date, most studies investigating PAP have been conducted in North America and western Europe with patient cohorts being predominantly white.30 Study samples more representative of the general population need to be a focus in future work.

Future Research
Psychedelic research is expanding into other areas of psychiatry including obsessive-compulsive disorder (OCD), body dysmorphic disorder, substance use disorders, posttraumatic stress disorder, anorexia nervosa, and binge eating disorder (Table). Two exploratory studies have conducted thematic analyses on the psychological effects of and participant perspectives regarding use of ayahuasca for eating disorder (ED) symptoms.31,32 Both studies reported reductions in ED symptoms along with increased self-love and acceptance. There are now several registered trials investigating the use of psilocybin for various EDs (Table). In addition, a preliminary open-label trial assessed the use of psilocybin for the treatment of OCD.33 Although the sample size was small (n = 9), there were marked decreases in OCD symptom severity for all participants. To date, there are 4 registered trials investigating psilocybin for the treatment of OCD (Table).

There has also been a large expansion into addictions research (eg, cocaine, alcohol, opioids). Although psilocybin remains the most-studied agent in substance use disorders, ibogaine is also receiving attention. Ibogaine is an indole alkaloid with dissociative properties that may exert therapeutic benefit for substance use disorders by reducing drug cravings, improving mood, and preventing withdrawal symptoms. Promising case reports and open-label trials in opioid addiction have demonstrated elimination of withdrawal symptoms and anticraving capacities following ibogaine administration.34-37 There are 3 ongoing trials registered in Spain, Brazil, and the United States to investigate ibogaine treatment in methadone detoxification, opioid withdrawal, and alcoholism (Table).
Concluding Thoughts

Classic psychedelic research is rapidly expanding, and preliminary evidence demonstrates therapeutic potential especially for the treatment of major depression and end-of-life distress. However, the field is facing several ethical and methodological challenges that need to be addressed. Larger, well-designed prospective trials are needed to confirm preliminary evidence for the therapeutic actions of psychedelics in individuals with mood and anxiety disorders, including depression and OCD.

To see the Table, go to PsychiatricTimes.com/view/george-suppl-figure

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Why do you think there has been so much interest in ketamine in the past few years? Why do you think ketamine is needed in psychiatry?

I think the interest in ketamine stems from the fact that, unfortunately, traditional antidepressant treatment options have not worked well enough for enough individuals. This has left so many people suffering. The finding that ketamine has potent and rapid antidepressant properties was an exciting development in the field of mental health. It brought not only an effective treatment option, but also one that works faster than traditional options that often took weeks to kick in.

In recent years, ketamine has become even more interesting for its psychedelic properties as well as its capacity to create a non-ordinary state of consciousness and allow individuals to see their life from a new perspective, revisit old traumas that they could not tap into previously, and see new ways to get unstuck in their life. This is why we are really excited at Numinus about what can happen when ketamine is paired with psychotherapy for individuals with difficult-to-treat psychiatric conditions.

For which psychiatric disorders might ketamine be helpful? Are any new studies showing new potential uses?

The initial research on ketamine was focused on depression and suicidality, so most of the research for mental health uses is on depressive disorders. Now there is a growing body of evidence not just for depression, suicidality, and bipolar depression but also now in other conditions such as posttraumatic stress disorder (PTSD), obsessive-compulsive disorder, and even eating disorders, showing potential for ketamine as a catalyst in the healing and recovery process. Ketamine is also being explored for addictive disorders, with some really positive results.

How does ketamine compare to traditional treatment strategies in terms of short- and long-term efficacy and safety?

Ketamine, as I mentioned previously, has been found to be a rapid antidepressant, meaning for the majority of individuals it helps alleviate depressive symptoms within 24-48 hours,
unlike traditional treatment options such as selective serotonin reuptake inhibitors, which often take weeks to start working. Not only is ketamine a rapid antidepressant, but it also has response rates that seem to outperform traditional treatment options; many studies with ketamine have shown 60%-70% response rates. Meaning, 60%-70% of individuals who receive the medicine have at least a 50% reduction in their depressive symptoms. Of note, although ketamine does appear to be a rapid and effective antidepressant for the majority of individuals, the effects have also been found to be temporary. On the one hand, it is not a daily pill that you have to take, but on the other hand, doses of ketamine may lead to improvement in a patient’s depressive symptoms for a limited number of days or weeks before the patient needs another treatment, or another kind of therapy or intervention.

When should a clinician consider referring their patient for ketamine therapy? When would it be contraindicated? Clinicians often consider referring a client for ketamine therapy when other treatments have failed. As the evidence continues to pile up in support of ketamine for a variety of mental health indications, many clinicians, including myself, are thinking about ketamine earlier in the treatment algorithm and not waiting until multiple other treatment options have failed. This is because ketamine has been shown—not just in the psychiatric studies, but in the decades of anesthesia research—to be a really safe option. We are finding that when paired with the right psychotherapy and psychological support, it can be an effective intervention to help patients get out of a rough depressive episode.

Ketamine is typically not given when patients have had a recent episode (or are in an episode) of mania or psychosis, because of the possibility of worsening psychotic and manic symptoms. Clinicians also need to screen for and consider other medical factors before prescribing a course of ketamine, such as cardiovascular status. For example, ketamine is known to briefly and mildly increase heart rate and blood pressure; therefore, individuals embarking on a course of ketamine therapy first should have any hypertension or serious cardiovascular disease well managed.

When should clinicians tell their patients about ketamine therapy? What are some of the common myths about ketamine therapy that might worry patients? Clinicians should make their clients aware of ketamine therapy as an option especially when depression is treatment resistant or when a response rate quicker than that of traditional therapies is needed. There are a number of myths about ketamine. For example, many individuals believe ketamine is quite addictive. Although it is true that caution needs to be used when prescribing ketamine, especially for individuals with a history of addiction, a growing body of evidence shows that when paired with psychotherapy and under the care of a skilled treatment team, ketamine can be anti-addictive. There are now positive studies in support of ketamine therapy to help individuals recover from problematic use of alcohol, opiates, cocaine, and even cannabis.

Where do you think ketamine therapy will be in psychiatric practice in the next 5 to 10 years? Some clinicians think ketamine is merely a stepping-stone toward other psychedelic compounds in development. I believe, however, that ketamine will remain an important tool in psychiatry for the foreseeable future because of its unique ability to help someone get out of a depressive episode quickly and because of the accessible way it brings about an altered state of consciousness when paired with psychedelic-assisted psychotherapies. So I see ketamine as always having a place in the individualized treatment algorithms for certain clients, especially in depression and the early phases of PTSD management.
The world has changed, and so has mental health care.

Numinus combines the latest advances in psychedelic medicine with evidence-based care, for an integrated approach to healing.