Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

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Original Paper

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Abstract

Assessments of lysergic acid diethylamide (LSD) in the treatment of alcoholism have not been based on quantitative meta-analysis. Hence, we performed a meta-analysis of randomized controlled trials in order to evaluate the clinical efficacy of LSD in the treatment of alcoholism. Two reviewers independently extracted the data, pooling the effects using odds ratios (ORs) by a generic inverse variance, random effects model. We identified six eligible trials, including 536 participants. There was evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI, 1.36–2.84; p = 0.0003). Between-trial heterogeneity for the treatment effects was negligible (I^2 = 0%). Secondary outcomes, risk of bias and limitations are discussed. A single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse.

Keywords

Alcoholism, alcohol-related disorders, hallucinogens, meta-analysis, psychedelics, substance-related disorders

Introduction

Alcohol is said to cause more overall harm than any other drug (Nutt et al., 2010). Alcohol contributes to about 4% of total mortality and about 5% of disability adjusted life-years to the global burden of disease (Rehm et al., 2009). Despite the often extreme individual and social consequences of alcohol misuse, many users find it challenging to stop drinking. Alcoholism, also called alcohol dependence, continues to be difficult to treat, and many patients do not achieve recovery from existing treatments (Schuckit, 2009).

Numerous clinical investigators have claimed that treating alcoholics with individual doses of lysergic acid diethylamide (LSD), in combination with psychosocial interventions, can help to prevent a relapse of alcohol misuse, for example, by eliciting insights into behavioural patterns and generating motivation to build a meaningful sober lifestyle (Dyck, 2008). LSD is well-known for inducing spectacular and profound effects on the mind (Henderson and Glass, 1994; Passie et al., 2008). It has previously been used in standard treatment programs for alcoholism at many clinics, but, unfortunately, assessments of the clinical value of LSD have not been based on formal systematic review and meta-analysis (Mangini, 1998). Hence, we have performed a quantitative evaluation of the effectiveness of LSD for alcoholism, based on data from randomized controlled clinical trials.

Methods

Search strategy and selection criteria

We searched the PubMed and PsycINFO databases (1943–2010), without language restrictions, using the following terms: *LSD, lysergic, lysergide, psychedelic**, or *hallucinogen**; and *alcohol*, addict**, or *dependence*. We independently inspected the search results by reading the titles and abstracts. We retrieved each potentially relevant publication located in the search and assessed it for inclusion, subsequently examining the reference lists of eligible studies and relevant review articles. We supplemented our search for trials by contacting experts. If publications lacked important information, we attempted to contact study investigators and institutions.

We specified inclusion and exclusion criteria and defined primary and secondary outcomes in the meta-analysis study protocol. We included randomized controlled trials of LSD for alcoholism, in which control condition involved any type of treatment, including doses of up to 50 mcg LSD as an active control. If a trial included multiple randomized treatment arms, all participants in the eligible LSD arms and all participants in the eligible control arms were pooled for analysis. We excluded participants with schizophrenia or psychosis from analysis, as psychosis is recognized as a contraindication for treatment with LSD (Johnson et al., 2008; Passie et al., 2008).

Data extraction

Both reviewers independently extracted data and rated the risk of bias of each included trial. Differences between the reviewers were resolved through discussion. The following were recorded

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from each trial where available: intervention characteristics (LSD dose, control condition, additional treatments); participant characteristics (number, gender, age, inclusion and exclusion criteria); information given to the participants on the study and the effects of LSD; trial characteristics (publication year, location, funding source); outcomes (primary and secondary outcomes, time of follow-up, method of outcome assessment); evaluation of each domain of the Cochrane risk of bias assessment tool (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting) (Higgins and Altman, 2008). Primary outcomes were alcohol misuse, defined as alcohol use or consequences of alcohol use, as systematically measured by interview or self-report at the first reported follow-up. Secondary outcomes were alcohol misuse at short-term (approximately 3 months), medium-term (approximately 6 months) and long-term (approximately 12 months) follow-up. We also extracted data on abstinence, reports of adverse events and any other secondary outcomes.

Data analysis

Categorical data on alcohol misuse were dichotomized into 'improved' or 'not improved'. We counted as 'improved' outcome categories indicating clear, substantial improvement in alcohol misuse. Dichotomous and continuous outcome data were pooled using the generic inverse variance method with a random effects model. We calculated the effects of intervention results with estimates of pooled odd ratios (ORs) and 95% confidence intervals (CI) using Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration). The percentage of outcome heterogeneity attributable to between-trial heterogeneity was assessed by the I^2 statistic. Participants lost to follow-up were counted as not improved. In a post hoc analysis of trials with available dichotomized data, we calculated the pooled benefit difference on improvement in alcohol misuse at first follow-up and also calculated the number needed to treat. The benefit difference (also known as the risk difference) for each trial is the percentage of improved patients in the LSD group minus the percentage of improved patients in the control group. The number needed to treat is the inverse of the pooled benefit difference and provides an estimate of the average number of patients needed to be treated with LSD rather than without LSD to achieve one additional patient with improved outcome on alcohol misuse.

