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

Bouza Carmen, Magro Angeles, Muñoz Ana & Amate José María

Agency for Health Technology Assessment, Madrid, Spain

Correspondence to:
Carmen Bouza
Agency for Health Technology Assessment
Instituto de Salud Carlos III
Sinesio Delgado 4
28029 Madrid
Spain
Fax: + 34 91 3877841
E-mail: cbouza@isciii.es

Submitted 11 August 2003;
initial review completed 15 October 2003;
final version accepted 13 March 2004

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

 doi:10.1111/j.1360-0443.2004.00763.x

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

intention-to-treat analysis and deemed significant at a value of $P < 0.05$. The number needed to treat (NNT) was calculated using the internet-accessible Visual Rx program (http://www.nntonline.net).

RESULTS

Figure 1 summarizes the search for relevant studies, showing those that met the inclusion criteria, those that were excluded due to duplication in the publication of results [10,17–19] and those that were finally included [9,20–51] after eliminating redundancies arising from the use of several databases.

Acamprosate versus placebo

Thirteen single or double-blind randomized clinical trials [20–32] (Table 1) evaluated the efficacy and safety of acamprosate versus placebo in a total of 4000 adult men and women, who had DSM-III or DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; American Psychiatric Association 1987) alcohol dependence and had undergone a previous detoxification process. All patients presented with no unstable medical pathology. All, except the study by Roussaux *et al.* [29], were conducted in an ambulatory setting and all included some type of psychosocial intervention. In some studies, standard adjustment of acamprosate dosage was made for patients' body weight, while the more recent studies relied on a fixed dose. Eleven were multicentre studies. The duration of the studies ranged from 3 to 24 months and they generally displayed good methodological quality and scientific evidence. All studies specified the withdrawals, seven reported the method employed for randomization [20–22,28,30–32], and all but one [25] report that the analysis of results was on an intention to treat basis. Eighty per cent of trials scored greater than or equal to 4 and 20% scored 3 on the Jadad scale, indicating good methodological quality. Hadorn's criteria showed 92% of studies as having grade A1 evidence.

Outcomes considered of primary interest were: abstinence rate, defined as the percentage of patients that complete the study without ingesting alcohol; cumulative abstinence duration (CAD), defined as the sum of the periods of abstinence during the study; and the rate of compliance with treatment. These outcomes proved substantially homogeneous.

Efficacy

Regarding the abstinence rate, given that Roussaux's study [29] entailed the institutionalization of patients during treatment it was considered inappropriate its inclusion in meta-analysis after performing a sensitivity analysis. The said study showed no differences between patients treated with acamprosate ($n = 63$) and those who received placebo ($n = 64$) in respect to the abstinence rate [Peto's OR (95% CI): 0.82 (0.39, 1.74),

