

**Perceptions of Safety, Subjective Effects, and Beliefs about
the Clinical Utility of Lysergic Acid Diethylamide (LSD) in
Healthy Participants: Qualitative Results**

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Abstract

Background. Classic psychedelics may be effective in the treatment of a number of mental health conditions, however, scalable treatment approaches are needed to maximize access to these novel therapeutics. In the current study, perceptions of safety, subjective effects, and beliefs about the clinical utility of lysergic acid diethylamide (LSD) were evaluated among healthy participants (N = 31) administered between 50-100 µg LSD in an abridged treatment paradigm designed for real-world implementation.

Methods. Semi-structured interviews assessed participants' expectations, their experience, and their thoughts on the safety and efficacy of the study design. These interviews were transcribed for thematic analysis relating to perceptions of safety, subjective effects, and beliefs about the clinical utility of LSD.

Findings. Most participants felt safe throughout the study, with a minority reporting concerns related to having a challenging experience with LSD that diminished over time. Participants attributed their feelings of safety to the study structure and support of their attendants, which allowed them to "let go" and immerse themselves in the experience without preoccupation. Furthermore, participants reported transcendent, mystical-type experiences characteristic of classic psychedelics, with almost half highlighting the prominent role played by music during the acute period of drug action. Finally, participants endorsed support for the clinical utility of LSD in controlled environments, expressing the belief that LSD is a safe drug with the potential to help others.

Interpretation. The current findings support the potential feasibility of this scalable intervention paradigm in clinical settings.

Funding. This study was funded by Eleusis Health Solutions Ltd.

Introduction

The discovery of the 5HT_{2A}R agonist (i.e., classic psychedelic) lysergic acid diethylamide (LSD) in 1943 sparked notable scientific interest, with thousands of manuscripts, dozens of books, and a number of international conferences focused on LSD-assisted psychotherapy (Masters, 1973; Grinspoon and Bakalar, 1979; Passie *et al.*, 2008; Nutt, King and Nichols, 2013). Due to a lack of modern methodological rigor most of the early clinical studies of LSD are best understood as inconclusive, yielding only pilot data suggesting safety and efficacy (Bonson, 2018). Nevertheless, among the most promising findings was LSD's potential to treat alcohol dependence (Krebs and Johansen, 2012) and other substance use disorders (Savage and McCabe, 1973) as well as end-of-life distress (Gasser *et al.*, 2014). Despite a clear medical and scientific rationale, legal proscriptions were enacted and funding was withdrawn, leading to a protracted moratorium on human research with LSD and other classic psychedelics.

Human research with classic psychedelics began to re-emerge in the 1990s (Strassman, 1994; Hasler *et al.*, 1997), however, and in 2014 results of the first modern clinical trial of LSD-assisted psychotherapy were published (Gasser *et al.*, 2014). Contemporary research suggests LSD has a favorable safety profile at doses ranging from 20-200 µg (Schmid *et al.*, 2015; Liechti, 2017; Family *et al.*, 2020), and several clinical trials of LSD are currently underway (NCT03153579; NCT03781128; NCT03866252).

As is characteristic of classic psychedelics, LSD can occasion transcendent, mystical-type experiences characterized by feelings of oneness or unity, profound insight, sacredness, deeply felt positive emotion, transcendence of time and space, and ineffability (Hendricks, 2018; Johnson *et al.*, 2019). LSD is not physiologically toxic, but like all classic psychedelics LSD can engender challenging experiences, colloquially known as “bad trips,” characterized by feelings of acute anxiety/fear/panic, paranoia, and depersonalization/derealization (Passie *et al.*, 2008; Gasser *et al.*, 2014; Schmid *et al.*, 2015; Johnson *et al.*, 2019). For this reason, modern research emphasizes the importance of several safety practices in the administration of classic psychedelics to minimize both the likelihood and impact of challenging experiences during clinical trials. These practices, articulated by Johnson and colleagues (Johnson, Richards and Griffiths, 2008), involve multiple intensive preparatory sessions over several days or weeks prior to drug administration, oversight of two attendants or “guides” during the acute period of drug action, and multiple follow-up psychotherapy “integration” sessions in the days or weeks following drug administration (see recent study by Davis and colleagues (Davis *et al.*, 2020)). Though these practices are sound in conception, they may nonetheless represent idealistic approaches that have yet to demonstrate their necessity. Indeed, the intensive nature of these practices raises concerns about their implementation in the real world, where cost-effectiveness is vital. More scalable approaches are essential to allow for broad accessibility to LSD-assisted psychotherapy as an affordable treatment modality.

