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

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Journal of Psychopharmacology: 2012, 26(7), p. 994–1002.

Could a single LSD trip precipitate such a radical re-evaluation of their lives that it proves a turning point for dependent drinkers? According to this synthesis of the research, across six randomised trials it can and it has, and the results rival approved medications. Nevertheless, LSD seems unlikely to be welcomed in to the alcohol treatment pharmacopeia.

Summary Numerous clinical investigators have claimed that treating alcoholics with individual doses of the powerful hallucinogenic drug lysergic acid diethylamide (LSD) can (combined with psychosocial interventions) help prevent relapse to alcohol misuse, for example, by eliciting insights into one's behaviour patterns and generating motivation to build a meaningful, sober lifestyle. In the past many clinics used it as part of their treatment programmes for alcoholism, but assessments of its clinical value have not been based on formal systematic review and meta-analytic amalgamation of findings. The featured review aimed to fill this gap by synthesising alcohol outcomes from trials which randomly allocated alcohol-dependent patients to LSD versus an alternative or control treatment.

A search identified six relevant trials involving 536 patients (325 of whom were administered full-strength LSD), almost exclusively men and nearly all treated as inpatients. All had been seeking treatment for alcoholism and been admitted to alcohol treatment programmes before being recruited to the trials. Results from the trials were published between 1966 and 1970. All but one was conducted in the USA; the remaining trial was from Canada. All administered a single full dose of LSD, effects of which were variously compared with low-dose LSD, d-amphetamine, ephedrine sulphate, or non-drug control conditions. Four of the six trials disguised both from patients and from clinicians whether full-dose LSD or an alternative had been administered to any particular patient.

Preparation for the LSD/control session varied from minimal to extensive; most studies provided a brief orientation, often with little or no description of the possible effects of LSD. During the session, commonly clinic staff simply observed patients and offered brief reassurance, though three studies conducted clinical interviews, psychotherapy, or offered guidance on making the most of the experience. Usually the session took place in comfortable surroundings with music available. Only in one study was the focal session extensively followed up by several sessions to discuss the patient's experiences.

Main findings

Across the six trials the analysts calculated the numbers of patients who after the session experienced clear and substantial remission in problem drinking, assuming that patients not followed up had not improved. At the trials' first follow-ups (two to 12 months after dosing), together there was a large and statistically significant advantage for patients administered full-strength LSD; across five of the trials it could be calculated that 59% of LSD patients had improved versus 38% of control patients. A substantial and significant advantage for LSD was also apparent at follow-ups two to three months after dosing and six months after, but by 12 months the gap was no longer statistically significant. Until the 12-month point, the trials were broadly consistent in the degree to which their results favoured LSD.

Three trials also reported whether patients sustained abstinence from drinking. Across these trials, up to three months after the treatments substantially and significantly more LSD patients had sustained abstinence, but by six months this advantage had faded and was no longer statistically significant. Until this final point, again the trials were consistent in the degree to which their results favoured LSD.

Eight acute adverse reactions were noted among the 325 patients administered full-strength LSD, including 'bizarre' behaviour and agitation and one grand mal seizure in a recently detoxified patient with a history of alcohol withdrawal seizures. Though no lasting harm was noted, there were a few transient adverse experiences in the following days and in one trial about a third of the participants said they had flashback-type experiences [Editor's note: none recorded as seriously distressing] during the year after taking the LSD, typically after drinking. Two of the three trials that reported this data found that significantly more LSD than control patients were later in employment.

Excluding trials which did not hide whether patients were given LSD did not materially affect the results, nor did other ways of restricting the analysis to the higher quality trials and the more specific alcohol outcome data.

The authors' conclusions

In a pooled analysis of six randomised controlled clinical trials, a single dose of LSD had significant beneficial effects on problem drinking and on abstinence, both of which were no longer statistically significant respectively 12 and six months after the drug had been taken. These findings are consistent with clinical experience and with data from less well controlled studies of LSD treatment for alcoholism. The effectiveness of a single dose of LSD compares well with the effectiveness of daily doses of naltrexone, acamprosate, or disulfiram, drugs approved today for the treatment of alcohol dependence.

It is uncommon for a psychiatric drug to have a positive treatment effect for months after a single dose. Weekly or monthly doses might extend these benefits. Also possibly worth trying are shorter-acting psychedelics such as mescaline, psilocybin, or dimethyltryptamine.

The puzzle is that despite these findings LSD has largely been overlooked as a treatment for alcoholism. Perhaps this was because the individual trials generally recruited too few patients to record statistically significant results, the authors tended to discount moderate or short-term effects, poor early trials created the mistaken impression that there were no well designed studies, and the complicated social and political history of LSD led to difficulties in obtaining regulatory approval for clinical trials.