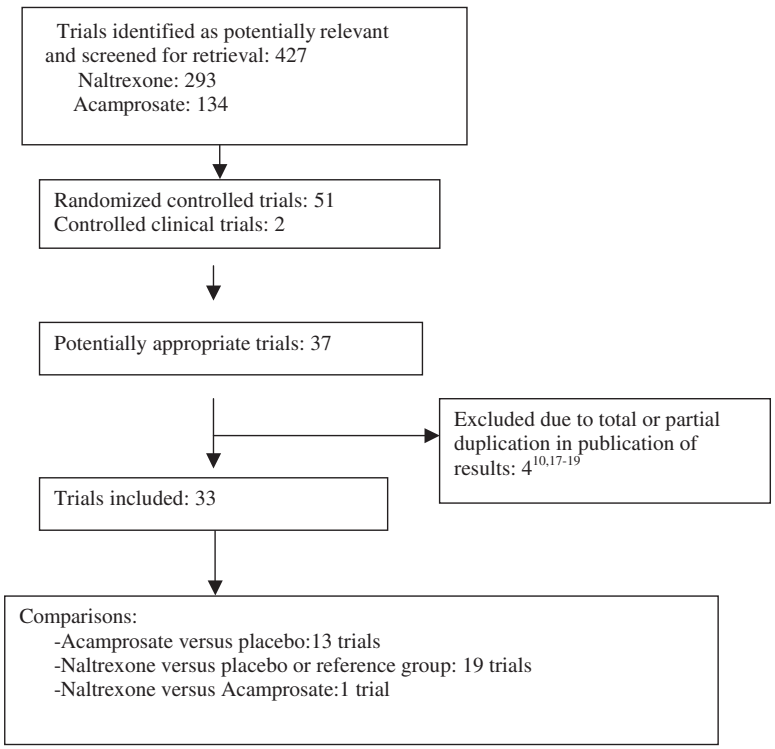

Figure 1 Process of inclusion of studies and useable information

Table 1 Acamprosate: characteristics of included studies.

Study	*Methods*	*Inclusion criteria*	*Interventions*	*Outcomes*	*Funding sources*
Besson 1998 [20]	Multi-centre, randomized, double-blind, placebo-controlled, 12-month treatment, 12-month post-treatment follow-up	18–65 years of age, 12-month history of DSM-III dependence, minimum of 5 days of abstinence GGT ≥2 ULN, MCV >95 fl	a = ≥60 kg: 1998 mg/day (*n* = 45), <60 kg: 1300 mg/day (*n* = 10), placebo (*n* = 55); disulfiram: a (*n* = 24) *P*:(*n* = 22); psychosocial support	Abstinence rate, CAD, craving, compliance, GGT, MCV.	Lipha, Inc.
Chick 2000 [21]	Multi-centre, randomized placebo-controlled, 6-month treatment, 1-month post-treatment follow-up	18–65 years of age, > 60 kg, 12-month history of DSM-III dependence, withdrawal from alcohol during the preceding 5 weeks, abstinent for at least 5 days	a = 1998 mg/day (*n* = 289); placebo (*n* = 292); cognitive-behavioral group therapy, out-patient support groups, educational groups, marital therapy, social skills training, Alcoholics Anonymous	Abstinence rate, CAD, craving, compliance, MCV, GGT, AST	Lipha Pharmaceuticals
Geerlings 1997 [22]	Multi-centre, randomized, double-blind, placebo-controlled, 6-month treatment, 6-month post-treatment follow-up	18–65 years of age, DSM-III criteria for alcohol dependence, abstinent for at least 5 days	a = ≥60 kg: 1998 mg/day, <60 kg: 1332 mg/day (*n* = 128); placebo: (*n* = 134); psychosocial support	Abstinence rate, CAD, time to first drink, compliance, MCV, GGT, AST, ALT, CDT	Lipha, Belgium
Gual 2001 [23]	Multi-centre, randomized, double-blind, placebo-controlled, 6-month study	18–65 years of age, 12-month history of DSM-III dependence, with alcohol consumption in the previous 7 days	a = 1998 mg/day (*n* = 141), placebo: (*n* = 147); psychosocial support	Abstinence rate, CAD, no. of abstinent days between the last drink and the end of the trial (SRD), GGT, CDT, craving, compliance	Merck Lipha, Spain
Ladewig 1993 [24]	Randomized, double-blind, placebo-controlled, 6-month treatment, 6-month post-treatment follow-up	DSM-III-R criteria for alcohol dependence, at least 5 days of abstinence	a = ≥60 kg: 1998 mg/day, <60 kg: 1332 mg/day (*n* = 29); placebo (*n* = 32)	Abstinence rate, CAD	Not available
Lhuintre 1990 [25]	Multi-centre, randomized, double-blind, placebo-controlled, 3-month study	18–65 years of age, at least one sign of alcohol dependence, GGT ≥2 normal value or MCV >98 fl	a = 1332 mg/day (*n* = 279), placebo: (*n* = 290); psychotherapy	Compliance, GGT, AST, MCV	Not available
Paille 1995 [26]	Multi-centre, randomized, double-blind, placebo-controlled, 12-month treatment, 6-month post-treatment follow-up	18–65 years of age, dependence DSM-III-R, abstinent from alcohol for 7–28 days	a = 1.3 g/day (*n* = 188); 2.0 g/day (*n* = 173); placebo: (*n* = 177); supportive psychotherapy	Abstinence rate, CAD, time to first drink, GGT, ALT, AST, MCV,craving, compliance	Not available
Pelc 1997 [27]	Multi-centre, randomized, double-blind, placebo-controlled, 3-month study	18–65 years of age, ≥60 kg, 12-month history of DSM-III-R dependence	a = 1332 mg/day (*n* = 63); 1998 mg/day (*n* = 63); placebo:(*n* = 62); counselling and social support	Abstinence rate, CAD, time to first drink, GGT, ALT, AST, MCV, compliance	Lipha, Belgium
Poldrugo 1997 [28]	Multi-centre, randomized, double-blind, placebo-controlled, 6-month treatment, 6-month post-treatment follow-up	18–65 years of age, dependence DSM-III, minimum of 5 days of abstinence, GGT ≥2 ULN, MCV >95 μ^3	a = ≥60 kg: 1998 mg/day, <60 kg: 1300 mg/day (*n* = 122); placebo (*n* = 124); community-based rehabilitation programme	Abstinence rate, CAD, time to first drink, craving, compliance, GGT, AST, ALT, MCV	Lipha, France

