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Repeated low doses of LSD in healthy adults: A placebo-controlled, dose–response study

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Abstract

The resurgence of interest in using psychedelic drugs, including lysergic acid diethylamide (LSD), in psychiatry has drawn attention to the medically unsupervised practice of 'microdosing'. Thousands of users claim that very low doses of LSD, taken at 3–4-day intervals, improve mood and cognitive function., However, few controlled studies have described the effects of the drug when taken in this way. Here, in a double-blind controlled study, we studied the effects of four repeated doses of LSD tartrate (13 or 26 μg) or placebo, administered to healthy adults at 3–4 day intervals, on mood, cognitive performance and responses to emotional tasks. Participants were randomly assigned to one of three drug conditions: placebo (N = 18), 13 μg LSD (N = 19), or 26 μg LSD (N = 19). They attended four 5-hour drug-administration sessions separated by 3–4 days, followed by a drug-free follow-up session 3–4 days after the last session. LSD (26 μg) produced modest subjective effects including increased ratings of 'feeling a drug effect' and both stimulant-like and LSD-like effects, but the drug did not improve mood or affect performance on psychomotor or most emotional tasks. No residual effects were detected on mood or task performance on the drug-free follow-up session. We conclude that within the context of a controlled setting and a limited number of administrations, repeated low doses of LSD are safe, but produce negligible changes in mood or cognition in healthy volunteers.

KEYWORDS
behavior, cognition, LSD, microdosing, mood, psychopharmacology

1 | INTRODUCTION

The practice of 'microdosing' of lysergic acid diethylamide (LSD) has received a great deal of media attention in recent years. Thousands of people report that ingesting very low doses of LSD once every 3 or 4 days produces a wide range of beneficial mood and cognitive effects.[1–5] They report benefits including improved mental function (e.g. relief of negative moods and depression), increased positive mood, energy level, work effectiveness and 'healthy habits', as well as relief from medical conditions such as migraines, pre-menstrual discomfort, traumatic brain injury and shingles. The drug is taken in doses of 10–20 μg, or about one-tenth of the dose that produces psychedelic experiences. Until now, the drug is being used without medical supervision, and there have been few controlled studies to determine its effects under these conditions. What are the direct effects of the drug, do these effects change with repeated dosing, and are there lasting psychological benefits?

There are good reasons to expect that a serotonergic drug like LSD might improve mood.

The serotonergic system is critically involved in the neurobiology of depression, and $5HT_{2A}$ signalling in particular may underlie the effectiveness of selective serotonin reuptake inhibitor (SSRI) antidepressants.[6] LSD acts as a direct agonist on serotonin receptors, whereas SSRI's block reuptake of serotonin and often take weeks to be clinically effective. LSD also acts on other neurotransmitter systems, including notably the dopamine system,[7] which has itself been the target of antidepressant drugs such as bupropion.[8] At higher doses, however, the altered states of consciousness induced by LSD appear to depend on its effects on 5HT2A.[9–11] Interestingly, there is some evidence for antidepressant effects of repeated low doses of LSD and other psychedelic drugs from animal models. Small, repeatedly administered doses of the psychedelic drug *N*,*N*-dimethyltryptamine (DMT) enhance fear extinction learning and time to immobility on the forced swim test in rodents, another metric of possible antidepressant effects.[12] In an animal model of antidepressant effects (olfactory bulbectomy), repeated small doses of LSD and other psychedelic drugs improved deficits in active avoidance learning, a defining feature of other antidepressant drugs.[13] The authors suggested that repeated activation of 5HT2A receptors led to a rebalancing of 5HT1A/2A receptors and a resulting downregulation of 5HT2A receptors that has been linked to effectiveness of antidepressants. LSD has a long history of use in psychotherapy, which has recently been revisited in clinical research studies. In the 1950s and 1960s, over 1000 studies were published supporting therapeutic effects of LSD in combination with psychotherapy.[14–16] Although the findings were promising, many of these early studies lacked adequate control groups and did not isolate drug effects from effects of the psychotherapy itself. More recently, several controlled clinical studies report therapeutic effects of moderate to high doses of LSD (200–800 μg) or psilocybin in the treatment of depression, end-of-life anxiety in terminally ill patients and addictive disorders.[17–19] These high-dose clinical studies are promising, suggesting that psychedelic drugs have the potential to yield lasting changes in mood and behaviour.[20]