The current protocol was developed to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of 50-100 µg LSD among healthy participants in a scalable intervention paradigm involving abbreviated preparation and integration, and a single attendant to assist each participant (additional details on the protocol can be found in Family *et al.*, under review). As described in a companion manuscript (Family *et al.*, under review), participants spent full days at the research site and their participation was framed around exploring creative problem solving regarding a work-related issue, results of which will be reported elsewhere. This framing allowed for the development of an operational protocol for an interventional trial and differentiates the current protocol from previous studies that have administered classic psychedelics to healthy participants (Carhart-Harris *et al.*, 2015; Schmid *et al.*, 2015; Carhart-Harris *et al.*, 2016; Dolder *et al.*, 2017; Preller *et al.*, 2019) that have evaluated only safety, pharmacokinetics, and/or neurobiological outcomes.

The objectives of the present report were to assess perceptions of safety, subjective effects, and beliefs about the clinical utility of LSD using data from semi-structured interviews among those who completed the current protocol. Findings suggest that participants felt safe throughout the entire protocol, experienced transcendent mystical states

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3 during the acute period of drug action, and took from their experience the belief that LSD could have clinical utility,
4 supporting the viability of this intervention paradigm in future clinical settings.
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8 **Methods**

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10 This was a phase 1, single-centre, dose-escalation study that used both open-label and double-blind placebo-
11 controlled crossover designs. The study protocol and informed consent form were reviewed and approved by the
12 independent ethics committee for the investigational site. The study was conducted in accordance with International
13 Conference on Harmonisation harmonized tripartite guideline on Good Clinical Practice and UK law. Each
14 participant provided written informed consent after adequate explanation of the aims, methods, anticipated benefits,
15 and potential hazards of the study.
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18 *Study design*

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20 Two sub-studies in different populations of healthy participants were carried out as follows: part 1 was an open-label
21 dose-escalation study in hallucinogen non-naïve participants, and part 2 was a double blind, placebo controlled,
22 randomized, crossover study in hallucinogen naïve participants. Hallucinogen non-naïve participants were those
23 who used LSD or any other classic psychedelic drug on more than three occasions in their lifetime. Hallucinogen
24 naïve participants were those who had not used LSD or any other classic psychedelic drug in the past seven years.
25

26 In part 1, 13 participants were randomly assigned to one of five cohorts (maximum three participants per cohort) and
27 received a single dose of 50 µg, 75 µg, or 100 µg LSD. In part 2, participants were assigned to one of eight cohorts
28 (maximum three participants per cohort), and then randomly assigned to the experimental non-crossover treatment
29 (n = 9) group or the placebo-controlled crossover group (n = 10). They received their assigned study treatment on
30 two separate occasions, as follows: participants either received 50 µg LSD followed by 75 µg LSD (experimental
31 non-cross group), or placebo followed by 75 µg LSD (placebo-controlled crossover group), with dosing separated
32 by seven days. All participants received their assigned study doses in an in-patient setting and follow-up visits were
33 conducted approximately one week and one month after the last dose.
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36 D-lysergic acid diethylamide (d-LSD, HPLC purity >99%, Onyx Scientific Limited, United Kingdom) was
37 dissolved in ethanol at 25mg/ml and prepared as a solution 50 µg or 4 µg d-LSD/mL in distilled water and
38 completed to a final volume of 25 ml with the addition of distilled water for oral administration. A shelf life of
39 78 hours was allocated to the doses, when stored in the defined container closure at a temperature of 2-8 °C, with the
40 start of the expiry period being defined as the time of combining the d-LSD with ethanol. Placebo was distilled
41 water only and presumed to be indistinguishable from the LSD solution.
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44 *Study participants*