Results

Description of studies

We identified six eligible randomized controlled trials (Bowen et al., 1970; Hollister et al., 1969; Ludwig et al., 1969; Pahnke et al., 1970; Smart et al., 1966; Tomsovic and Edwards, 1970), including additional reports on three of the trials (Kurland et al., 1971; Ludwig et al., 1970; Smart et al., 1967). Details of the search are shown in Figure 1, details of the included studies are shown in Tables 1 and 2. Among the excluded studies were five non-randomized controlled trials (Ables and Eng, 1967; Ables et al., 1970; Jensen, 1962; Jensen, 1963; Van Dusen et al., 1967), one quasi-randomized controlled trial (allocation by alternating assignment) (Osmond et al., 1967), two randomized controlled trials without any outcome data related to alcohol use (both measured only general psychological variables) (Denson and Sydiaha, 1970; Ditman et al., 1970), and one randomized controlled trial without extractable outcome data on alcohol misuse (this trial reported only 'no statistically significant difference' between LSD and control groups on alcohol misuse at 12 months follow-up) (Johnson, 1969).

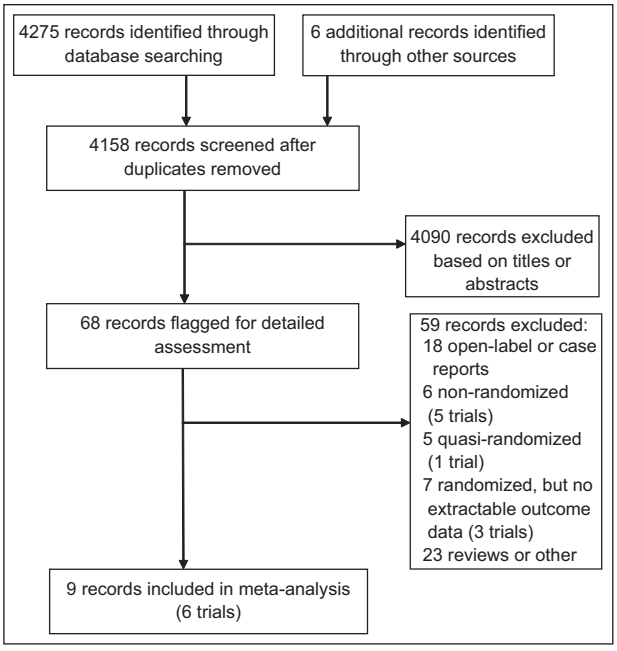

Figure 1. Selection of trials for meta-analysis.

The six eligible trials included a total of 536 adults; of these 325 (61%) had been randomly assigned to receive full-dose LSD and 211 (39%) to a control condition. Participants were male inpatients, except for two females and a small number of day-care patients in one of the trials (Smart et al., 1966). All participants were seeking treatment for 'alcoholism' as their primary problem and had been admitted to alcohol-focused treatment programs before clinical trial recruitment, see Table 1. Note, the DSM-I defined alcoholism as a 'well established addiction to alcohol without recognizable underlying disorder' (American Psychiatric Association, 1952).

Among the reported exclusion criteria, trials excluded potential volunteers with 'psychiatric complications' (Bowen et al., 1970), with a 'past history of schizophrenic reaction or severe affective disorder' (Hollister et al., 1969), or overt psychosis (Ludwig et al., 1969; Smart et al., 1966; Tomsovic and Edwards, 1970). One trial included a subgroup of patients with schizophrenia (Tomsovic and Edwards, 1970), which we excluded from the meta-analysis. Two trials included additional non-randomized control groups or non-randomized sub-studies, which we also excluded from the meta-analysis (Bowen et al., 1970; Tomsovic and Edwards, 1970).

Single oral doses of LSD ranged from approximately 210 mcg (3 mcg/kg) to 800 mcg, with a median dose of 500 mcg, see Table 1. No studies used multiple doses of LSD. The control conditions included low-dose LSD (25 mcg or 50 mcg), d-amphetamine (60

Table 1. Included randomized controlled trials of LSD for alcoholism.