Roussaux 1996 [29]	Randomized, double-blind, placebo-controlled, 3-month study	DSM-III criteria for dependence, minimum of 14 days of abstinence	a = 1998 mg/day (n = 63); placebo: (n = 64); group, individualized and family counselling	Abstinence rate, GGT, MCV, craving, compliance	Not available
Sass 1996 [30]	Multi-centre, randomized, double-blind, placebo-controlled, 12-month treatment, 12-month post-treatment follow-up	DSM-III-R criteria for dependence, abstinence 14–28 days	a = ≥60 kg: 1998 mg/day, <60 kg: 1300 mg/day (n = 136); placebo: (n = 136); supportive therapy	Abstinence rate, CAD, time to first drink, craving, compliance, CDT, GGT, MCV	Lipha, Essen, Germany
Tempesta 2000 [31]	Multi-centre, randomized, double-blind, placebo-controlled, 6-month treatment, 3-month post-treatment follow-up	18–65 years of age, DSM-III-R dependence, 2-month history of alcohol dependence, 5 days of abstinence, GGT ≥2 ULN and/or MCV ≥95 fl	a = 1998 mg/day (n = 164); placebo: (n = 166). Individual behavior-orientated supportive counselling and Alcoholics Anonymous attendance	Abstinence rate, CAD, time to first drink, craving, compliance	Lipha, France
Whitworth 1996 [32]	Multi-centre, randomized, double-blind, placebo-controlled, 12-month treatment, 12-month post-treatment follow-up	18–65 years of age, dependence DSM-III, minimum of 5 days of abstinence, GGT ≥2 ULN and/or MCV ≥93 fL	a = ≥60 kg: 1998 mg/day, <60 kg: 1300 mg/day (n = 224); placebo: (n = 224)	Abstinence rate, CAD, time to first drink, MCV, AST, ALT, GGT	Lipha, France

DSM-III, DSM-II-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition–revised; American Psychiatric Association; a: acamprosate; p: placebo; GGT: gamma-glutamyl transferase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CDT: carbohydrate-deficient transferrin; MCV: mean corpuscular volume; fl: femtolitre = μm^3; ULN: upper limit of normal; CAD: cumulative abstinence duration; SRD: stable recovery duration

P = 0.6]. However, as Fig. 2 shows, the result of the meta-analysis conducted with 12 studies demonstrates that acamprosate raised the continuous abstinence rate with a calculated NNT of 10 (95% CI: 7–15). Similarly, as Fig. 3 shows, treatment with acamprosate was associated with significantly favourable effects in cumulative abstinence duration. In fact, acamprosate doubled the days of cumulative abstinence in the seven studies that supplied data.