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46 Healthy men and women aged 21 to 65 years old were screened within 28 days of randomization. Participants who
47 met all inclusion and no exclusion criteria and provided written informed consent were assigned to a cohort based on
48 availability. For both part 1 and part 2, eligibility was based on a participant meeting the study inclusion criteria and
49 none of the exclusion criteria. Eligibility was also dependent on the outcome of an interview with a physician that
50 was performed as part of the screening process. Complete inclusion and exclusion criteria for both parts are reported
51 in Family et al. (under review).
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54 Thirty-two participants were determined eligible for this study. The average age of participants was 28.8 years.
55 Twenty-eight self-identified as men and four as women. The day after participants completed the final drug dose,
56 they were interviewed by the research team. The interviews took place in an office space in the same clinical trial
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3 unit. The interviewers were either one of the video crew accompanied by a member of the research team, or a
4 member of the research team. One participant was not interviewed because he was withdrawn from the study due to
5 nicotine intake after his first dose, which was a placebo dose, leaving us with a sample of 31 participants.
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8 In semi-structured interviews, the participants were asked about their expectations and the outcome of their project-
9 related work, their experience overall, and their thoughts on the safety and efficacy of the study. These interviews
10 were video-recorded and later transcribed and uploaded into NVivo12 for thematic analysis. Two members of the
11 research team coded the transcripts relating to perceptions of safety, subjective effects, and beliefs about the clinical
12 utility of LSD. These two team members began by engaging in initial coding of the first five interviews
13 independently and then coming together to compare codes. Any discrepancies in coding were discussed until
14 agreement on coding was met. They then coded the next five transcripts independently and compared them. At this
15 stage the coders had a high degree of consistency in coding. They continued this process until they had coded all
16 transcripts and compared them. Once all transcripts were coded for themes relating to perceptions of safety,
17 subjective effects, and beliefs about the clinical utility of LSD, the lead coders developed axial codes that were
18 reflected in the results. Such a style of coding is consistent with general standards of qualitative research analysis
19 (Kvale and Brinkmann, 2009).
20

21 **Results: Perceptions of Safety**

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23 When assessing the safety of a protocol it is important to examine objective or quantifiable measures of harm (e.g.,
24 adverse events or abnormal values in physiological measures). However, to get a complete understanding of safety
25 the subjective perceptions of safety among the participants must also be considered. The objective measures of
26 safety for the current protocol are reported elsewhere (Family et al., under review). Accordingly, the focus of this
27 paper is to investigate participants' perceptions of safety using qualitative data from a structured interview
28 conducted after their participation in the in-patient segment of the study, which included treatment with LSD.
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31 To assess general perceptions of safety, participants were asked how safe they felt during the protocol. Twenty-three
32 of the 31 participants expressed that they felt safe throughout the entire process. Participant 01, responded to the
33 question about safety by saying, "Completely safe. I think the safest experience ever in the sense I couldn't harm
34 myself in no way." Similarly, Participant 06 responded, "I think I felt incredibly safe, you know, especially as I was
35 cannulated and people were taking blood from me and I knew I was under constant observation. I think I felt
36 remarkably comfortable and at ease." The eight who expressed some anxiety about the study said that these feelings
37 emerged at the beginning but dissipated as the study went along. They were initially concerned about the effects of
38 LSD, believing that they may have "an anxiety attack in the middle of the trip and, you know, freak out in some
39 way" (Participant 04). However, even those with initial concerns said they felt safe by the end of the study.
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42 LSD may cause users to feel a loss of control, which may engender anxiety. Accordingly, participants were asked if
43 they thought they had lost control at any point during the experiment (note: two participants were not directly asked
44 if they lost control during the interview). Twenty-six of the participants responded in ways similar to Participant 31
45 who said, "I don't think I felt I lost control at any point." Those five who did say they lost control made a point of
46 explaining that losing control was the point of the experiment and that it was an intentional and planned loss of
47 control. They felt safe and secure in knowing that it was okay to do so. Participant 16 said, "I think that's part of the
48 point [laughs]." He then went on to question what was meant by losing control saying: "What do we mean by lose
49 control? I mean it's kind of weird, I thought I was fully involved in the experience and I was enjoying it and to a
50 larger extent I was directing the experience I would say, so in that respect I didn't lose control but the whole
51 experience is a loss of control." Others believed that losing control was expected, but this loss of control was not
52 associated with feeling at risk or in danger. As participant 21 said:
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3 I never felt like I was in danger. For most of the time during the highest intensity trips I couldn't move, so
4 that kind of keeps you safe in a way [laughs] and I had no desire to move and I was having a lovely time.
5 And, even when I did have maybe a distressing idea, I'd been told that these ideas are very fluid and if you
6 don't like something you can just ... leave it and it will turn into something else or don't worry too much.
7