	LSD (*n*)	Control (*n*)	Blinding of patients, staff, outcome assessors	Participant characteristics[a]	Age (years)	Alcohol misuse outcome, criteria for improvement (months follow-up)	Retention at first follow-up	Location (Funding)
Smart et al., 1966	800 mcg (10)	60 mg ephedrine sulfate (10) or no drug (10)	Double-blind, independent assessors	Male and female alcoholics, 'all had a long history of excessive and uncontrolled drinking'	Median 38.5, range 26–59	Drinking History Questionnaire, % change in time abstinent, continuous (6 mo)	100%	ARF, Toronto, Canada (NR)
Hollister et al., 1969	600 mcg (36)	60 mg d-amphetamine (36)	Double-blind, independent assessors	Male veterans, 'acute alcoholic episode' within 2 weeks of admission, 'all were problem drinkers'	Median 45, range 31–51	Drinking Behaviour Interview, score ≤ 10, 'Abstinent' or 'Social' drinking (2, 6 mo)[b]	81% LSD; 64% control	VA Hospital, Palo Alto, CA, USA (NIMH)
Ludwig et al., 1969	3 mcg/kg, ~210 mcg (132)	No drug, sit alone and write for 3 hr (44)	Double-blind until LSD session, independent assessors	Male alcoholics, up to four previous admissions for treatment of alcoholism	Range 21–55	Abstinence (1, 3 mo); Behavior Rating Scale, change score ≥ 5, 'Much improved' (6, 12 mo)[b]	100%	MSH, Madison, WI, USA (NIMH)
Bowen et al., 1970	500 mcg (22)	25 mcg LSD (22)	Double-blind, not stated if assessors independent[c]	Male veterans, voluntarily applied for treatment of alcoholism	Median 44.5	Adjustment Scale, score ≥ 6, 'Good adjustment' (12 mo)	100%	VA Hospital, Topeka, KS, USA (NR)
Pahnke et al., 1970	450 mcg (73)	50 mcg LSD (44)	Double-blind, independent assessors	Male alcoholics, voluntarily applied for treatment of alcoholism	NR	Drinking Behaviour Scale, score ≥ 8, 'Minimal departure from total abstinence' (6, 12 mo)	88% LSD; 91% control	MPRC, Baltimore, MD, USA (NIMH)
Tomsovic & Edwards, 1970	500 mcg (52)	Treatment as usual (45)	Double-blind until LSD session, self-report assessment[c]	Male alcoholics, average 12 years of problem drinking	Mean 43	Drinking Adjustment Scale, no more than 1 drinking episode in follow-up period, 'Much improved' (3, 6, 12 mo)[b]	92% LSD; 73% control	VA Hospital, Sheridan, WY, USA (VA)

ARF: Alcoholism and Drug Addiction Research Foundation; MPRC: Maryland Psychiatric Research Center; MSH: Mendota State Hospital; NIMH: National Institute of Mental Health; NR: not reported; VA: Veterans Administration.

[a]All participants were recruited after admission to alcoholism treatment programs.

[b]Provided data on abstinence from alcohol.

[c]Assessment also included interview of close relative.

mg), ephedrine sulphate (60 mg), or non-drug control conditions, see Table 1.

Before the experimental drug session, all participants had equivalent treatment within each trial; however, between the trials the preparation for the experimental drug session varied from minimal to extensive, with most studies providing brief orientation, often with little or no description of the possible effects of LSD. During the experimental drug session, the most common treatment was simple observation with brief reassurance by clinic staff, only three studies included treatment groups who received clinical interviews, psychotherapy, or active guidance. In four studies, the experimental drug session took place in comfortable surroundings with music available. After the experimental drug session, only one study included multiple review sessions focused on discussing the experiences during the drug session, while the other studies provided only one brief review session or no review session at all. See Table 2 and the original study publications for details of the treatment protocols.

Each trial used clearly defined, standardized methods to assess outcomes on alcohol misuse, although methods varied between trials, see Table 1. Extracted dichotomous or categorical outcomes included maintained abstinence from alcohol, alcohol use rating scales, or composite alcohol use and social adjustment rating scales; the one continuous outcome was percentage change in time abstinent from alcohol. Based on examining each categorical scale, outcome categories labelled 'slight or questionable' (Tomsovic and Edwards, 1970), 'moderate' (Ludwig et al., 1969), or 'fair' (Bowen et al., 1970) were counted as 'unimproved'; however, note that including these outcome categories indicating possibly trivial improvement as 'improved' does not substantially change the results.

Effect of LSD on alcohol misuse

The pooled odds ratio on improvement in alcohol misuse between the LSD and control groups was 1.96 (95% CI, 1.36–2.84; $p = 0.0003$) at the first reported follow-up, see Figure 2. Among the five trials with dichotomized data, 185 of 315 (59%) LSD patients and 73 of 191 (38%) control patients were improved at the first reported follow-up, and the pooled benefit difference was 16% (95% CI, 8%–25%; $p = 0.0003$), or, equivalently, the number needed to treat is six. Including an estimated dichotomized outcome for the one trial that reported only continuous outcome data

Table 2. Details of treatment programs in included trials of LSD for alcoholism.

	Treatment program (approximate length in days)	Preparation for LSD session	Treatment during experimental session	Setting of experimental session room	Aftercare related to experimental session
Smart et al., 1966	Individual and group therapy within a therapeutic community	Brief orientation; not told name of LSD nor that an active control drug was used	3 h interview, followed by occasional observation	No music or visual stimuli; all patients strapped to bed by waist belt	One follow-up review session with interviewer
Hollister et al., 1969	Brief counselling on alcohol misuse; focus on alcohol withdrawal (7)	Brief orientation; not told name of LSD nor that an active control drug was used	Brief supportive reassurance; emphasis on self-examination	Music, comfortable furniture	None mentioned; discharged within 48 hours; overall 'little or no specific psychotherapy'
Ludwig et al., 1969	Highly structured intensive milieu therapy, including group therapy (30)	Brief orientation; minimal discussion of LSD effects	3 h (a) psychotherapy, (b) hypnosis + psychotherapy, or (c) silent observation, followed by occasional observation	Not described	No follow-up with experimental session therapist
Bowen et al., 1970	Interpersonal skill training in groups (60)	Several group orientation lectures on LSD effects	Supportive reassurance; emphasis on non-verbal introspection	Music, flowers, pictures, 'tasteful furniture', two quiet rooms	None mentioned
Pahnke et al., 1970	Intensive individual psychotherapy (49)	Extensive individual preparation for LSD	Guidance aimed at eliciting a 'peak or transcendental experience'	Music, flowers, pictures, 'comfortable living room'	Multiple follow-up review sessions
Tomsovic & Edwards, 1970	Group psychotherapy (90)	Lecture and reading material; review of problems and treatment intentions	Supportive reassurance; not encouraged to talk extensively	Music, flowers, pictures, scenic view, quiet room	One follow-up review session in group therapy

