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Psychedelic Therapy: A Primer for Primary Care Clinicians—Lysergic Acid Diethylamide (LSD)

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Background: Lysergic acid diethylamide (LSD) is a hallucinogenic agent. In the mid-20th century, it was used to augment psychoanalysis and to treat alcohol use disorder. However, LSD was banned in 1970 in part because of concerns that it could bring about or exacerbate mental illness. Its therapeutic potential remains incompletely understood.

Areas of Uncertainty: While uncontrolled recreational use of LSD can, in rare instances, lead to long-term psychosis, adverse events in clinical trials of LSD, such as anxiety, headache, and nausea, have almost always been mild and transient. Serious adverse events, such as intense panic, suicidal ideation, and psychosis, were reported in either none or very few of the participants. However, patient selection criteria, optimal dosing strategy, and appropriate clinical follow-up guidelines remain to be established.

Therapeutic Advances: Preliminary data suggest that LSD may be effective for the management of alcohol use disorder, anxiety, and depression. In trials of LSD for treating anxiety and depression associated with life-threatening illnesses, 77% of participants demonstrate durable relief at 1 year post-treatment. Top-line data from a large-scale phase IIb trial (n = 198) indicate that 50% of participants experience remission from generalized anxiety disorder after a single 100 μg dose of LSD. According to a meta-analysis of RCTs on LSD from the mid-20th century, single-dose regimens of LSD significantly improve alcohol use disorder ($P < 0.0003$) with an odds ratio (OR) of 1.96.

Limitations: Only one large-scale clinical trial (>50 participants) has been conducted on LSD in the contemporary era of psychedelic research. Further studies with large sample sizes are needed to explore potential clinical applications.

Conclusions: Preliminary data suggest that LSD may be one of the most potent treatments for anxiety in patients both with and without a life-threatening illness. LSD may also be beneficial for treating depression and substance use disorders.

Keywords: psychedelics, LSD, hallucinogenics, alcohol use disorder, anxiety, generalized anxiety disorder, end-of-life anxiety, depression, major depressive disorder, empathy, pain

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CLINICAL CASE

A 26-year-old man with a history of severe generalized anxiety disorder (GAD) presents to his third psychiatrist in 2 years complaining of persistent worry, insomnia, muscle tension, and fatigue. Physical examination is unremarkable. Vital signs are within normal limits (heart rate: 72; respiratory rate: 18). The patient has seen his primary care physician several times over the preceding 2 years to assess an underlying medical condition. However, physical examination and laboratory studies have all been normal. The patient has previously undergone treatment with sertraline (up to 200 mg once daily) and fluoxetine (up to 80 mg once daily augmented with buspirone 10 mg twice daily). The patient is currently receiving desvenlafaxine 50 mg once daily augmented with 2 mg of aripiprazole once daily; his GAD-7 score has decreased only marginally, from 21 to 19. He continues to complain of severe anxiety. In addition, the patient has gained 3.5 kg since beginning the aripiprazole therapy 2 months prior, and his hemoglobin A1C has increased from 5.4% to 6.2% over the past 6 months.

BACKGROUND

History

Lysergic acid diethylamide (LSD) was first synthesized by Albert Hoffman in 1938 as a potential central nervous system stimulant for use in recovery from anesthesia. An accidental laboratory exposure 5 years later resulted in a profound consciousness-altering experience, prompting Hoffman and colleagues to engage in further experimentation. The drug was subsequently promoted for use in analytical psychotherapy where it was found to be effective for the treatment of alcohol use disorder (AUD).[1] However, as the drug rose in popularity during the 1960s, recreational use triggered some instances of long-term psychosis.[2] Sensationalized media reports, coupled with the role of LSD in the counterculture movement, sparked a moral panic from the establishment.[2] Under the Controlled Substances Act of 1970, the Nixon administration classified LSD as a Schedule I drug, putting a halt to serious medical investigation for nearly 50 years.

