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REVIEW

Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review

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ABSTRACT

Aims To ascertain the efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence.

Methods Systematic review of the literature (1990–2002) and meta-analysis of full published randomized and controlled clinical trials assessing acamprosate or naltrexone therapy in alcohol dependence. Estimates of effect were calculated according to the fixed-effects model.

Measurements Relapse and abstinence rates, cumulative abstinence duration and treatment compliance were considered as primary outcomes.

Findings Thirty-three studies met the inclusion criteria. Acamprosate was associated with a significant improvement in abstinence rate [odds ratio (OR): 1.88 (1.57, 2.25), $P < 0.001$] and days of cumulative abstinence [WMD: 26.55 (17.56, 36.54]. Short-term administration of naltrexone reduced the relapse rate significantly [OR: 0.62 (0.52, 0.75), $P < 0.001$], but was not associated with a significant modification in the abstinence rate [OR: 1.26 (0.97,1.64), $P = 0.08$]. There were insufficient data to ascertain naltrexone's efficacy over more prolonged periods. Acamprosate had a good safety pattern and was associated with a significant improvement in treatment compliance [OR: 1.29 (1.13,1.47), $P < 0.001$]. Naltrexone's side effects were more numerous, yet the drug was nevertheless tolerated acceptably without being associated with a lower adherence to treatment (OR: 0.94 (0.80, 1.1), $P = 0.5$). However, overall compliance was relatively low with both medications.

Conclusions Both acamprosate and naltrexone are effective as adjuvant therapies for alcohol dependence in adults. Acamprosate appears to be especially useful in a therapeutic approach targeted at achieving abstinence, whereas naltrexone seems more indicated in programmes geared to controlled consumption. Both drugs are safe and acceptably tolerated but issues of compliance need to be addressed adequately to assure their usefulness in clinical practice.

KEYWORDS Acamprosate, alcohol dependence, alcoholism treatment, meta-analysis, naltrexone.

INTRODUCTION

At present, alcohol dependence constitutes one of the most serious public health problems, not only because of its high prevalence and impact on the personal, family, occupational and social spheres, but also because of its economic and medical consequences [1–8]. Treatment of alcohol dependence, the favourable effects of which have been demonstrated clearly in terms of related morbidity and mortality [4] and health-care costs [8], has made substantial progress in recent decades. Indeed, drugs are now available that seemingly improve on the results

yielded by standard techniques employed to date in the management of such patients [4–7].

In the forefront of the pharmacological options currently available are naltrexone and acamprosate. Naltrexone is a pure opioid antagonist, whose favourable effects were first noticed in the early 1990s [7,9–11]. Although its mechanism of action is not known fully, naltrexone exerts a competitive antagonism with respect to the opioid receptors: this, in turn, blocks the release of alcohol-induced dopamine, thereby reducing the stimulus and reinforcing effects of ethanol, and with it the ensuing craving to drink and loss of control [11]. Acamprosate (calcium acetylhomotaurinate) is a simple derivative of the essential taurine amino acid and displays a structural resemblance to gamma-amino butyric acid (GABA). Acamprosate enhances GABA reception and the transmission of the GABAergic system, reduced by chronic exposure to alcohol, and interferes with glutamate action in different pathways, such as the N-methyl-D-aspartate (NMDA) receptors [12]. Acamprosate also acts on the calcium channels and reduces central nervous system hyperexcitability induced by suppression of alcohol [13].

However, experience with both drugs in the field of dependency is still limited. While some countries have officially approved acamprosate for treatment of alcohol dependence, others are still engaged in gathering evidence on its efficacy and safety. Naltrexone has been approved since 1994 for the treatment of alcohol dependence but the record shows that its use is less than might have been expected and that such underuse is due to the existence of considerable uncertainty surrounding its activity and possible toxicity [5].

The aim of this study was to analyse the collected body of evidence regarding the efficacy and safety of naltrexone and acamprosate for treatment of alcohol dependence.

METHODS

This review confined itself to full published, randomized and controlled clinical trials in peer review journals, which compared naltrexone or acamprosate with placebo or a reference group without medication, in adults with alcohol dependence. We excluded studies that had fewer than 10 participants, duration of less than 2 weeks, proceedings of meetings or congresses and publications that contained no relevant primary clinical data or failed to report results quantitatively. Studies were identified by means of a systematic search of the MEDLINE (SilverPlatter WebSPIRS), CINAHL (WebSPIRS) and EMBASE (Pollution and Toxicology, WebSPIRS) electronic databases, with no language restriction, covering the period January 1990–September 2002 and employing the following terms: alcohol-related-disorders, therapy, opioid-antagonists, narcotic-antagonists/therapeutic use, naltrexone, acamprosate, randomized-controlled-trial, clinical-trial. Similarly, the Cochrane Controlled Trials Register was examined, and bibliographies of relevant articles were examined manually for additional studies.

Two reviewers evaluated and extracted the data independently. To extract data, we designed a specific form that included the following: study design and scope; duration of treatment and follow-up period; inclusion and exclusion criteria; sample size and method employed for the calculation of same; interventions; type of randomization; baseline population characteristics; clinical outcomes and compliance with treatment. Duplicate articles were removed. During the trial selection and data extraction we were not masked to authors, institutions, journal or interventions assessed.

Quality assessment

Methodological quality and grade of scientific evidence was evaluated for each selected paper using the Jadad scale [14] and Hadorn's guidelines [15], respectively.

Data analysis

RevMan 4.1 software (Cochrane Collaboration 2000) was used to obtain a quantitative overall measure of the effect of naltrexone and acamprosate on the outcomes of interest. The studies were combined, by analogy, in terms of type of intervention, scope, treatment period and outcomes. Only those studies in which the analysis and the form of presentation of results was comparable and showed no statistically significant heterogeneity were included. This was evaluated with the Q statistic ($P > 0.05$) and potential reasons for heterogeneity were explored. The meta-analysis was conducted using a fixed-effect model with dichotomous outcomes being analysed by means of Peto's odds ratio (OR) (95% confidence interval) and continuous outcomes using weighted mean difference [95% confidence interval (CI)]. Scores obtained in the assessment of methodological quality allocated no weight to the meta-analysis. Sensitivity analyses were performed to assess the influence of methodological issues such as study setting, inclusion criteria—particularly the presence or absence of another dependence and the existence of a prior phase of detoxification or abstinence, study size and study quality on the effect estimation. In accordance with some recent literature we have not used funnel plots to examine the possibility of publication bias, given the limitations and potential misleading results of these graphs [16]. Heterogeneous data were analysed individually. Results were drawn largely from

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