The efficacy of disulfiram for the treatment of alcohol use disorder
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CRD summary
The review concluded that supervised treatment with disulfiram has some effect on short-term abstinence, relapse and number of drinking days in patients with alcohol dependency or abuse, but suggested a need for long-term, high-quality studies. The authors' conclusions were suitably cautious in reflecting the limitations of the evidence available, and are likely to be reliable.

Authors' objectives
To review the effect of disulfiram in the treatment of patients with alcohol use disorders.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched; search terms were reported, but search dates were not. Reference lists and related articles were searched to identify additional articles.

Study selection
Randomised controlled trials (RCTs) were eligible if they investigated disulfiram in various doses with or without a control group and/or investigated disulfiram against placebo, no treatment, or other medical or behavioral treatments. Patients had to be aged 15 years or older and be diagnosed with an alcohol use disorder. Alcohol use disorders were defined as an intake of alcohol above 20g/day for women and above 30g/day for men and included hazardous and harmful use as well as the alcohol dependency syndrome. The primary outcome was continuous intake below 20g/day for women and 30g/day for men, including abstinence at follow-up. Included studies had to have used an intention-to-treat analysis. Studies which combined disulfiram with other treatments were excluded.

Most studies were of male patients with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases and Related Health Problems (ICD) classification systems. Patients in some studies were undergoing detoxification at study onset. In a few studies, some patients were expected to have been abstinent before enrolment. Baseline alcohol consumption ranged from six to seven units (each of 12g) per day, to nine to 11 units (each of 10g) per day. Studies were published from 1979 to 2010 in India, Denmark, USA, Austria, Finland and Italy.

Disulfiram doses were mostly 200 or 250mg per day, although doses of 1mg (considered as placebo) or 800mg per day were also used. Comparators included placebo, no treatment, acamprosate, topiramate, naltrexone, riboflavine, and G-hydroxybutyrate. In most studies patients also received (voluntary) cognitive therapy, psychotherapy, or alcohol counselling. The median compliance rate was 85% (range 19 to 100), and the median follow-up rate was 93% (range 18 to 100). Outcome definitions varied across trials.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
The Cochrane Collaboration's tool was used to evaluate risk of bias by assessing sequence generation, allocation concealment, blinding, handling of incomplete outcome data, selective reporting and other bias. Blinding was considered adequate if only the investigator of outcomes was blinded.

The authors did not state how many reviewers evaluated risk of bias.

Data extraction
Data were extracted to calculate odds ratios (OR) with 95% confidence intervals (CI) for alcohol abstinence.

The authors did not state how many reviewers extracted data.
Methods of synthesis
Meta-analyses were performed to calculate pooled odds ratios and 95% confidence intervals, using a fixed-effect model. Meta-analyses were not considered appropriate if $I^2$ values for heterogeneity exceeded 40%; when this occurred a narrative synthesis was presented.

Results of the review
Eleven RCTs were included, studying a total of 1,527 participants (range 26 to 605). Overall, the studies had moderate risk of bias. Sequence generation and allocation concealment methods resulted in a low risk assessment in all but one of the studies (occurring in four studies). All studies were at low risk of bias regarding incomplete outcome data and selective reporting. One study was at a high risk of bias due to other bias. Study duration ranged between two and 12 months (mean eight months).

Four of six studies that compared supervised disulfiram with other abstinence pharmacotherapy reported significantly more abstinence with disulfiram; five of the six studies reported significantly more days until relapse following treatment with disulfiram. The remaining study did not report any statistically significant differences.

One of three studies that compared unsupervised disulfiram with placebo reported significantly more abstinence. One study also reported significantly fewer drinking days with disulfiram treatment. In a meta-analysis of two studies looking at abstinence at 12 months following unsupervised disulfiram compared to placebo, there was an effect which favoured disulfiram but the difference was not statistically significant.

Two studies compared disulfiram with no treatment: one showed a significant increased abstinence for three weeks with disulfiram. In a meta-analysis unsupervised disulfiram resulted in increased abstinence when compared to other or no treatment (OR 1.59, 95% CI 1.07 to 2.37, $I^2=34\%$, three RCTs).

Authors' conclusions
Supervised treatment with disulfiram had some effect on short-term abstinence and days until relapse, as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. However, there was a need for homogeneous, long-term, high-quality studies.

CRD commentary
The review addressed a clear question and was supported by reproducible inclusion criteria. Attempts to identify relevant studies were undertaken by searching electronic databases and checking references but there was no search for unpublished studies and it was unclear whether language restrictions were used, so the possibility of missing studies or language/publication bias could not be ruled out. Suitable methods were employed to reduce the risks of reviewer error and bias for the study selection processes, but the authors did not report on whether such methods were used when extracting data and assessing study quality. Risk of bias was assessed and was used in interpreting the results of the review. Sufficient study details were provided and appropriate methods were used to pool data and to assess and investigate heterogeneity. The authors' conclusions were suitably cautious in reflecting the limitations of the evidence available, and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that more research was needed to ascertain the traits generally associated with a successful outcome to select the people that would benefit the most from treatment with disulfiram. There was also a need for homogeneous, long-term, high-quality studies.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.