8 The last sentence of this statement supports the importance of adequately preparing participants for their
9 experiences, which was done in the current study.
10

11 Overall, the participants expressed that they felt safe and at limited risk of danger due to the protocol. The feelings
12 of safety they expressed were largely generated by two primary aspects of the protocol: (1) the overall structure and
13 (2) the presence of attendants.
14

15 *Structure of the Protocol*

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18 The study took place in a Phase I clinical unit in London, UK, and participants were compensated for travel
19 expenses and for participating in the study in accordance with ethical approval. The days' events were structured,
20 and staff guided participants as to where to go and what was to come. This defined structure was partly designed to
21 enhance participant safety and foster feelings of trust so that participants could feel comfortable and "let go." To
22 assess the success of this structure for facilitating feelings of safety, participants were asked if the structure of the
23 protocol reduced or mitigated possible negative experiences. All participants said something positive about the
24 structure of the protocol, though some were ambivalent. The aspects of the structure that the participants found
25 effective at minimizing their concerns of negative experiences were (1) the presence of staff throughout the process;
26 (2) the clearly defined schedule; and (3) legally sanctioned use of medical grade LSD.
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29 Participants' days were structured so that they knew when each event of the day took place. For twenty-three
30 participants this meant that they did not have to worry about keeping up with where to be or how to get there.
31 Participant 24 described what the protocol was like: "The setup was quite helpful in the way that it was quite clear
32 what to do: lay down, close the eyeshades, listen to the music. ... You didn't need to take any decisions. ... You
33 don't have to think about what is to come."
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35 For the majority of participants, being in a structured setting aided in enhancing their experiences and contributing
36 to feelings of security during the process. However, eight participants were ambivalent about the tight structure and
37 schedule. These participants suggested that the structure felt safe but it may have inhibited their experiences.
38 Namely, they said that the constraints associated with being administered LSD in a formal setting prevented them
39 from being able to fully explore the world around them during the acute period of drug action. Participant 22 said, "I
40 wanted a bit of fresh air. ... If anything I felt too safe. So, yeah, I just wanted to feel that breeze. ... But, yeah, it was
41 more than safe." Participant 26 also expressed the ambivalence of the setting:
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44 It's a bit awkward being in a hospital, but it's also kind of comforting because it is in the back of your head
45 that you know there's lots of people here who know what they're doing and you can think, 'Well, what if
46 I'm like this for days?' But you kind of think, 'Well, I'm in the best environment really because there's
47 medics.' ... I wouldn't say [its] the best place to be 'cause I guess the best place to be is somewhere in a
48 forest or something like that, but as far as, you know, if somebody's anxious about their health or
49 something like that, I would say this was an optimal environment.
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51
52 Others expressed that they would have preferred to be with close friends rather than with strangers. Participant 22
53 said, "I remember saying, I just wanna be with a couple of my mates and just talk through this like strange situation
54 that is going on." In short, these eight participants believed that they felt safe throughout the protocol, but that the
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3 safety protocols diminished their autonomy and ability to experience the effects of LSD in ways they would have
4 preferred.
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6 *Perceptions of Attendants* 7