Chemistry and mechanism of action

While other classical psychedelics are tryptamines (e.g. N,N-dimethyltryptamine [DMT] and psilocybin) and phenethylamines (e.g. mescaline), LSD is an ergoline, which can be considered rigid analogs of tryptamines.[3] All ergolines consist of a tetracyclic core comprising a bicyclic indole fused to a bicyclic quinoline.[4] In the case of LSD, the tetracyclic core is lysergic acid, which is derived from ergot alkaloids. Ergot is the spore form of the fungus *Claviceps purpurea*, and it has been known for its toxic as well as therapeutic and hallucinatory properties since ancient times.[5] In LSD, a diethylamide group is bound to lysergic acid, hence the name lysergic acid diethylamide. This diethylamide group accounts for many of LSD's unique pharmacological properties, such as its conformational selectivity for serotonin receptors and its high potency in vivo.[6,7]

In humans, LSD is metabolized rapidly and completely into a number of structurally similar metabolites.[8] Only 1% of orally administered LSD is excreted in its original form into urine.[8–10] Most metabolism of LSD takes place in liver tissue, where it undergoes N-dealkylation and/or oxidation.[10] The elimination half-life of LSD is 3.6 hours, and its rate of excretion is highest 4–6 hours after consumption.[11,12] The primary metabolite of LSD, 2-Oxo-3-hydroxy-LSD, can be found in urine up to 4 days after administration.[13]

Like other classical psychedelics, such as DMT and psilocybin, LSD has very high affinity for the serotonin-2A (5-HT_{2A}) receptor. In human cells, its inhibition constant (K_i), which is inversely correlated with affinity, is as low as 0.091 nM.[14] Furthermore, blocking the 5-HT_{2A} receptor with antagonists such as ketanserin either subdues or eliminates the subjective effects of LSD, suggesting that LSD's action at the 5-HT_{2A} receptor is its primary mechanism of action.[15–17] However, what distinguishes LSD from other psychedelics is its "promiscuous" binding profile: its affinity for not only a variety of other serotonin receptors but also for dopaminergic and adrenergic receptors.[18]

The inadequacy of existing psychiatric treatments

As mentioned in Part I, existing medications for psychiatric conditions such as depression are only effective in a minority of patients. The NIH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial of 2008 showed that the remission rate for patients receiving selective serotonin reuptake inhibitors was only 28%–33%, and additional treatment strategies were necessary to achieve a significant response in most patients.[19] Several subsequent studies revealed disappointing outcomes among patients with GAD, with nearly 50% failing to achieve remission with first-line pharmacologic therapy.[20] Other studies investigating antidepressants and second-generation antipsychotics for the treatment of AUD established that psychopharmacological agents offered limited clinical utility. One double-blind trial of the selective serotonin reuptake inhibitor sertraline

showed that there was no significant difference in drinking outcomes between sertraline and placebo (percent days drinking with sertraline: 17.8 ± 32.4; percent days drinking with placebo: 25.4 ± 30.4; $P = 0.96$).[21] An additional study evaluating olanzapine revealed that the second-generation antipsychotic olanzapine was actually less effective than placebo for treating AUD (rate of relapse under olanzapine: 37.9%; rate of relapse under placebo: 29%).[22] Moreover, serious adverse effects of psychiatric medications—including type 2 diabetes, skin discoloration (acanthosis nigricans), and loss of control over facial motion (tardive dyskinesia), weight gain, increased cholesterol—were found to be more common than early data had indicated.[23–25] The underwhelming clinical efficacy coupled with emerging evidence of severe adverse effects sparked a renewed interest in novel therapies, prompting investigators to revisit previously published data on LSD and other psychedelic agents.

AREAS OF UNCERTAINTY

One of the reasons that LSD was banned in 1970 was its apparent tendency to cause psychosis, yet this risk is largely overinflated.[2] It is true that recreational users sometimes undergo deeply unpleasant experiences characterized by panic, disturbing visions, and paranoia. In one survey of 10,293 recreational users of LSD, difficult trips even led 1% of responders to seek emergency medical treatment (EMT).[26] Nevertheless, nearly 90% of those who sought EMT believed that they recovered psychologically within 2–4 hours, and, in general, difficult trips are temporary experiences. The major contributors to difficult trips were poor setting and mindset, excessive dosing, and the consumption of other drugs alongside the LSD. In other words, the difficult trip could have been avoided if the LSD had been administered in a controlled environment. Personal or family history of schizophrenia, bipolar disorder, or other psychiatric conditions is another major contributing factor to difficult trips.[27] In one experimental study with 1200 participants, the single individual who experienced psychosis lasting more than 48 hours after taking LSD also had a sibling with schizophrenia.[28] Overall, incidences of long-term mental illnesses induced by LSD are rare. Two large-scale population studies in the United States, each with over 130,000 responders, found no significant association between lifetime psychedelic use and mental health problems.[29,30] A comprehensive review recently concluded that, despite the risk of challenging experiences, psychedelics are psychologically safe.[31] Furthermore, novel tools such as the Psychedelic Preparedness Scale show promise for mitigating difficult trips.[32]