Several studies have documented subjective and physiological effects of single low doses of LSD,[21–23] but relatively few studies have examined effects of repeated low doses of LSD, the pattern known as microdosing. One study[24,25] examined the effects of six repeated doses, taken every 4 days, of 5, 10 and 20 μg LSD or placebo in 48 healthy older adults (mean age 63). The drug was well tolerated and produced modest effects on a measure of time perception: Subjects over-reproduced temporal intervals of 2000 ms and longer, especially in the 10 μg condition. However, the drug did not significantly alter mood, or impair cognition, balance or proprioception. Another recent study[26] used an innovative design in which experienced users of microdoses of LSD or psilocybin ingested drug or placebo under double-blind conditions in their home environments. Subjects ($N = 191$) were instructed on blinding their preferred psychedelic drug and dose (obtained from their own sources) and a placebo using online instructions for use during a 4-week dosing period. All subjects, regardless of drug condition, reported improvements in well-being and cognition across the 4 weeks of treatment. This suggested the drug had little effect on these measures. Subjects did report acute subjective effects from the drug (compared with placebo), including increased energy, mood and creativity and post-acute decreases in anxiety. However, when the authors removed the data from subjects who correctly identified the drug as active (thereby breaking the double blind), these drug effects were no longer significant. Even though there were no lasting improvements in mood or cognition, the authors reasoned that any apparent benefits from the drug could have been due to expectancy or placebo effects. The Szigeti study raises interesting questions about whether detectable subjective effects truly nullify any observed therapeutic benefits because the blind is broken or whether therapeutic benefits can occur at doses that are detectable by the users. This presents a challenge for psychiatric research, because it is possible that some beneficial effects occur at doses that produce detectable acute effects. Indeed, individuals with a low threshold for detecting the drug's effects may be especially sensitive to its antidepressant effects.

In the present study, we administered repeated doses of LSD (13 or 26 μg LSD tartrate, which is equivalent to a dose of 10 or 20 μg of LSD base) or placebo to healthy volunteers under controlled and fully blinded conditions. The subjects were not experienced with microdosing and were informed that they might receive any of several drug types during the study (e.g. stimulant, sedative and hallucinogen). Participants attended four 5-h laboratory sessions in which they received LSD or placebo, once session every 3–4 days, followed by one drug-free session 3–4 days later. We assessed mood and performance on cognitive and emotional tasks during the drug administration sessions and at follow-up. We hypothesized that repeated doses of drug, compared with placebo, would improve mood and cognitive performance and that these effects would persist to the follow-up session.

2 | MATERIALS AND METHODS

2.1 | Design

Participants ($N = 56$) were healthy adults aged 18–35 who reported having used a psychedelic drug or MDMA at least once in their lifetime. After screening, they were randomly assigned to one of three conditions to receive placebo, LSD (13 μg) or LSD (26 μg) during four 5-h laboratory sessions, conducted at 3- to 4-day intervals (Figure 1). After ingesting their dose, subjects completed mood questionnaires every hour (for detailed descriptions of all subjective/self-report measures, see Supporting Information), and cardiovascular measures were obtained. On Sessions 1 and 4, and at the follow-up session, subjects also completed cognitive and behavioural tasks (for detailed descriptions of all tasks, see Supporting Information). Primary outcome measures were ratings of mood and performance on cognitive tasks during drug sessions and at the drug-free follow-up.

2.2 | Subjects

Participants were recruited by flyers and social media ads. Subjects provided informed consent before beginning the study, and the study was approved by the University of Chicago Institutional Review Board. Initial eligibility criteria were age 18–35, fluent in English, minimum high school education, BMI 19–30, not taking medications and