8 The protocol for the study included having an attendant be available at all times while the subject was under the
9 influence of LSD. The current protocol had attendants from a variety of backgrounds. Ten attendants (six women
10 and four men) were hired to sit with subjects. These attendants had backgrounds in psychotherapy (n=2), breath
11 work (n=4), cognitive science (3), and literature (n=1). Their role was to attend the baseline session and the drug
12 treatment session to provide support by practicing some of the basic components of the competencies of a
13 psychedelic therapist (Phelps, 2017): namely, being knowledgeable and able to answer questions about the drug
14 experience, supporting the session by building trust with the participant, practicing mindfulness, and empathetic
15 listening. They also were responsible for any logistical issues, like providing the participant with any immediate
16 requirements of pen/paper, food, water, or being escorted to the restroom.
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19 When asked what they thought about having an attendant with them during the trial, the participants were in near
20 universal agreement that having an attendant was beneficial to their experience. All participants expressed very
21 positive reactions to the attendants, believing that they very much facilitated a good experience. Echoing this,
22 participant 17 said, "I think it's the whole idea that you're being looked after gives you freedom to actually let go."
23 Participant 28 said, "I couldn't have done it without the assistant." The reasons for the beneficial experiences fell in
24 two broad categories: emotional security and practical benefits.
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27 Emotional security included statements relating to how the attendants helped ease any emotional uncertainty or
28 anxiety. Eighteen participants mentioned such ideas. Those who mentioned the emotional security said that they felt
29 a bond with their attendants, which they believed might have been due to the effects of LSD. Participant 01 said of
30 his attendant: "I love my assistant. It's my dad now I have two fathers. [smiles] And, so it's really important to have
31 an assistant because it can help you during the task." Similarly, participant 29 said of his attendant: "I cannot
32 imagine doing this without a person. And the other part is a little bit like it gives confidence. So you feel like
33 because there's someone there that can help you any time then you feel more like relaxed and you can just enjoy the
34 experience. So very useful, yeah."
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37 Practical benefits included statements relating to how the attendants were able to satisfy any needs they had. Many
38 of these needs included having access to writing equipment, directions to restrooms, help in case of medical
39 emergencies, and access to food and drinks. Twenty-three participants mentioned practical benefits. Some
40 appreciated having someone to help with simple needs. As participant 05 said, "Yeah, [the attendant] asked like all
41 the time, 'Is everything okay?' And he was really attentive. ... Can I have some water please? And can we switch on
42 the heating?" Participant 06 said, "It was very nice having somebody to take me to the bathroom." Participant 07
43 said of the attendant:
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45 He completely looked after me for since I've been here. So, you know, where I need to go, food I need to
46 eat, what I need to be doing, my experiences, if I have any problems. He's like the go-to person for
47 comfort: so comfort in the room, changing light levels, simple things like opening the window, which I
48 couldn't even see so [laughs].
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51 Participant 03 succinctly summed up why attendants helped: "Worries were contracted out. I didn't have to think
52 about being too hot or too cold or where my food was going to come from."
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54 We should note that seven of the participants said that they understood why attendants were present, but that they
55 did not know if the attendant was needed. Participant 22 said that he "didn't have the independence because they do
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3 so much for you.” He recognized the need for the attendant, but also thought having one stifled his independence.
4 Participant 23 said, “I didn’t feel like I needed them there but I understand that that’s almost the definition of their
5 success is that I didn’t feel imposed upon or imposing upon them. So, if they weren’t there I don’t see that I would
6 have had a significantly different time. ... I think they helped with physical things, like I might have found it hard to
7 carry my tray over to my table or something, so that was great.”
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10 Participant 14 said:

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12 Well it was very comforting knowing that someone was there in case I needed anything. At the same time
13 though sometimes I really thought I would like to be alone here because I’m accessing myself and I really
14 need to focus on my own and I feel a bit shy about being in the room with someone else, just exploring
15 inside me. But I really couldn’t distract myself and just say it out loud so I just lived with it.
16

17 In general, these ambivalent participants expressed a concern that the attendant would at times get in the way of
18 their experiences. The attending behaviors of checking in on participants to ensure they were doing well were seen
19 as bringing them out of the pleasurable moment. Nevertheless, each of these participants did say that they
20 understood why the attendant was there and that having them helped for many situations.
21