Clinical trials of LSD regulate three of the factors that tend to lead to adverse effects: the environment in which LSD is taken, dosing, and personal or family history of mental illness among participants. (People with such a history are excluded from the trials.) Therefore, unlike recreational use, clinical trials provide an opportunity to observe the effects of LSD when it is administered in a controlled setting. Among the two modern (21st century) double-blind clinical trials of LSD that have been published, one reported that all adverse effects were mild and transient; severe adverse events such as psychosis or suicidal ideation did not occur.[33] The other found only one serious adverse event—acute anxiety—among 42 participants. However, this was transient, and the participant experienced no long-term symptoms.[34] In both trials, adverse events primarily consisted of anxiety, nausea, and headache, but these only affected a minority of participants. In fact, in one trial, anxiety was actually less common in the group that received LSD than in the placebo group (participants in both groups were experiencing anxiety associated with a life-threatening illness).[33]

Physiologically, LSD is also safe. LSD elevates heart rate, blood pressure, and body temperature.[31,33,35–38] However, a review of the literature found that none of these effects was statistically significant.[39] Furthermore, lifetime LSD use is not significantly associated with heart disease.[40] Nevertheless, individuals with pre-existing cardiovascular conditions may be at risk.

Overdose deaths from LSD are extremely rare. A fatal dose of LSD has been estimated at 100 mg, which is approximately 1000 times the standard recreational dose (0.1 mg).[41] A review of five known overdose deaths from LSD concluded that some of the fatalities were caused by extraneous circumstances, such as excessive physical force that was used by the police to subdue users who had become unruly during a difficult trip.[42]

There are no data that suggest a risk of physical dependence or withdrawal symptoms with LSD, although limited survey data collected from recreational users indicate that tolerance increases with repeated use.[43] However, in most recreational settings, LSD is used relatively infrequently, and tolerance resolves after five days of abstinence.[44] Nevertheless, further investigation into the risk of tolerance will be required before LSD can be used clinically.

Overall, preliminary evidence indicates that LSD has a tolerable safety profile, with a low rate of serious adverse effects when administered in a controlled environment. However, larger-scale clinical trials need

to be conducted to determine rare yet serious adverse events.

THERAPEUTIC ADVANCES

The first modern review of LSD data from the mid-20th century was conducted by Krebs and Johanson.[45] Their meta-analysis included six randomized controlled trials performed between the 1940s and 1970s investigating the use of LSD for AUD. Their data supported a potential beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI: 1.36—2.84; $P = 0.0003$) and concluded that "a single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse." In five of the trials reviewed in the Krebs meta-analysis, partial or complete abstinence from alcohol use among the LSD group was reported at six months (OR: 1.66, 95% CI: 1.11–2.47, $P = 0.01$). In four of the trials, a treatment response was reported at 12 months of follow-up, but the pooled odds ratio did not reach statistical significance (OR, 1.19, 95% CI: 0.74–1.90, $P = 0.47$). In a subsequent meta-analysis of 21 studies published between 1949 and 1973 evaluating psychedelics, predominantly LSD, for the management of mood disorders, investigators found that 79.2% of subjects exhibited a clinician-rated improvement in symptoms.[46] However, the data are highly heterogeneous because several of the studies were conducted before the development of validated assessment tool. The authors also noted that LSD was safe, with only a few cases (8) of adverse effects reported among 423 individuals included in the pooled trials.

The first randomized controlled trial of LSD in the 21st century was a double-blind, active placebo-controlled trial investigating the safety and efficacy of LSD as an adjunct to psychotherapy for patients experiencing anxiety associated with terminal or life-threatening illness.[33] Subjects in this study were divided into 2 augmented psychotherapy groups: a treatment group receiving 200 μg (0.2 mg) of LSD and an active placebo group receiving only 20 μg of LSD which produced a short-lived and mild but detectable LSD effect. Anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI), a validated instrument. The higher dose of LSD significantly reduced trait and state anxiety by 21.8% ($d = 1.1$, $P = 0.033$) and 15% ($d = 1.2$, $P = 0.021$), respectively. Of note, the active placebo group exhibited *increased* anxiety. The effects of LSD were sustained in a 12-month follow-up, where statistically significant improvements included facilitated access to emotions in 66.7% of participants in the treatment group, reduced death anxiety in 77.8% of participants, and better quality of life in 66.7% of participants.[47] No severe adverse effects were reported within either group.