Disparity in the measurement and expression of secondary outcomes, such as degree of craving and hepatic enzyme levels, barred effect estimations. With respect to craving, individualized analysis of the results led to diverging results: whereas Chick [21] observed a significantly favourable effect for acamprosate on assessment at 1 month of conclusion of treatment, other authors failed to observe significant differences versus the control group at 12 months of treatment, whether in terms of the percentage of patients without craving [23] (acamprosate 26%, placebo 16%, P = 0.52), change over baseline levels [29] (acamprosate: 1.75 versus 0.20; placebo: 1.67 versus 0.05), or mean values on a visual analogue scale [30] (acamprosate: 65 ± 42; placebo: 71 ± 38; OR = –6 (–19.77, 7.77); P = 0.4). In so far as gamma-glutamyl transferase (GGT) was concerned, 11 studies included this as an outcome of interest and some reported a significantly favourable trend in the acamprosate group [23,25,26,29,30]. However, the disparity and sometimes inadequate description of results and even the lack of quantitative data [20–22,27,32] hampered the pooled effect estimation.

Safety

Acamprosate produced few side effects with mainly diarrhoea and, occasionally, headaches, dizziness and pruritus being described. Gastrointestinal symptoms were the most common adverse effects, observed affecting about 17% of patients in the acamprosate group and 11% in the placebo group (Table 2). However, the meta-analysis from 10 studies with available data (Table 2) shows that gastrointestinal adverse effects were significantly more common in the acamprosate than in the control group. Nevertheless, no statistically significant differences were observed between groups in terms of premature withdrawals from treatment due to adverse effects. Furthermore, as Table 2 shows, acamprosate improved overall adherence to treatment with a calculated NNT of 16 (95% CI: 11–33).

Naltrexone versus placebo or reference control group

The fundamental characteristics of the studies included are listed in Table 3. Of the 19 studies included, only one

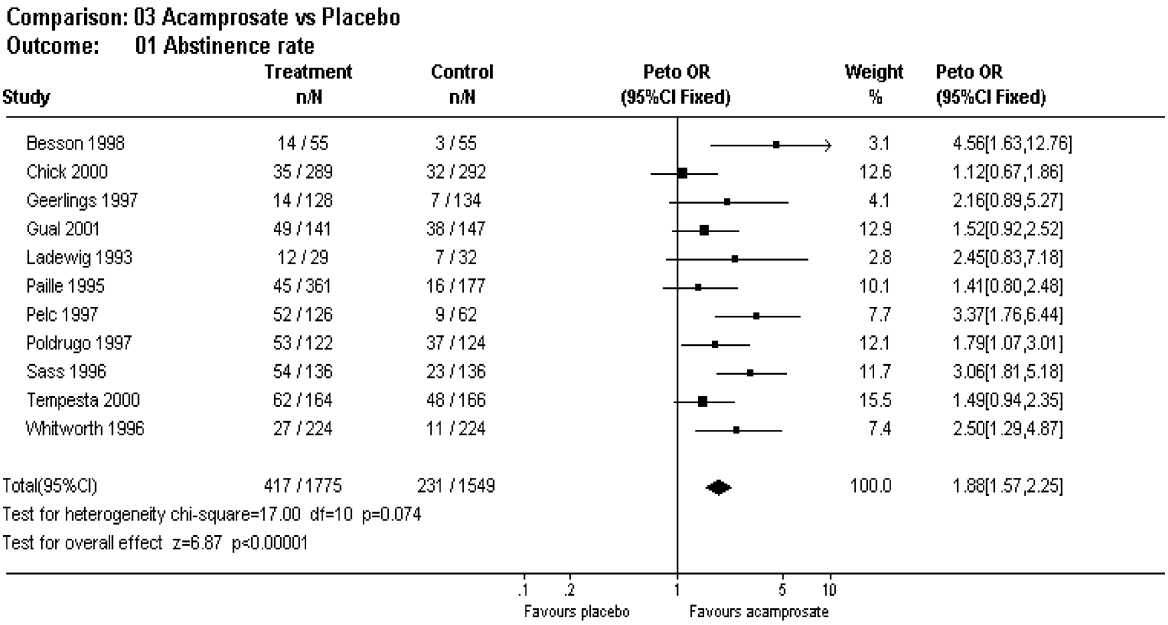

Figure 2 Acamprosate versus placebo: results of the meta-analysis on abstinence rate. Fixed-effects model. OR: odds ratio; CI: confidence interval.