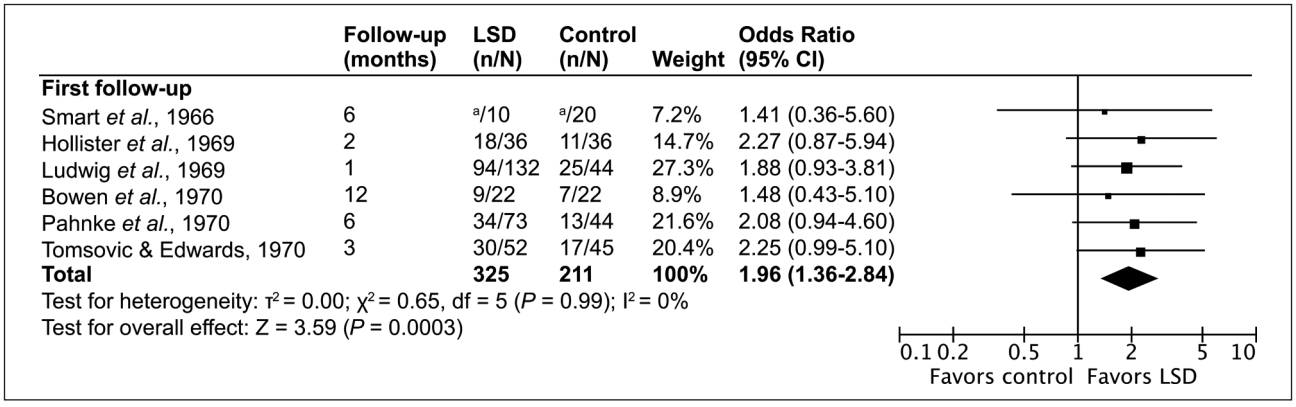

Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.
[a]Continuous outcome data.

does not change the calculated pooled benefit difference or number needed to treat.

There was a significant beneficial effect of LSD on alcohol misuse in the short-term and medium-term, which was not statistically significant in the long-term, see Figure 3. At short-term follow-up (2–3 months post-treatment), three trials reported treatment response, and the pooled odds ratio between the LSD and control groups was 1.85 (95% CI, 1.14–3.00; $p = 0.01$). At medium-term follow-up (6 months post-treatment), five trials reported treatment response, and the pooled odds ratio between the LSD and control groups was 1.66 (95% CI, 1.11–2.47; $p = 0.01$). At long-term follow-up (12 months post-treatment), four trials reported treatment response, and the pooled odds ratio between the LSD and control groups was 1.19 (95% CI, 0.74–1.90; $p = 0.47$).

Heterogeneity of the between-trial treatment outcome was negligible in the pooled comparisons for alcohol misuse at the first reported follow-up, short-term follow-up and medium-term follow-up ($I^2 = 0\%$, for all $p \geq 0.60$ for the χ^2 test), and heterogeneity was low at long-term follow-up ($I^2 = 15\%$, $p = 0.32$ for the χ^2 test).

Effect of LSD on abstinence from alcohol

Among the three trials that reported maintained abstinence from alcohol use, there was a beneficial effect of LSD at the first reported

