Forging a New Era of Psychiatry

Definium THERAPEUTICS

What is LSD?

Lysergide is a semi-synthetic compound derived from ergot fungus.

First synthesized in the 1930s by Swiss chemist Albert Hofmann in his search for antifungal agents, its acute perceptual, cognitive, and affective effects were discovered accidentally—an event that transformed psychiatric research.[1,2]

As a classic psychedelic, LSD temporarily alters perception, cognition, and emotions, while remaining physiologically safe, non-addictive, and free from withdrawal symptoms.[3]

LSD has demonstrated a favorable safety profile in modern, controlled clinical environments, including results from Definium's Phase 2b clinical trial published in the Journal of the American Medical Association (JAMA).[4,5]

How does LSD work?

While its precise mechanism of action in the treatment of psychiatric illness is unknown, researchers hypothesize that LSD activates serotonin 5-HT2A receptors in the central nervous system.[1,2] In addition, LSD is a catalyst for neuroplasticity—increasing the creation of new neurons, parts of neurons, and connections between neurons.[6] These processes are believed to facilitate the deep encoding of more positive mental states through changes in how neurons interrelate in parts of the brain that mediate emotional processing.

Therapeutic Potential of LSD

LSD is one of the most extensively studied psychopharmaceuticals in history, with over 1,000 published reports.[1]

LSD was extensively studied for more than 30 years after its discovery in the 1930s. A well-documented effect of LSD, established in the 1960s, was alleviation of anxiety and depression.[1] Despite its promising efficacy and safety, due to a variety of cultural, social, and political forces, barriers to conducting research grew. LSD was first made illegal in 1968 and two years later was classified as a Schedule I drug under the Controlled Substances Act in 1970, halting research.

Interest has since been reignited for LSD's potential to address significant unmet needs in psychiatry, and today Definium is leading this resurgence, advancing controlled clinical trials of DT120 Orally Disintegrating Tablet (ODT) – its proprietary, pharmaceutically optimized form of LSD – to explore its potential to transform treatment for generalized anxiety disorder (GAD) and major depressive disorder (MDD), and posttraumatic stress disorder (PTSD). For the millions affected by GAD, the need is urgent: despite its heavy personal and societal toll, no new treatment has been approved in nearly two decades for GAD.[7] And for patients who experience MDD, two-thirds do not achieve remission after receiving first-line therapy,[8,9] and 30% fail to achieve remission from two or more lines of therapy.[10,11]

U.S. Food and Drug Administration's (FDA) Breakthrough Therapy Designation

Based on the significant unmet medical need in the treatment of GAD, along with the initial clinical data from the Phase 2b study and other research conducted by Definium, the FDA granted Breakthrough Therapy Designation for the DT120 program in GAD. The FDA's Breakthrough Therapy Designation recognizes preliminary clinical evidence that a treatment may offer a substantial improvement over existing options for a serious condition, enabling increased interactions with the agency and the potential for a faster review.

Who should be treated with LSD?

Currently, LSD is not FDA-approved for therapeutic use. Ongoing clinical trials with rigorous clinical protocols, thoughtful patient selection, and structured integration support are underway. Results from these trials will provide further insight into which patient populations, if any, are most likely to benefit from potential treatment with LSD.

How is the safe and responsible development and clinical use of LSD ensured?

Therapeutic psychedelics, such as LSD, must be developed and thoroughly investigated within the frameworks of modern clinical trials. This includes rigorous preclinical toxicology studies, carefully designed dose-finding and efficacy trials, and adherence to Good Clinical Practice (GCP) standards. Development must follow Chemistry, Manufacturing, and Controls (CMC) and quality guidelines, with protocols aligned with the FDA's guidance to ensure consistency, reproducibility, and patient safety.

Approval by the FDA is the only pathway to ensure that patients can access this potentially transformative treatment in the healthcare system. If approved by the FDA, FDA-approved labeling, and when necessary, Risk Evaluation and Mitigation Strategies (REMS) provide critical safeguards, while professional associations can establish best-practice guidelines and training curricula based on clinical trial data and real-world evidence. Licensed and credentialed health professionals are central to safe administration, supported by structured monitoring and informed consent processes that protect patients.

What happens in an LSD dosing session?

In a clinical trial, an LSD dosing session is conducted in a comfortable, supportive environment with medical professionals called Dosing Session Monitors (DSMs) who passively observe and assist participants. A healthcare provider is on call to provide medical oversight. To prepare for the session, participants dress in comfortable clothing and can bring personal items such as journals, books, pen and paper, and a pillow and blanket. In addition, an in-person meeting prior to the dosing session is foundational in developing trust and rapport with the DSMs.

After thorough screening and informed consent, participants receive a standardized oral dose, low oral dose or a placebo depending on the study. The experience can generally be divided into 5 phases: onset (approximately 15-30 minutes after taking the dose), maximum effect (approximately 2 to 3 hours after dosing), plateau (approximately 3 to 5 hours after dosing), resolution (approximately 4 to 6 hours after dosing), and completion (approximately 6 to 10 hours after dosing). Participant experiences often include a range of effects, including visual, emotional and physical experiences.

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