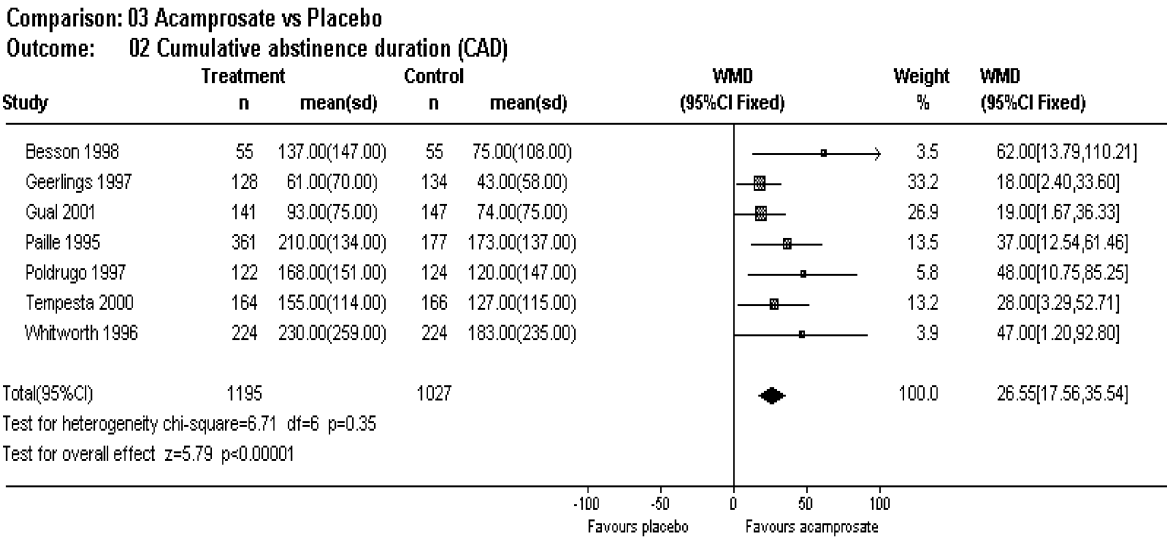

Figure 3 Acamprosate versus placebo: results of the meta-analysis on cumulative abstinence duration (days). Fixed-effects model. WMD: weighted mean difference

was controlled without randomized allocation [36], one had an open-label design [43] and the remainder were single- or double-blind randomized clinical trials. Of these, four [35,44,45,50] specified the method employed for randomization; eight [9,38–42,45,46] made express reference to masking in the assessment of results; and all but two [41,50] reported the withdrawals. Five [35–37,42,44] were multi-centre studies. Ten trials [9,35,38–40,42,44–46,51] scored greater than or equal to 3 on the Jadad scale, indicating good quality, while Hadorn's criteria showed 65% as having grade A1 evidence.

There was a total of 3205 participants, made up of adult men and women with DSM-III-R or DSM-IV (Diagnostic and Statistical Manual of Mental Disorders; American Psychiatric Association 1994) alcohol dependence. In general, with the exception of four studies [33,34,38,39], the inclusion criteria resulted in a population comprising individuals who had undergone a phase of alcohol detoxification and presented with no

Table 2 Effects of acamprosate as an adjunct to psychosocial interventions compared with placebo: overall results of the review for dichotomous outcome measures.

Outcome	*No. of studies contributing data*	*Total no. of patients*	*Acamprosate (cases/total of patients)*	*Placebo (cases/total of patients)*	*Test for heterogeneity*	*Mean effect size, Peto's OR (95% CI), P-value*
Compliance with treatment	12 [20–23,25–32]	3959	1100/2088	884/1871	c^2: 14.83; $P = 0.19$	1.29 (1.13, 1.47), <0.001
Gastrointestinal side effects	10 [20–23,25–27,30–32]	3425	314/1832	178/1593	c^2: 9.90; $P = 0.36$	1.69 (1.38, 2.07), <0.001
Discontinuation due to adverse effects	9 [20–23,27,28,30–32]	2697	38/1357	29/1340	c^2: 9.46; $P = 0.31$	1.29 (0.79, 2.11), 0.3