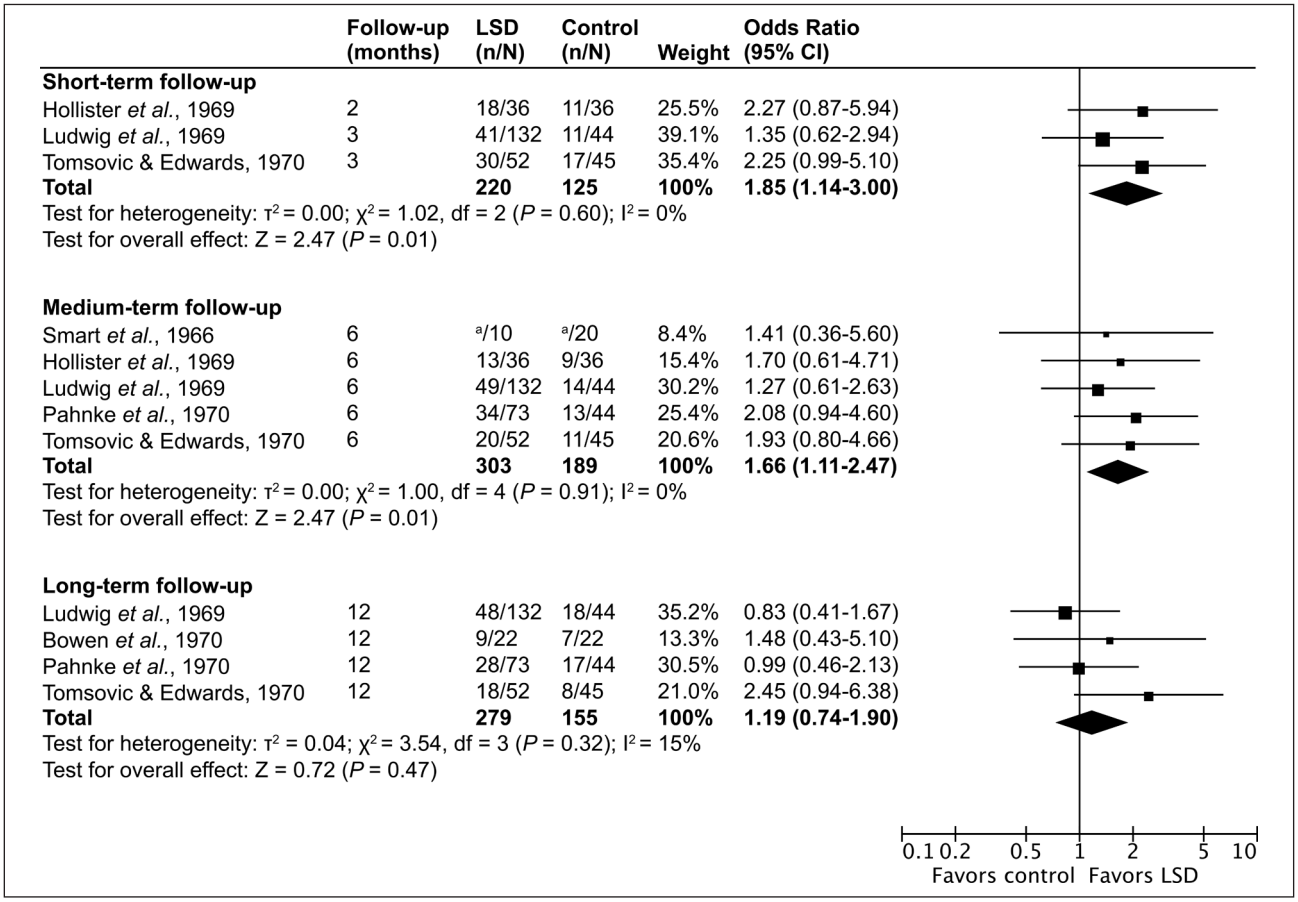

Figure 3. Improvement in alcohol misuse at short-, medium- and long-term follow-up after LSD versus control treatments.
[a]Continuous outcome data.

follow-up (1–3 months post-treatment) (OR, 2.07; 95% CI, 1.26–3.42; $p = 0.004$) and short-term follow-up (2–3 months post-treatment) (OR, 1.80; 95% CI, 1.07–3.04; $p = 0.03$), which was not statistically significant at medium-term follow-up (6 months post-treatment) (OR, 1.42; 95% CI, 0.65–3.10; $p = 0.38$), see Figure 4.

Heterogeneity of the between-trial treatment outcome was negligible in the pooled comparisons for abstinence at first reported follow-up and short-term follow-up ($I^2 = 0\%$, for both $p \geq 0.38$ for the χ^2 test), while heterogeneity was moderate at medium-term follow-up ($I^2 = 44\%$, $p = 0.41$ for the χ^2 test).

Adverse events

Five trials reported a total of eight acute adverse reactions to LSD, without any lasting harmful effects. Trial investigators did not specifically mention whether there were adverse events among participants in the control conditions. During the LSD experience, two people 'acted bizarrely' (Tomsovic and Edwards, 1970), one person became agitated (Hollister et al., 1969), another person had a grand mal seizure during a period of agitation (this patient had a history of alcohol withdrawal seizures and had been abstinent from alcohol for only a few days) (Hollister et al., 1969) and two people had unspecified 'adverse reactions' (Ludwig et al., 1969). In the days after LSD, one person experienced transient 'moderate confusion' (Hollister et al., 1969) and one person had a transient 'adverse reaction' (Pahnke et al., 1970). Additionally, investigators in one trial reported mild adverse reactions to LSD in a small number of participants, including nausea, vomiting and 'moderate agitation' that was relieved by social support, relaxation, or changing the lights and music (Hollister et al., 1969). Furthermore, in one trial, about a third of the participants who received LSD reported briefly experiencing 'any perceptual thought or feeling experience which impressed the patient with its vividness and which was clearly related to the [LSD] experience' on one or a few occasions within a year after LSD, typically after using alcohol (Tomsovic and Edwards, 1970), while participants in another trial specifically did not mention such experiences at follow-up (Hollister et al., 1969).