The next randomized controlled trial, albeit not on a clinical population, of LSD in 2016 investigated the drug's effects on empathy in healthy participants.[38] The Dolder group pooled data from 2 similar studies using a double-blind, placebo-controlled, cross-over study design. The first study included 24 participants who received 100 μg of LSD and a placebo, and the second study included 16 participants who received 200 μg of LSD and a placebo. The effects of the drug on emotional processing were assessed 24 hours later using the Facial Emotion Recognition Task (FERT), Multifaceted Empathy Test (MET), and Social Value Orientation (SVO) test, which defines prosociality based on the altruistic allocation of economic resources. Subjective mood was also assessed using Visual Analog Scales (VAS) and the Adjective Mood Rating Scale (ARMS). Investigators found that LSD increased both explicit and implicit emotional empathy as well as prosociality (significant effect of drug: $F_{1,38} = 4.31$, $P < 0.05$). The subjective mood assessment demonstrated increased well-being and happiness. Vital signs were monitored throughout the study period and were not significantly different between the treatment and placebo groups (systolic blood pressure: 129 ±2.0 and 142 ± 2.1, P = nonsignificant and heart rate: 70.6 ± 1.8 and 79.1 ± 2.7, P = nonsignificant in the placebo and 100 μg LSD groups, respectively). No severe adverse effects were reported. The study was conducted among healthy volunteers, and, thus, the clinical applicability to other cohorts was limited. Nevertheless, authors posited that the empathy enhancing effects of LSD could help facilitate the therapeutic alliance among patients undergoing psychotherapy.

In 2018, a similar study evaluated the effects of a single 200 μg dose of LSD on mood and anxiety among 16 healthy volunteers using a randomized, double-blind, cross-over study design.[35] One and 12 months after the LSD session, study subjects completed multiple surveys designed to assess the sustained effects of the LSD treatment session, including the validated STAI-state anxiety scale and several additional questionnaires, such as the Persisting Effects Questionnaire (PEQ), Mysticism Scale (MS), Death Transcendence Scale (DTS), and Neo-Five-Factor Inventory (NFFI). The sum total of the surveys revealed sustained positive effects. Patients reported positive changes in mood (Spearman rank correlation coefficient [R_s] = 0.56, $P < 0.05$), behavior ($R_s = 0.53$, $P < 0.05$), and well-being/life satisfaction ($R_s = 0.53$, $P < 0.05$) on the PEQ and changes in the MS total score ($R_s = 0.62$, $P < 0.05$) and DTS total score ($R_s = 0.76$, $P < 0.01$) at 12 months. No adverse effects were reported at short-term or long-term follow-up.

In addition to the research on its psychological and psychiatric effects, LSD has been investigated as a potential analgesic. In a 2021 study, 24 healthy volunteers were recruited to participate in a randomized, double-blind, placebo-controlled, within-subject study in which they received a single oral dose of placebo or 5 μg, 10 μg, or 20 μg LSD on four consecutive days.[48] The participants engaged in the "Cold Pressor Test" of pain perception 1.5 and 5 hours after receiving the placebo or LSD. Mean pain tolerance and subjective ratings of painfulness, unpleasantness, and stress during the test revealed that 20 μg LSD significantly increased pain tolerance ($P = 0.006$) and decreased painfulness ($P = 0.012$) and unpleasantness ($P = 0.008$) compared to placebo. The lower doses of LSD did not produce a significant analgesic effect. Elevations in blood pressure among the 10 μg and 20 μg groups were not clinically significant. The study provided the first evidence that LSD might be a safe and effective analgesic.