Fixed-effects model. OR: odds ratio; CI: confidence interval.

unstable medical pathology. Only Morris [46] included patients with psychiatric pathology and all, except Hersh [39], excluded patients with active non-nicotine drug addiction. Apart from Knox [40], all studies were conducted in an ambulatory setting, and some type of psychosocial therapy was provided in all cases. Standard dosage was usually 50 mg/day. Only in two cases [42,43] was naltrexone administered in a fixed dose for more than 3 months. Heinala's study [38] had a particular design with naltrexone being administered in a fixed dose for 12 weeks and in a targeted mode, only when craving was high, for 20 weeks. To maintain clinical homogeneity, this latter phase of the study was not included in the meta-analysis. Two studies [34,47] consisted of the follow-up phase of previously treated patients [9,33].

Outcomes deemed to be of primary interest were mainly relapse and abstinence rates. Relapse was defined variously as: intake of ≥5 standard drinks per day for men and ≥4 for women [9,33–35,37–39,41]; intake of ≥6 drinks for men and ≥4 for women [42]; intake of ≥6 drinks for men and ≥5 for women [45]; intake on more than 5 days per week; and 5 or more drinks per episode of intake or blood alcohol count (BAC) >100 mg/dl [38,43,46,48,50,51]. In all cases, abstainers were deemed to be participants who ingested no amount of alcohol during the study. Practically all the studies measured degree of compliance with treatment.

With respect to amount consumed, the most frequent secondary outcomes were percentage of drinking days, percentage of days of abstinence and number of drinks per drinking day. Days of heavy drinking and total alcohol consumption were described in some cases only.

Efficacy

For assessment purposes, the studies were grouped by duration of treatment phase.

Short-term therapy (≤12 weeks). In view of the fact that Knox's study [40] entailed the institutionalization of patients during treatment, its inclusion in the meta-analysis was thought to be inappropriate. Furthermore, given that Hersh [39] included patients with alcohol and cocaine dependence, a sensitivity analysis was performed on the following outcomes: relapse, drinking days, time to relapse, number of drinks per drinking day and compliance. On the basis of the results, this study was excluded solely in respect of time to relapse.

In terms of primary outcomes, administration of naltrexone was associated with a significant improvement in the relapse rate during the active treatment phase (Fig. 4) with an NNT of 9 (95% CI: 6–14) as well as the follow-up period (Table 4). In contrast, although there was a trend to show favourable effects on the abstinence rate during the active treatment phase with naltrexone, the effect estimation did not reach statistical significance (Fig. 5). Similarly, naltrexone was not shown to have any significantly favourable effect on the abstinence rate during follow-up (Table 4) although this outcome was measured in only two studies [34,47].

Naltrexone was associated with a statistically favourable effect regarding the following secondary outcomes: time to relapse; percentage of drinking days; number of drinks per drinking day; days of abstinence; total consumption during treatment; and GGT and AST levels (Table 5). In contrast, there were no differences *vis-à-vis* the reference group in time to first intake or percentage of carbohydrate-deficient transferrin.

In so far as craving was concerned, although 15 studies included this as an outcome of interest, several [35,38,48] failed to analyse it and the rest used different instruments for its measurement, including the Obsessive Compulsive Drinking Scale (OCDS) scale [33,34,41,44], the Visual Analog Scale [9,37,50,51] and the Alcohol Urges Questionnaire [39,40]. Consequently, we subdivided estimation of the effect by instrument employed for measurement and availability of complete data (Table 5).

Table 3 Naltrexone: characteristics of included studies.