22 **Results: Subjective Effects**

23
24 Use of LSD has been shown to occasion transcendent, mystical-type experiences where users feel awe, wonder,
25 amazement, and deep connections with others. These experiences are relevant to the clinical application of the
26 current protocol insofar that such experiences are thought to underlie the therapeutic efficacy of classic psychedelics
27 (Hendricks, 2018; Johnson *et al.*, 2019). Accordingly, it was important to determine if participants had such
28 experiences after being administered LSD. Participants were asked to describe their experiences during the protocol,
29 including what they perceived as the most enjoyable aspect of it. Participants described experiencing deeply felt
30 positive mood/euphoria, pseudohallucinations/visual effects, and a connection with others (and their work), which
31 they said were the most enjoyable parts of the study. In fact, every participant referenced the acute effects of LSD
32 when asked what was most enjoyable about the study.
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35 For some participants, the euphoria brought on by LSD was the most enjoyable aspect of the study. Participant 06
36 replied, “Now I felt euphoria before with other drugs, but this one was, I think the best word to describe it was a
37 very deep, rich euphoria. ... And with that came a very intense sensation of well-being, happiness with myself,
38 happiness with my surroundings, and just a contentment with the way my thoughts and mind processes were going.”
39 For some, these feelings lasted throughout the day. Participant 9 said, “it was quite euphoric in terms of it allows
40 you to, I was smiling the entire day. There was no feelings of fear, no feelings of worry.” Finally, participant 20
41 said:
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44 I feel the most enjoyable moment was when I met happiness in my trip. I really met happiness and I met
45 love. I really met the feelings. I could see them and I could feel them, and it was very enjoyable. It was
46 great because it was not connected—it was not happiness for something that has happened or happiness for
47 something that I saw or whatever. And it was not love for someone, love for something. They were just
48 there, pure emotions that I could embrace and really see, feel, and probably taste as well.
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50 Participants also discussed experiencing pseudohallucinations (audio and visual), which they found pleasant and
51 contributed to their euphoric feelings. Participant 29 said:
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54 The most enjoyable part was the visuals that I got when the effect of the drug started. It was the diamond
55 sparkling-like colors and they were so, so enjoyable. I was just looking at them and they were making so
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3 many different patterns. And the feeling of joy inside, the feeling of peace inside. And the feeling of awe
4 and wonder that I've never seen this before.
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6 Similarly, participant 15 described the visuals in a favorable manner:
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8 I mean yeah for that particularly that was just a very vivid moment where just everything was sort of white
9 and this kaleidoscope tunnel around me. Yeah, kaleidoscope tunnel vision everywhere. In terms of other
10 visualizations, I mean there was hundreds throughout the day. Yeah, and every moment, like say,
11 everything would be sort of segmented. So for one minute I could be I don't know in my mind's eye just
12 like riding down the Euphrates in like a boat at the start of civilization, and then at the next, however much
13 time had passed later, I'd be yeah, staring at a mark on—well I didn't realize it was a mark I was just
14 staring into sort of some kind of space and there was um, with my eyes open or maybe closed I couldn't
15 tell, and there was just sort of um, sort of visions going on around me and one particular very strong vision
16 which looked like a black hole swallowing things and that happened to be a mark on the ceiling for
17 example, yeah. But yeah, it was quite powerful, some of the visions, and really interesting.
18
19

20 When describing their experiences after being administered LSD, the participants highlighted how they felt
21 connected with others and the world. For example, participant 06 said, "I felt a very deep sense of connection with
22 my environment and the people around me after I took it and a greater sense of well-being and comfort with
23 myself." The current protocol was framed around the effect of LSD on creativity for problems the participants were
24 working on for their jobs or in school. They said that these feelings of connectedness gave them additional
25 motivation to work on their problems because they saw how their work related to the world more broadly.
26
27