Other outcomes

Other reported trial outcomes were difficult to assess and summarize in detail, owing to large variation in the approaches between the trials and lack of data for statistical analysis. However,

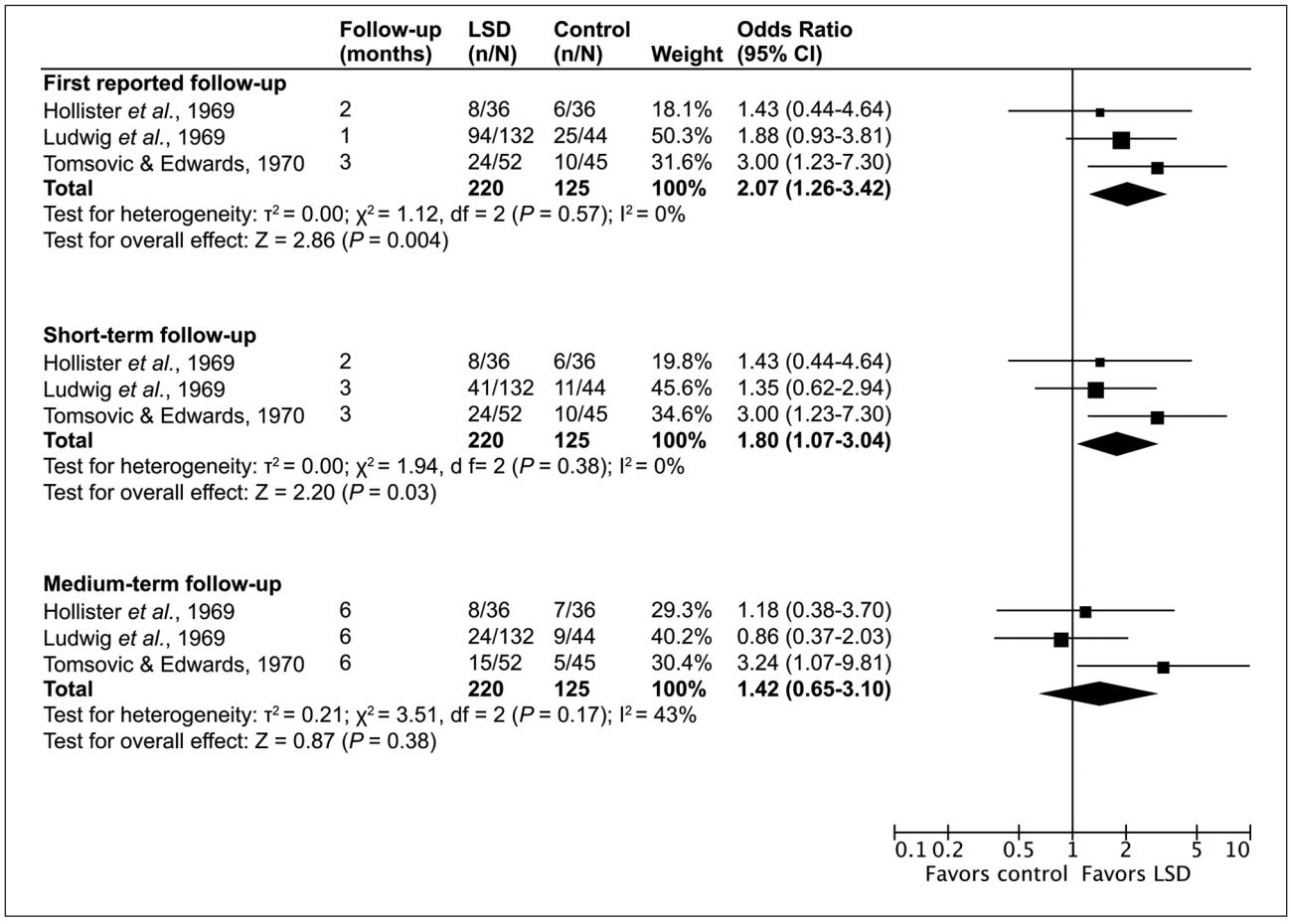

Figure 4. Maintained abstinence from alcohol after LSD versus control treatments.

no trials reported any detrimental effects of LSD on psychosocial functioning or other outcomes. Of note, two of the three trials that reported data on employment found statistically significant improvements in employment in participants who received LSD compared to those assigned to control conditions (Hollister et al., 1969; Smart et al., 1966) but not Ludwig et al., (1969).

Risk of bias

Based on the definitions from the Cochrane risk of bias assessment tool (Higgins and Altman, 2008), no trials were judged to have a high risk of bias related to sequence generation or allocation concealment. All trials used random assignment and attempted to conceal allocation; however, most trials did not describe methods in detail. Two trials were judged to have a high risk of bias due to inadequate blinding of patients or staff because treatment allocation was concealed only until the time of the possible LSD session (Ludwig et al., 1969; Tomsovic and Edwards, 1970); the other four trials used double-blind designs with active placebos. All trials were judged to have low or an unclear risk of bias due to blinding of outcome assessment; in four trials outcome was assessed by treatment-independent, allocation-blind interviewers (Hollister et al., 1969; Ludwig et al., 1969; Pahnke et al., 1970; Smart et al., 1966), in one trial the outcome assessor was not explicitly described as allocation-blind (Bowen et al., 1970) and in the remaining trial outcome assessment was collected by self-report questionnaire, confirmed by telephone interview with a close relation (Tomsovic and Edwards, 1970). Two trials were judged to have a high risk of bias due to incomplete outcome data because participants were excluded if they did not complete the intended treatment program (Bowen et al., 1970) or if they received additional doses of LSD (Pahnke et al., 1970). Retention rates were generally high, see Table 1, but two studies had substantial rates of missing participants at follow-up (Hollister et al., 1969; Tomsovic and Edwards, 1970). However, authors of both of these trials expressed that missing participants had probably relapsed to problem alcohol use, consistent with the strategy of considering missing participants as unimproved. Two trials were judged to have a high risk of bias because of possible selective outcome reporting (Hollister et al., 1969; Ludwig et al., 1969); both of these trials de-emphasized evidence for a treatment effect at short-term follow-up and gave more detailed outcome data on alcohol misuse at medium-term or late-term follow-up; note, we were not able to obtain the protocol for any of the trials. One trial was judged to have a high risk of bias due to baseline imbalance (Pahnke et al., 1970); in this trial, participants who received full-dose LSD were less likely than control participants to be divorced, and more likely to have four or less prior admissions for alcohol treatment, or to have graduated from high-school. Importantly, however, also in this trial the treatment groups were matched on baseline ratings of alcohol misuse.

