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

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CRD summary

This review found that one dose of lysergic acid diethylamide (LSD) had statistically significant short-term benefits, in decreasing alcohol misuse and improving alcohol abstinence, in patients with alcoholism, but these were not maintained at one year. The authors' cautious conclusions are likely to be reliable, but might not be generalisable from the 1960's to today's clinical populations.

Authors' objectives

To evaluate the effectiveness of lysergic acid diethylamide (LSD) in the treatment of alcoholism.

Searching

PubMed and PsycINFO were searched for relevant studies, from 1943 to 2010, in any language; search terms were reported. The references lists of the included studies and review articles were checked, and experts were contacted, to identify additional studies.

Study selection

Eligible for inclusion were randomised controlled trials of LSD, compared with any treatment, including active control doses of up to 50 micrograms (mcg) of LSD, in patients with alcoholism. Studies of patients with schizophrenia or psychosis were excluded.

Most of the included trials were conducted in the USA; one was conducted in Canada. All the trials were published between 1966 and 1970. Where reported, the age of the patients ranged from 21 to 59 years. The treatment programmes ranged in duration from seven to 90 days, and involved individual or group therapy or both. One trial was conducted within a therapeutic community. During exposure to a dose of LSD, patients were observed; or given supportive reassurance for self-examination or introspection, psychotherapy, or guidance aimed at attainment of transcendental experiences. The dose of LSD ranged from 210 to 800mcg in the intervention groups. Comparators were treatment as usual, ephedrine (60mg) d-amphetamine (60mg) and LSD at doses of 25 or 50mcg.

The primary outcomes were alcohol misuse, defined as alcohol use or consequences of alcohol use, measured by interview or self-report at the first follow-up. Secondary outcomes were alcohol misuse at short term (approximately three months), medium term (approximately six months) and long term (approximately 12 months). Other outcomes were abstinence, reports of adverse events, and other non-specified secondary outcomes.

Both reviewers independently selected the studies.

Assessment of study quality

Two reviewers independently assessed the methodological quality of the included trials, using the Cochrane risk of bias tool. This had criteria for sequence generation, allocation concealment, blinding, treatment of incomplete outcome data, and selective outcome reporting.

Data extraction

The data were extracted by both reviewers independently to calculate odds ratios, and 95% confidence intervals. Trial authors or institutions were contacted for missing data, where necessary.

Methods of synthesis

Pooled odds ratios and 95% confidence intervals were calculated, using a random-effects model. The presence of statistical heterogeneity was assessed using I^2. The numbers-needed-to-treat for benefit were calculated.

Results of the review

Six randomised controlled trials, with 536 patients, were included in the review. Patients who were lost to follow-up were treated as "not improved". All the trials reported randomisation and attempts to conceal allocation. Two trials were judged to have a high risk of bias due to inadequate blinding of patients and staff, two had incomplete outcome data, and two had selective outcome reporting. One trial was judged to have a high risk of bias due to baseline imbalances between groups. Follow-up in the trials ranged from three to 12 months.

With LSD there were significant benefits for alcohol use and misuse at the first available follow-up (OR 1.96, 95% CI 1.36 to 2.84; I^2=0; six trials), at two or three months after treatment (OR 1.85, 95% CI 1.14 to 3.00; I^2=0; three trials), and at six months follow-up (OR 1.66, 95% CI 1.11 to 2.47; I^2=0; five trials). There were no significant benefits, with LSD or control, for alcohol misuse at 12 months (I^2=15%; four trials).

There were statistically significant benefits with LSD, compared with control, for the maintenance of abstinence from alcohol use, at the first reported follow-up (OR 2.07, 95% CI 1.26 to 3.42; I^2=0; three trials), and at short-term follow-up (OR 1.80, 95% CI 1.07 to 3.04; I^2=0; three trials), but not at medium-term follow-up (I^2=43%; three trials).

Sensitivity analyses found that the beneficial effects of LSD at first follow-up remained statistically significant when the following trials were excluded: any two of the four larger trials; trials with high risks of bias on each domain of the quality assessment; and two trials with lower retention rates; as well as when the analysis was restricted to outcomes that were specific to alcohol use.

Five trials reported a total of eight acute adverse events, which included a seizure, moderate confusion and agitation, nausea, vomiting, and acting in a bizarre fashion.

Authors' conclusions

One dose of LSD had significant benefits at the short-term follow-up, but the benefits were not maintained at longer follow-up times of 12 months after treatment.

CRD commentary

The review addressed a clear question and the criteria for the inclusion of trials were outlined. Two appropriate databases were searched, for relevant trials, with no language restrictions, and some attempts were made to identify unpublished studies, reducing the risk of publication bias. Steps were taken to minimise errors and bias at each stage of the review process. Trial quality was assessed, using validated methods, and the included trials were of medium quality.

The authors' decision to combine the results in a meta-analysis appears to have been justified; there was minimal statistical heterogeneity for the primary outcomes. Trial quality was used to explore the results in appropriate sensitivity analyses. The included trials were conducted between 1966 and 1970, which may have affected the reporting of the methods of the trials and it might not be possible to generalise these results to similar populations with alcoholism, because of the differences in health care systems, treatment and research methods. The authors outlined the limitations of their review, which were the limited descriptions of the enrolled patients and the risk of publication bias.

The review was generally well conducted and the authors' cautious conclusions are likely to be reliable, but they might not be generalisable to today's clinical populations.

Implications of the review for practice and research

Practice: The authors stated that LSD and similar psychedelic substances were physically safe, but acute psychiatric events, such as anxiety and confusion, should be anticipated and it should be administered to informed patients, in a comfortable environment.

Research: The authors stated that further clinical trials should investigate a range of doses of LSD combined with evidence-based alcohol relapse prevention treatments. Shorter-acting psychedelics, such as mescaline, psilocybin (magic mushrooms) or dimethyltryptamine, should be investigated. Trials should assess if subgroups exist for whom these treatments have more benefit or greater risk of adverse events.

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