Study	*Methods*	*Inclusion criteria*	*Interventions*	*Outcomes*	*Funding sources*
Anton 1999 [33]	12-week randomized, double-blind, placebo-controlled	21–65 years of age, DSM-III-R dependence, average consumption ≥5 drinks/day in the last 30 days, abstinent from alcohol for 5 days, stable living situation	nx 50 mg/day (n = 68), placebo (n = 63), cognitive behavioral therapy	Time to relapse, % of abstinent days, drinks/drinking day, craving, GGT, CDT	NIAAA
Anton 2001 [34]	6-month follow-up study after the completion of Anton 1999	s Anton 1999	No interventions		NIAAA
Chick 2000 [35]	Multi-centre, randomized, double-blind, placebo-controlled, 12-week study	18–65 years of age, DSM-III-R dependence, abstinent from alcohol for 5–30 days, enrolled in an alcohol rehabilitation programme	nx 50 mg/day (n = 90), placebo (n = 85), psychosocial treatment	Time to heavy drinking, time to first drink, alcohol consumption, craving, GGT, AST, ALT	Dupont Pharmaceuticals Co.
Croop 1997 [36]	Non-randomized, open-label, 12-week study	>18 years of age, enrolled in an alcohol rehabilitation programme, abstinent from alcohol for 1–6 weeks	nx 50 mg/day (n = 570); no medication (n = 295), psychosocial treatment programme	Adverse effects, liver function tests	Dupont Merck Pharmaceutical Co.
Guardia 2002 [37]	12-week, multi-centre, randomized, double-blind, placebo-controlled	18–60 years of age, DSM-IV dependence	nx 50 mg/day (n = 101), placebo (n = 101), supportive group therapy	Relapse rate, time to first drink, alcohol consumption, craving, % of abstinent days, total days drinking, total drinks, drinks/drinking day, GGT, CDT	Pharmazam/Zambón SA
Heinala 2001 [32]	Randomized, double-blind, placebo-controlled, 12-week induction period, 20-week targeted medication	21–65 years of age, non-abstinent, DSM-IV dependence, stable living situation	nx 50 mg/day (n = 63), placebo (n = 58), psychosocial treatment: cognitive coping skills or supportive therapy	Relapse rate, consumption, craving	Finnish Alcohol Research Foundation; The National Public Health Institute
Hersh 1998 [39]	Randomized, double-blind, placebo-controlled	18–45 years of age, dual cocaine and alcohol abuse or dependence DSM-III-R	nx 50 mg/day (n = 31), placebo (n = 33), relapse prevention psychotherapy	Time to first drink, time to first heavy drink, drinking days, heavy drinking days, GGT, craving	NIH
Knox 1999 [40]	Randomized, double-blind, placebo-controlled, 20-days treatment, 6-month follow-up	18–65 years of age, DSM-IV dependence, prior detoxification	nx 50 mg/day (n = 31), placebo (n = 32), cognitive behavioral therapy; in-patient treatment setting	Abstinence rate, craving	Not available