The most recently published clinical trial of LSD was a phase II, double-blind, placebo-controlled study in 2023 that assessed the effects of 200 μg of LSD on 42 participants who experienced anxiety either with or without a life-threatening illness.[34] The primary outcome measure was the STAI-Global (STAI-G) score, which measures both state and trait anxiety; secondary

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

Study	Type	Dose	Sample	Findings
33,47	Double-blind, active placebo-controlled RCT with cross-over	200 μg LSD or 20 μg LSD	12 participants experiencing anxiety associated with life-threatening illness	2 months after treatment, trait anxiety significantly decreased by 21.8% ($d = 1.1$, $P = 0.033$); state anxiety significantly decreased by 15% ($d = 1.2$, $P = 0.021$); effects sustained at 12-month follow-up
34	Double-blind, inactive placebo-controlled RCT with cross-over	200 μg LSD or inactive placebo	42 participants experiencing anxiety with or without a life-threatening illness	16 weeks after treatment, reduction in global ratings of anxiety was 16.2 points greater in LSD group ($d = 0.87$, $P = 0.0074$); decreases in HAM-D-21 and BDI depression scores were also significant
49	Double-blind, dose–response RCT (Phase II; top-line)	25 or 50 or 100 or 200 μg LSD or inactive placebo	198 participants with GAD	4 weeks after treatment, decrease in HAM-A scores was 7.6 points greater in 100 μg group compared with the placebo group ($d = 0.88$, $P < 0.0004$); 50% of participants in remission by week 4
50	Double-blind, active placebo-controlled RCT (Phase II; top-line)	100 μg + 200 μg LSD or 25 μg + 25 μg LSD; treatments spaced 4 weeks apart	27 participants with MDD	6 weeks after first treatment, decrease in IDS-C scores was 9.3 points greater in experimental group compared with the placebo group ($P = 0.02$); effects were sustained 16 weeks after first treatment ($P = 0.008$)

Note that studies on healthy individuals are not included in this table.
BDI, Beck Depression Inventory; GAD, Generalized Anxiety Disorder; HAM-A, Hamilton Anxiety Rating Scale; HAM-D-21, Hamilton Depression Rating Scale, 21-item; IDS-C, Inventory of Depressive Symptomatology, clinician-rated; MDD, major depressive disorder.

measures included scores on the Hamilton Depression Scale, 21-item version (HAM-D-21), and Beck Depression Inventory (BDI), among others. Sixteen weeks after treatment, LSD significantly diminished anxiety; STAI-G scores increased in the placebo group by 1.3 points, whereas they decreased in the LSD group by 14.9 points ($d = 0.87$, $P = 0.0074$). The differences were even more significant at eight ($d = 1.0$, $P = 0.0018$) and two weeks ($d = 1.6$, $P < 0.0001$) after treatment. Reductions in depression scores at 16 weeks were also significant (HAM-D-21: $d = 1.1$, $P = 0.0004$; BDI: $d = 0.82$, $P = 0.022$). The rate of adverse effects was low, with only a single participant reporting acute, severe, transient anxiety. Notably, several patients in the trial were undergoing anxiety treatment with antidepressants and/or psychotherapy before and after the treatment. These patients experienced improvements in symptomatology, suggesting that LSD may augment or enhance conventional therapies for depression and anxiety.

Finally, top-line data from a phase IIb clinical trial sponsored by Mind Medicine (MindMed) indicate that a single 100 μg dose of LSD significantly reduced anxiety by 7.6 points on the Hamilton Anxiety Rating Scale (HAM-A), relative to placebo, 4 weeks after treatment ($d = 0.88$, $P < 0.0004$).[49] Fifty percent of participants experienced remission (HAM-A ≤ 7) by the fourth week. This is by far the largest clinical trial of LSD to date; it enrolled 198 participants with GAD. Three other doses of LSD were administered in the study—25, 50, and 200 μg—but 100 μg proved to be the most clinically effective. In addition, top-line data from an investigator-initiated phase II clinical trial, also sponsored by MindMed, suggest that LSD may also be effective for treating major depressive disorder.[50] In this trial, 27 participants received either two sessions of medium-dose to high-dose LSD (100 μg followed by 200 μg 4 weeks later) or two sessions of active placebo (25 μg LSD). Six weeks after the first session, the experimental group exhibited a statistically significant decrease of 9.3 points in depression symptoms, as measured by Inventory of Depressive Symptomatology (IDS-C) scores, compared with the placebo group ($P = 0.02$). The antidepressant effect was sustained up to 16 weeks after the first treatment ($P = 0.008$) (Table 1).