Table 3. Data from recent meta-analyses of randomized controlled clinical trials on the effectiveness of LSD, naltrexone, acamprosate and disulfiram for alcoholism or alcohol dependence.

Outcome	LSD, single dose		Naltrexone, daily		Acamprosate, daily		Disulfiram, daily	
	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT
Improvement on alcohol misuse, or return to heavy drinking	16% (8%, 25%)	6	11% (7%, 15%)	9	1% (-2%, 5%)	100	Not reported	
Maintained abstinence, or return to any drinking	15% (4%, 25%)	7	3% (1%, 6%)	33	11% (7%, 15%)	9	11% (-1%, 22%)	9

LSD outcomes are at first follow-up after single dose and are compared to no drug or active placebo. Naltrexone and acamprosate outcomes are during daily drug treatment and are compared to placebo. Disulfiram outcomes are during daily unsupervised drug treatment and are compared to other or no treatment. Data on naltrexone, acamprosate and disulfiram extracted from published meta-analyses (Rösner et al., 2010a, 2010b; Krampe and Ehrenreich, 2010). Pooled benefit differences calculated using a random-effects, inverse variance method. Benefit difference = % patients with beneficial outcome in experimental – % patients with beneficial outcome in control. Number needed to treat (NNT) = 1/(benefit difference).

Sensitivity analysis

For the primary outcome, improvement on alcohol misuse at first follow-up, the beneficial effect of LSD remained statistically significant ($p \leq 0.02$) when excluding any two of the four larger trials, with or without excluding either or both of the two smaller trials. In a series of post hoc sensitivity analyses, excluding all trials with a high risk of bias on each domain of the Cochrane risk of bias assessment tool did not substantially change the primary outcome. In particular, the effect of LSD increased and remained significant when we excluded the two trials that used non-blinded control conditions without an active placebo. Furthermore, the primary outcome did not change when we limited analysis to the four trials reporting outcome specifically on alcohol use, rather than composite scores of alcohol use and social functioning, or when we excluded the two trials with lower retention rates.

The findings on secondary outcomes of alcohol misuse at short-term and medium-term follow-up and abstinence at first and short-term follow-up are more sensitive to removing trials. In particular, none of the secondary outcomes remain statistically significant ($p \geq 0.06$) after removing the trial with the most favourable effect of LSD in each respective analysis. Note that the analyses of secondary outcomes are based on only three to five trials each.

Discussion

In a pooled analysis of six randomized controlled clinical trials, a single dose of LSD had a significant beneficial effect on alcohol misuse at the first reported follow-up assessment, which ranged from 1 to 12 months after discharge from each treatment program. This treatment effect from LSD on alcohol misuse was also seen at 2 to 3 months and at 6 months, but was not statistically significant at 12 months post-treatment. Among the three trials that reported total abstinence from alcohol use, there was also a significant beneficial effect of LSD at the first reported follow-up, which ranged from 1 to 3 months after discharge from each treatment program.

The findings from randomized controlled trials of a sustained treatment effect of a single dose of LSD on alcohol misuse, which may fade within 12 months, are consistent with many reports of clinical experience and with data from most non-randomized controlled and open-label studies of LSD for alcoholism (reviewed in Mangini (1998)). In particular, a quasi-randomized trial reported beneficial effects of LSD on alcohol misuse at 3 months post-treatment (Osmond et al., 1967). Additionally, four non-randomized controlled studies reported beneficial effects of LSD on alcohol misuse at follow-up periods ranging from 6 to 18 months. However, these studies were poorly described (Ables and Eng, 1967; Ables et al., 1970; Jensen, 1962; Jensen, 1963). Also consistent with our findings, three controlled studies, excluded from this meta-analysis because the control groups were non-randomized (Bowen et al., 1970; Van Dusen et al., 1967) or because of lack of extractable data (Johnson, 1969), reported no significant treatment effect of a single dose of LSD on alcohol misuse at 12 to 18 months follow-up. Importantly, in the Bowen et al. (1970) and Van Dusen et al. (1967) studies, the comparison group did not volunteer to possibly receive LSD, probably creating selection bias (see, for example, Ditman et al. (1970) on differences between alcoholics who volunteer and those who decline to participate in an LSD study), and in the Johnson (1969) study all patients were administered the tranquilizer chlorpromazine during the acute LSD effects, probably attenuating the LSD effects. Additionally, in a randomized controlled trial of a single dose of LSD for heroin addiction, daily urine test data covering the entire follow-up period showed a significantly lower rate of relapse in the LSD group compared to no drug group at 3, 6, 9 and 12 months post-treatment (Savage and McCabe, 1973).

