Review: studies with sufficient follow up do not show a clear benefit for pharmacotherapy in alcohol dependence

Garbutt JC, West SL, Carey TS, et al. ***Pharmacological treatment of alcohol dependence. A review of the evidence.*** *JAMA 1999 Apr 14;**281**:1318–25.*

QUESTION: What is the efficacy of 5 classes of drugs (disulfiram, opioid antagonists [naltrexone and nalmefene], acamprosate, serotonergic agents, and lithium) for treating alcohol dependence?

Data sources

Studies were identified by searching Medline, HealthSTAR, the American Society of Health-System Pharmacists International Pharmaceutical Abstracts, EMBASE/Excerpta Medica, Alcohol and Alcohol Problems Database, PsycINFO, and the *Cochrane Library* with terms for drugs of interest and related classes of drugs, alcoholism, alcohol drinking, and study design characteristics. Published abstracts and US Food and Drug Administration documents were also reviewed.

Study selection

Studies published in English, French, or German from 1966 to December 1997 were selected if they included ≥10 adults who were dependent on alcohol and were treated in any setting. Children, infants, or pregnant women were excluded.

Data extraction

Reviewers assessed the quality of studies by using a quality rating score and extracted data on participants, follow up, trial duration, number of drinking and non-drinking days, return to drinking, time to first drink, alcohol consumed per unit of time, craving, and relapse.

Main results

41 studies met the selection criteria. 5 randomised controlled trials (RCTs) (n = 1207) used a double blind, placebo controlled design to evaluate oral disulfiram, 200 to 250 mg/day; only 2 studies reported >80% follow up. One of these studies reported a beneficial effect for drinking days but no effect for return to drinking or time to first drink; the other study reported no effect for drinking days and alcohol consumed per unit of time. 6 RCTs (n = 282, 5 placebo controlled) evaluated disulfiram implants, 800 to 1000 mg, but only 2 studies reported >80% follow up. Both RCTs reported a lack of effect on drinking days, time to first drink, and alcohol consumed per unit of time, and 1 RCT reported a lack of effect on return to drinking. 8 RCTs evaluated serotonergic agents in patients with comorbid conditions. 5 double blind, placebo controlled RCTs (n = 227) used fluoxetine. Only 2 of these RCTs reported >80% follow up, and neither reported a beneficial effect. 1 RCT evaluated citalopram, 1 evaluated ondansetron, and 1 evaluated buspirone, but none reported >80% follow up. In patients with anxiety or mood disorders, only 1 RCT (n = 51) had >80% follow up and reported a beneficial effect for fluoxetine on drinking days and alcohol consumed per unit of time but no effect for return to drinking and time to first drink. RCTs that evaluated naltrexone, 50 mg/day (3 placebo controlled, n = 271); acamprosate, 1300 to 2000 mg/day (9 double blind, n = 2170); and lithium (6 RCTs, n = 823) had <80% follow up.

Conclusions

Many studies on alcohol dependence do not have sufficient follow up. Studies with sufficient follow up do not show a clear benefit for pharmacotherapy in alcohol dependence.

COMMENTARY

This carefully done systematic review by Garbutt *et al* summarises the current evidence. The authors concluded that the overall evidence shows that the opiate antagonist naltrexone and acamprosate were "clearly superior to placebo for treatment of alcohol dependence."* Some of the positive experiences from alcohol seem mediated through opiate mechanisms, and naltrexone substantially decreased the rate of relapse to heavy drinking and the frequency of drinking. Acamprosate, with effects on gamma-aminobutyric acid and other neurotransmitters, is approved in Europe and is undergoing several clinical trials in the US but is not yet released. Well designed RCTs consistently showed substantial improvements in non-drinking and drinking days compared with placebo.

These medications were always used in conjunction with psychosocial interventions and should continue to be so. None represents a pharmacological "cure" for alcoholism. Many more studies are needed to define more precisely their place in alcoholism treatment, including timing and duration of treatment and appropriate patient populations. Nevertheless, although the high rate of patient dropouts is a common issue in alcohol studies, valuable knowledge is steadily being gained about this increasingly important element in the treatment of alcoholism.

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*Coordinating editor's note

We did not include information on studies of naltrexone and acamprosate in the abstract because the follow up for these studies did not meet the *Evidence-Based Mental Health* standard of ≥80% follow up. The authors point out, however, that this level of follow up is difficult to achieve in many studies of treatments for alcoholism and in this patient population; the studies that were included in the review met many other stringent quality criteria.

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A modified version of the abstract and commentary also appears in ACP Journal Club and Evidence-Based Medicine.