CONCLUSION

In the 1960s, LSD became notorious as a drug that could induce long-term psychosis. Fifty years later, it has become clear that these fears are largely overwrought. While LSD can trigger mental health problems in rare instances of recreational use, contemporary clinical trials have observed almost no cases of serious adverse events. In the contemporary era of psychedelic research, data from 2 randomized controlled trials have indicated that LSD is highly effective for treating anxiety in participants both with and without a life-threatening illness. However, the larger of these trials only enrolled 42 participants. More trials with bigger sample sizes are needed to confirm the therapeutic benefits of LSD.

REFERENCES

1. Tanne JH. Humphry osmond. *BMJ*. 2004;328:713.
2. Pollan M. *How to Change Your Mind: The New Science of Psychedelics*. London: Allen Lane; 2018.
3. Wang S, Zhu A, Paudel S, et al. Structure–Activity relationship and evaluation of phenethylamine and tryptamine derivatives for affinity towards 5-hydroxytryptamine type 2A receptor. *Biomol Ther*. 2023;31:176–182.
4. Schiff PL. Ergot and its alkaloids. *Am J Pharm Educ*. 2006; 70:98.
5. Jastrzębski MK, Kaczor AA, Wróbel TM. Methods of lysergic acid synthesis—the key ergot alkaloid. *Molecules*. 2022;27:7322.
6. Nichols DE, Monte A, Huang X, et al. Stereoselective pharmacological effects of lysergic acid amides possessing chirality in the amide substituent. *Behav Brain Res*. 1996;73:117–119.
7. Wacker D, Wang S, McCorvy JD, et al. Crystal structure of an LSD-bound human serotonin receptor. *Cell*. 2017; 168:377–389.e12.
8. Canezin J, Cailleux A, Turcant A, et al. Determination of LSD and its metabolites in human biological fluids by high-performance liquid chromatography with electrospray tandem mass spectrometry. *J Chromatogr B, Biomed Sci Appl*. 2001;765:15–27.
9. Lim HK, Andrenyak D, Francom P, et al. Quantification of LSD and N-demethyl-LSD in urine by gas chromatography/resonance electron capture ionization mass spectrometry. *Anal Chem*. 1988;60:1420–1425.
10. Libânio Osório Marta RF. Metabolism of lysergic acid diethylamide (LSD): an update. *Drug Metab Rev*. 2019; 51:378–387.
11. Faed EM, McLeod WR. A urine screening test for lysergide (LSD-25). *J Chromatogr Sci*. 1973;11:4–6.
12. Passie T, Halpern JH, Stichtenoth DO, et al. The pharmacology of lysergic acid diethylamide: a review. *CNS Neurosci Ther*. 2008;14:295–314.
13. Reuschel SA, Percey SE, Liu S, et al. Quantitative determination of LSD and a major metabolite, 2-oxo-3-hydroxy-LSD, in human urine by solid-phase extraction and gas chromatography-tandem mass spectrometry. *J Anal Toxicol*. 1999;23:306–312.
14. Eshleman AJ, Wolfrum KM, Reed JF, et al. Neurochemical pharmacology of psychoactive substituted N--benzylphenethylamines: high potency agonists at 5-HT2A receptors. *Biochem Pharmacol*. 2018;158:27–34.