Importantly, all the patients in the reviewed trials were recruited after admission to alcohol treatment programmes with a primary diagnosis of alcoholism, making it likely that they were representative of typical clinical practice. However, three trials either concealed that LSD might be used or gave little information about its likely effects, and in two of these patients were left alone during much of the time LSD was active. Including patients who might not have opted for LSD treatment or were unprepared for it may have attenuated the drug's positive impacts and increased the risk of negative impacts.

Based on extensive animal research and human experience, there is now widespread recognition that LSD and similar psychedelic substances are physically safe, but acute psychological adverse events such as anxiety and confusion should be anticipated, and administration should occur in a comfortable environment with informed participants.

FINDINGS The furore over LSD's non-medical use in the 1960s at first restricted experimentation on its therapeutic properties and then all but closed it down, leaving a corpus of studies characteristic of their time, many of which can be questioned for their methodological adequacy.

The featured analysis sifted through these for what according to modern criteria would be considered the most reliable trials. All tried to eliminate differences between the patients by randomising them to the drug or to an alternative, and most tried to focus on the effects of the drug rather than expectations of these effects by ensuring that neither patients nor clinicians could tell which drug was being administered from its look or taste.

Though each individual trial almost uniformly found no statistically significant differences, amalgamating their results reveals that together they offer strong evidence that the LSD patients had better drinking outcomes than their comparators. The generalisability of this finding is strongly bolstered by the general commonality of the effects across the trials. If LSD has had these effects, its role is reminiscent of the 'conversion' experiences during which alcoholics radically re-evaluate themselves and experience an identity transformation which renders continued (heavy) drinking unthinkable – including the "spiritual awakening" of AA lore.

There is however an inherent limitation to the randomised trial format for a substance like LSD with such distinctive effects that biased results can arise not just from recruiting ill-informed non-volunteers, but also from recruiting well-informed volunteers. This conundrum means that trials of the kind selected by the featured review cannot on their own settle the issue of whether the drug helps alcoholics to stop drinking heavily. Details below.

The featured review points out that trials in which the patients were not all well informed volunteers may have disadvantaged LSD because they did not adequately prepare their patients for the experience, increasing the risk of its seeming bewildering and frightening rather than enlightening. Also, had the patients all been well informed, some may have refused to join the trial.

While this is the case, recruiting only well informed volunteers also has its drawbacks. They may be unrepresentative of alcoholics in general, though representative of patients who might opt for this treatment in routine practice. More importantly, patients willing to try LSD may be demoralised and disappointed when they find they have been randomly allocated to a dummy pill or another drug, a fact which (assuming they *have* been well informed) would be difficult to hide from them given full-strength LSD's characteristic effects, even if the medications are made to look and taste the same.

The one of the six trials which seems to have recorded the most consistently large favourable impacts of LSD was thought to have suffered from this effect. Explaining why control group patients fared worse than the general run of patients at the unit, the researchers feared they "may have inadvertently introduced a strong deprivation effect in which the non-schizophrenic [control] patients ... felt disappointed because they did not receive the 'magical drug'." It was they felt, an instance of the "difficulties of achieving control over the placebo effect of a drug that has spectacular mind-altering properties, and where research is contaminated by expectations of benefit".

Justifiably, in its analysis of this study the featured review compared how the LSD patients fared against these possibly disappointed control patients, noting a large gap in favour of LSD. The study did however offer an alternative benchmark – the unit's general performance – and against this LSD's advantage was appreciably smaller. For example, at the three-month follow-up 58% of the LSD patients were known to have been abstinent or much improved, virtually the same (55%) as the unit's general run of patients, but much better (38%) than the LSD trial's control group.

UK context

In Britain LSD is classified under the Misuse of Drugs Act as having no medical uses. It can only legally be used for experimental purposes under the terms of a Home Office licence specially obtained for that purpose. LSD does however have a history of medical use prior to this restriction. Allegedly poor controls over this use led in 1999 to legal action against the NHS by former psychiatric patients. They spoke of "huge" doses being given without their formal consent and after inadequate information. Without admitting liability, in 2002 the NHS agreed to pay 43 of these patients a total of £195,000 to settle the action before it came to court.

Release of the featured review sparked some controversy in the UK when the Department of Health's NHS Choices web site highlighted the adverse effects noted in the review, said it left patients and doctors unclear about the long-term effects beyond impacts on drinking, and concluded that: "Given the potential danger, it seems unlikely that LSD would be considered for future testing in people with alcohol dependence". Among others, that verdict was queried by psychopharmacologist David Nutt, former leading UK government adviser, who argued that LSD's record in alcoholism rivalled that of other approaches. But even assuming LSD is as effective as say naltrexone or acamprosate, these medications have the great advantage being approved, available and non-controversial. Without persuasive indications not just of equivalence to current medications but of appreciably greater efficacy and cost-effectiveness, it seems very unlikely that NHS services would take the trouble to obtain the required permissions to trial the drug, or risk the fallout from alleged or actual adverse effects from a drug not licensed in the UK for any medical purpose.

Last revised 29 July 2013. First uploaded 19 July 2013

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