28 Fourteen participants said their perception of the music was among the most enjoyable aspects of the study. During
29 the protocol when participants were experiencing the effects of LSD a pre-arranged playlist was played, which
30 included a mix of ambient, classical, and neo-classical music, although some participants chose to play their own
31 music instead. Participant 24 stated, "I was feeling music very, very emotionally. There were different bits of music
32 that were playing, and they would completely, totally change the emotions I would have." Participant 17 said, "The
33 best thing was listening to music and have synesthesia effect where I could see the music and taste it. So, this violin
34 classical music would like freeze in the air and just being crunchy and taste like coconut, so it was quite new,
35 enjoyable." Participant 27 said, "Listening to the music under the influence was just amazing." Finally, participant
36 20 reported:
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39 So, I was following the music. And the music was very vivid, was very dynamic, and it was very visual. I
40 could really follow it as if I was following some strings that were growing in some directions. I could feel
41 that it was directing me toward different feelings. And I realized that at some point I arrived, say, in
42 Happiness Island or whatever, and that's how I found it, and the same for love. ... It was very, very
43 different because listening under LSD I was giving to it some meaning. I think that the music was kind of
44 the sea in which I was traveling through with my vessel, say, but I could still decide where to go. So, I
45 could decide whether I wanted to explore that side of the music or something else and that's how I reached
46 happiness and really, I was so happy. I can hardly describe it.
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49 Despite one participant saying the "music was a bit annoying," such accounts suggest the value in providing music
50 to enhance mystical-type experience during the protocols.
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52 Of note, three participants referenced their bonding with the study team as among the most enjoyable aspects of the
53 study. Participant 27, for instance, stated, "It was a really nice setting and the people were really nice. You know, I
54 just enjoyed dinner with the people, and they treated us so well, giving us great food and rooms and things, so that
55 was definitely the best part or one of the best parts."
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Results: Beliefs about the Clinical Utility of LSD

Participants were asked what they might tell others, including regulators, about their experience in the study. The assumption was that if they felt they benefitted from their participation, they would endorse the clinical utility of LSD. Twenty-six of the 29 participants who were asked what they would say to regulators if asked about LSD said that they would encourage them to either make LSD legal or at the least allow scientists to study it more. These respondents said they would speak favorably about LSD to regulators for two reasons. First, they believed that LSD was a relatively safe drug that has the potential to help people. Participant 11 reflected this positive perception of the benefits of LSD in general. When asked what he would say to regulators, participants 11 said:

That this drug has a lot of potential to help people in a great number of ways, and also teach us a lot about human consciousness and that it's a great shame that more research can't be undertaken on this substance. Both in terms of the people who are not able to benefit from this and also in terms of our not expanding our understanding of who we are and how we operate.

The other reason was more about the need for better science on the topic and that regulators should at least provide more opportunities to clinically test the benefits of the drug. Participant 30's comment reflected this argument:

With all regulations that they're to protect people. If there's any kind of change to these kind of regulations it should be conducted in a very, very, very controlled way. There should be a lot of checks and sanctions on who has access to these kind of substances and how people are introduced to them and the context in which they are given them? I think the regulators should consider lowering all of the sanctions but responsibly.

The remaining three participants said that they would have nothing to say to regulators and offered little on the topic even after probing.

Four participants expressed enthusiasm for the utility of the LSD for clinical help when administered in controlled environments. Participant 18 said:

There should be special pharmacies where depressed physicists can come and just ask for a dose and just lie down for the night in a single bedroom and come very, very happy and with a smile on their face the other day and everything changes, yeah. Because as I noticed it has no side effects, so why not? Of course, it shouldn't be open to the public but under restricted conditions I would be very up for it.

Participant 31 said, "With the screening process, making sure people are completely mentally capable and safe to take it, it's boundlessly useful and beneficial and I think it has so many legs for like real-world therapies and um, just helping. It's like no other drug that I've observed. Like there's seemingly no negatives, but I guess we're still investigating that just to make sure." Finally, participant 29 expressed the belief that LSD administered in controlled and supportive settings could be a useful treatment for alcohol misuse:

Yeah [laughs] that's a little bit embarrassing. But anyway, I really like and enjoy drinking, I just don't go and do it like every day of my life. But I can handle quite a lot of alcohol and all that. So, I enjoy it a lot. And the first time I tried the dose I was thinking oh I should have a drink on Sunday with my friends. I didn't want to see or smell any alcohol during the whole week, and I feel the same way now. So, I don't know if there's an inhibition for that after the LSD, and I think I asked you about that. So, experiencing that myself I can tell that that could be a way to solve that.