Given the evidence for a beneficial effect of LSD on alcoholism, it is puzzling why this treatment approach has been largely overlooked. Based on reviewing the literature, we have four suggestions for why this happened. First, the randomized controlled trials were underpowered and most did not reach statistical significance when considered individually. Second, trial authors expected unrealistic results and tended to discount moderate or short-term effects. Third, early non-randomized clinical trials were poorly described and had methodological problems, creating the mistaken impression that well-designed studies did not exist. Finally, the complicated social and political history of LSD led to increasing difficulties in obtaining regulatory approval for clinical trials (reviewed in Mangini (1998)).

The effectiveness of a single dose of LSD compares well with the effectiveness of daily naltrexone, acamprosate, or disulfiram (Krampe and Ehrenreich, 2010; Rösner et al., 2010a, 2010b), see Table 3 for data from recent meta-analyses of these three commonly prescribed, approved medications for reducing relapse in alcohol dependence.

Regarding the effects of the LSD experience, investigators of one trial noted, 'It was rather common for patients to claim significant insights into their problems, to feel that they had been given a new lease on life, and to make a strong resolution to discontinue their drinking' (Ludwig et al., 1969). Investigators of another trial noted, 'It was not unusual for patients following their LSD experience to become much more self-accepting, to show greater openness and accessibility, and to adopt a more positive, optimistic view of their capacities to face future problems' (Bowen et al., 1970). The subjective effects and neurobiological mechanisms of LSD are similar to other psychedelic substances such as mescaline (contained in peyote and other psychedelic cactus), psilocybin (magic mushrooms) and dimethyltryptamine (ayahuasca) that have been used by humans for thousands of years (Bruhn et al., 2002; McGlothlin, 1964), and in clinical studies the effects of psychedelics are often regarded as highly valued and meaningful (Griffiths et al., 2006; Grob et al., 2011; Studerus et al., 2011). Regular consumption of peyote and ayahuasca have been claimed by indigenous groups to be helpful in maintaining sobriety from alcohol and other addictive drugs (Albaugh and Anderson, 1974; Fábregas et al., 2010).

Estimates of the rate of adverse events of LSD in alcoholics and others should include data from non-randomized as well as randomized trials. Based on extensive animal research and human experience, there is now widespread recognition that LSD and similar psychedelic substances are physically safe, but acute psychiatric adverse events such as anxiety and confusion should be anticipated, and LSD administration should occur in a comfortable environment with informed participants (Johnson et al., 2008; Passie et al., 2008).

Several matters in this meta-analysis deserve discussion. First, trials typically lacked detailed descriptions of the populations studied, including diagnosis methods. However, all participants were recruited into the trials after admission to alcohol treatment programs with a primary diagnosis of alcoholism, making it likely that the patients are representative of typical clinical practice. Second, there were not enough trials to examine the effect of LSD dose or other treatment variables; all of the trials used a high or very high dose of LSD and employed different treatment frameworks. Third, it is possible that additional randomized controlled trials were never published or were missed by our literature search. Fourth, three trials either concealed that LSD might be used (Hollister et al., 1969; Smart et al., 1966) or gave very little information about its likely effects (Ludwig et al., 1969), and in two of these trials participants were left alone in a room during much of the LSD effects (Ludwig et al., 1969; Smart et al., 1966); including people who might be reluctant to participate in a trial of LSD or who were unprepared for the LSD effects may have attenuated the treatment effect and increased the risk of adverse events. Fifth, blinding is a common problem to clinical trials of active interventions, including most pharmacological and behavioural treatments; most trials included in this meta-analysis attempted to minimize risks of bias related to blinding by using active placebos and/or using explicitly treatment-independent, allocation-blind interviewers for outcome assessment. However, the use of low-dose LSD as an active placebo in two of the trials may have attenuated the between-group treatment effect. Finally, primary outcome measures on improvement in alcohol misuse varied between trials; however, all of the clinical trials used standardized questionnaires. Additionally, three trials also reported data on the same clearly-defined outcome: maintained abstinence from alcohol use.

It is uncommon for a psychiatric drug to have a positive treatment effect for months after a single dose. Indeed, investigators of one LSD trial noted, 'most alcoholics report a waning of the initial inspiration, euphoria, and good intentions gleaned from the LSD experience when they are again confronted with the former stresses and difficulties in their lives' (Bowen et al., 1970). As suggested by many investigators, repeated doses of LSD – for example weekly or monthly – might elicit more sustained effects on alcohol misuse than a single dose of LSD (Bowen et al., 1970; Osmond et al., 1967; Savage and McCabe, 1973; Smart et al., 1966). We need further data on whether subgroups of individuals exist for whom LSD present an increased beneficial effect or risk for adverse events. Future clinical trials could combine a range of doses of LSD with current evidence-based alcohol relapse prevention treatments. As an alternative to LSD, it may be worthwhile to evaluate shorter-acting psychedelics, such as mescaline, psilocybin, or dimethyltryptamine.

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