15. Becker AM, Klaiber A, Holze F, et al. Ketanserin reverses the acute response to LSD in a randomized, double-blind, placebo-controlled, crossover study in healthy participants. *Int J Neuropsychopharmacol*. 2023;26:97–106.
16. Preller KH, Herdener M, Pokorny T, et al. The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. *Curr Biol*. 2017;27:451–457.
17. Preller KH, Burt JB, Ji JL, et al. Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. *eLife*. 2018;7:e35082.
18. Rickli A, Luethi D, Reinisch J, et al. Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). *Neuropharmacology*. 2015;99:546–553.
19. 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.
20. Strawn JR, Geracioti L, Rajdev N, et al. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. *Expert Opin Pharmacother*. 2018;19:1057–1070.
21. Pettinati HM, Volpicelli JR, Luck G, et al. Double-blind clinical trial of sertraline treatment for alcohol dependence. *J Clin Psychopharmacol*. 2001;21:143–153.
22. Guardia J, Segura L, Gonzalvo B, et al. A double-blind, placebo-controlled study of olanzapine in the treatment of alcohol-dependence disorder. *Alcohol Clin Exp Res*. 2004;28:736–745.
23. 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.
24. Manu P, Al-Dhaher Z, Dargani N, et al. Acanthosis nigricans during treatment with aripiprazole. *Am J Ther*. 2014;21:e90–e93.
25. Carbon M, Kane JM, Leucht S, et al. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;17:330–340.
26. Kopra EI, Ferris JA, Rucker JJ, et al. Adverse experiences resulting in emergency medical treatment seeking following the use of lysergic acid diethylamide (LSD). *J Psychopharmacol*. 2022;36:956–964.
27. Bremler R, Katati N, Shergill P, et al. Case analysis of long-term negative psychological responses to psychedelics. *Sci Rep*. 2023;13:15998.
28. Cohen S. Lysergic acid diethylamide: side effects and complications. *J Nerv Ment Dis*. 1960;130:30–40.
29. Johansen P-Ø, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. *J Psychopharmacol*. 2015;29:270–279.
30. Krebs TS, Johansen P-Ø. Psychedelics and mental health: a population study. *PLoS One*. 2013;8:e63972.
31. Schlag AK, Aday J, Salam I, et al. Adverse effects of psychedelics: from anecdotes and misinformation to systematic science. *J Psychopharmacol*. 2022;36:258–272.
32. McAlpine R, Blackburne G, Kamboj S. Development and psychometric validation of a novel scale for measuring "psychedelic preparedness. *Sci Rep*. 2024;14:3280.
33. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis*. 2014;202:513–520.
34. Holze F, Gasser P, Müller F, et al. Lysergic acid diethylamide–assisted therapy in patients with anxiety with and without a life-threatening illness: a randomized, double-blind, placebo-controlled phase II STUDY. *Biol Psychiatry*. 2023;93:215–223.
35. Schmid Y, Enzler F, Gasser P, et al. Acute effects of lysergic acid diethylamide in healthy subjects. *Biol Psychiatry*. 2015;78:544–553.
36. Holze F, Vizeli P, Müller F, et al. Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacology*. 2020;45:462–471.
37. Holze F, Vizeli P, Ley L, et al. Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*. 2021;46:537–544.
38. Dolder PC, Schmid Y, Müller F, et al. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. *Neuropsychopharmacology*. 2016;41:2638–2646.
39. Wsół A. Cardiovascular safety of psychedelic medicine: current status and future directions. *Pharmacol Rep*. 2023;75:1362–1380.
40. Simonsson O, Osika W, Carhart-Harris R, et al. Associations between lifetime classic psychedelic use and cardiometabolic diseases. *Sci Rep*. 2021;11:14427.
41. Gable RS. Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *Am J Drug Alcohol Abuse*. 1993;19:263–281.
42. Nichols DE, Grob CS. Is LSD toxic? *Forensic Sci Int*. 2018;284:141–145.
43. Das S, Barnwal P, Ramasamy A, et al. Lysergic acid diethylamide: a drug of "use"? *Ther Adv Psychopharmacol*. 2016;6:214–228.
44. Buchborn T, Grecksch G, Dieterich DC, et al. Chapter 79 - tolerance to lysergic acid diethylamide: overview, correlates, and clinical implications. In: Preedy VR, ed. *Neuropathology of Drug Addictions and Substance Misuse*. San Diego: Academic Press; 2016:846–858.
45. Krebs TS, Johansen P-Ø. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *J Psychopharmacol*. 2012;26:994–1002.
46. Rucker JJ, Jelen LA, Flynn S, et al. Psychedelics in the treatment of unipolar mood disorders: a systematic review. *J Psychopharmacol*. 2016;30:1220–1229.
47. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *J Psychopharmacol*. 2015;29:57–68.
48. Ramaekers JG, Hutten N, Mason NL, et al. A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *J Psychopharmacol*. 2021;35:398–405.

49. Jacobs M. *MindMed Announces Positive Topline Results from Phase 2b Trial of MM-120 in Generalized Anxiety Disorder*. Available at: https://www.businesswire.com/news/home/20231214537387/en/MindMed-Announces-Positive-Topline-Results-from-Phase-2b-Trial-of-MM-120-in-Generalized-Anxiety-Disorder. Accessed January 11, 2024.

50. O'Brien D. *MindMed Collaborators Announce Positive Topline Data from Phase 2 Trial of Lysergide (LSD) in Major Depressive Disorder (MDD)*. MindMed. Available at: https://mindmed.co/news/press-release/mindmed-collaborators-announce-positive-topline-data-from-phase-2-trial-of-lysergide-lsd-in-major-depressive-disorder-mdd/. Accessed January 12, 2024.