Such statements suggest that the participants believed they benefitted from the participation in the protocol.

Discussion

The objectives of the present study were to assess perceptions of safety, subjective effects, and beliefs about the clinical utility of LSD among healthy participants in a scalable intervention paradigm. In contrast to more intensive approaches with classic psychedelics (Johnson, Richards and Griffiths, 2008; Davis *et al.*, 2020), the current paradigm involved abbreviated preparation and integration, and a single attendant to assist each participant. Most of the participants (23 of 31) felt safe for the duration of their participation in this paradigm, with a minority (8 of 31) reporting concerns about having a challenging experience with LSD. Addressing the potential of challenging experiences during the pre-drug preparation period and resolving them during the acute period of drug action is a focal point in the administration of classic psychedelics to humans (Johnson, Richards and Griffiths, 2008). Consistent with this focus, those participants reporting concerns of a challenging experience reported that these concerns dissipated with time. Importantly, participants attributed their feelings of safety to the structure of the current paradigm and the emotional and practical support provided by the attendants. Consistent with a recent analysis indicating that a mental state of surrender predicts positive experience whereas preoccupation predicts adverse experience with the classic psychedelic psilocybin (Russ *et al.*, 2019), participants indicated that the study structure and attendant support allowed them to “let go” during their experience with LSD. Though some participants expressed that the study structure (8 of 31 participants) and attendant presence (7 of 31 participants) may have stifled their independence, they nevertheless acknowledged the benefit of a controlled and supportive environment in ensuring safety. These findings highlight the importance of structure and interpersonal support in the administration of classic psychedelics, and show that they can be established in a condensed and practical timeline.

With regard to subjective effects, participants reported transcendent, mystical-type experiences characteristic of classic psychedelics like LSD. Though this finding was not unanticipated, it is nonetheless critical to note because mystical experiences are believed to be a key mechanism through which classic psychedelics exert their beneficial effects. Indeed, mystical experiences might be considered a proxy for therapeutic response (Hendricks, 2018; Johnson *et al.*, 2019). These findings therefore suggest that the current intervention paradigm may hold promise of efficacy in clinical populations. Almost half of the participants (14 of 31) reported that their perception of music was among the most enjoyable aspects of the protocol. Though music has long been used in classic psychedelic-assisted psychotherapy, it remains an understudied topic. Nevertheless, emerging evidence supports the central role of music in this milieu (Barrett, Preller and Kaelen, 2018; Kaelen *et al.*, 2018). The current findings are consistent with this growing body of evidence and support the important contribution of music to the current paradigm.

Finally, participants endorsed near-universal support for the clinical utility of LSD. They reported the belief that LSD is a relatively safe drug with the potential to help others, and expressed support for additional scientific study on its clinical applications. Although participants were supportive of the clinical utility of LSD, a number emphasized caution, urging for appropriate screening of participants and administration in controlled environments similar to the current protocol. Interestingly, one participant stated that LSD-assisted treatment could be effective in treatment of alcohol misuse. This is consistent with a major line of research in the older body of LSD literature (Krebs and Johansen, 2012). In sum, these findings suggest that participants believed they benefitted from their participation, further supporting the potential efficacy of the current paradigm in clinical populations.

Results of the current research should be interpreted in light of certain limitations. Most notably, participants were healthy and did not meet criteria for any mental health conditions. It may be that individuals suffering from anxiety, mood, substance use, or other disorders require more extensive pre-drug preparation, support during the acute period of drug action, and post-drug integration. Whether the current findings generalize to clinical populations is a question for future research. Similarly, the generalizability of the current findings to less affluent Western cultural contexts, samples with larger proportions of women, and studies using larger doses of LSD requires further interrogation.

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3 These limitations notwithstanding, the current study evaluates a scalable LSD intervention paradigm, with
4 qualitative data supporting its safety as well as its potential therapeutic efficacy and clinical utility. As the intensive
5 nature of the predominant classic psychedelic-assisted treatment approach may limit its real-world implementation,
6 the current findings provide a foundation for future clinical research, with the ultimate goal of promoting broad
7 accessibility to LSD-assisted psychotherapy.
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For Peer Review

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