Kranzler 2000 [41]	Randomized, double-blind, 12-week study	18–60 years of age, DSM-III-R dependence, abstinent from alcohol for at least 3 days	nx 50 mg/day (n = 61), placebo (n = 63), nefazodone: 400 mg/day (n = 59), behavioral psychosocial therapy	Abstinence rate, time to first drink, time to relapse, drinking days, drinks/drinking day, craving, GGT	NIH
Krystal 2001 [42]	Multi-centre, double-blind, placebo-controlled,12-month study, 6-month post-treatment follow-up	>18 years of age, veterans, recent history of drinking to intoxication, abstinent from alcohol for 5 days, DSM-IV dependence	nx 50 mg/day 12 months (n = 209); nx 50 mg/day 3 months, placebo 9 months (n = 209); placebo 12 months (n = 209), 12-Step counselling	13 weeks: time to relapse 12 months: % drinking days, drinks/ drinking day	Dupont Pharmaceuticals
Landabaso 1999 [43]	Randomized, open-label, 6-month treatment, 18-month follow-up	Dependence or abuse DSM-IV and 3 or more previous treatments with aversion agents in the 3 years prior to the study	nx 25 mg/day (n = 15), control (n = 15). Usual aversion therapy for 1 year; counselling	Abstinence rate, relapse rate, accumulated relapse incidence, alcohol consumption	Not available
Latt 2002 [44]	Multi-centre, randomized double-blind, placebo-controlled 12-week study	18–70 years of age, dependence DSM-IV	nx 50 mg/day (n = 56); placebo (n = 51), psychosocial therapy offered	Relapse rate, days to relapse, side effects	Northern Sydney Health, Orphan Australia, Dupont Pharma and the Kris Morris Trust Fund for Drug and Alcohol Services
Monti 2001 [45]	Randomized, double-blind, placebo-controlled, 12-week treatment, 9-month follow-up	Dependence DSM-IV	nx 50 mg/day (n = 64), placebo (n = 64), cue exposure-coping skills training; communication skills training	Abstinence rate, drinking days, drinks/drinking day, time to first drink, time to relapse, craving	NIAAA
Morris 2000 [46]	12-week randomized, double-blind, placebo-controlled	Male, 18–65 years of age, dependence DSM-III-R, Michigan Alcohol Screening Test >5, abstinent from alcohol for 3–30 days	nx 50 mg/day (n = 55), placebo (n = 56), education support group	Abstinence, relapse rate, drinking days, pattern of alcohol use, GGT, ALT	VA
O'Malley 1992 [9]	12-week randomized, double-blind, placebo-controlled	18–65 years of age, dependence DSM-III-R, abstinent from alcohol for 7–30 days	nx 50 mg/day (n = 52), placebo (n = 52), psychosocial therapy: coping skills/relapse prevention therapy; supportive therapy	Time to relapse, time to first drink, craving, drinking days	NIAAA, NIDA
O'Malley 1996 [47]	6-month follow-up study after th completion of O'Malley 1992	As O'Malley 1992	No interventions		NIAAA
Oslin 1997 [42]	12-week randomized, double-blind, placebo-controlled	50–70 years of age, DSM-III-R dependence	nx (n = 21), placebo (n = 23), group therapy	Relapse rate, time to relapse, time to first drink, craving, GGT, AST, adverse effects	Dupont Merck Pharmaceuticals

Table 1 *Cont.*

Study	*Methods*	*Inclusion criteria*	*Interventions*	*Outcomes*	*Funding sources*
Rubio 2001 [49]	Randomized, 12-month, single-blinded	Male, 18–65 years of age, dependence DSM-III-R, recent detoxification, stable family environment	nx 50 mg/day (n = 77), acamprosate 1665–1998 mg/day (n = 80), supportive group therapy offered	Accumulated abstinence (days), relapse, time to relapse, drinks consumed per week, drinks consumed at a time, craving, GGT, abandonment of pharmacological treatment, discontinuation rate	Fundación Cerebro y Mente
Volpicelli 1995 [50]	12-week, randomized, double-blind, placebo-controlled	Male veterans, 21–65 years of age, Michigan Alcohol Screening	nx 50 mg/day (n = 54), placebo (n = 45), supportive group therapy	Relapse rate, craving, drinking days, GGT, AST Time to relapse to heavy drinking, drinking days, craving, GGT, AST	NIAAA, NIDA NIAAA, NIDA, VA
Volpicelli 1997 [51]	12-week, randomized, double-blind, placebo-controlled	Test ≥5, prior detoxification 21–65 years of age, dependence DSM-III-R, prior detoxification	nx 50 mg/day (n = 48), placebo (n = 49), counselling		

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition–revised; American Psychiatric Association 1987; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association 1994; nx: naltrexone. CDT: carbohydrate-deficient-transferrin level, GGT: gamma-glutamyltransferase. AST: aspartate aminotransferase. ALT: alanine aminotransferase. NIAAA: National Institute on Alcohol Abuse and Alcoholism, NIDA: National Institute on Drug Abuse Center.VA: Veterans Affairs Research. NIH: National Institutes of Health.

The results indicate that naltrexone appears to reduce craving during the treatment phase but that its possible beneficial effect is lost during follow-up [34] [WMD (95% CI): 0.40 (–2.11, 1.31), $P = 0.6$].

In almost all the studies, drug therapy was supplemented with two types of interventions, i.e. a phase of previous abstinence or detoxification, and application of psychosocial therapy. With respect to the former, four studies [33,34,38,39] evaluated the effects of naltrexone without any preceding period of abstinence or detoxification and yet reproduced the general results (data not shown). All studies incorporated some type of psychosocial therapy, although these were very different in structure and intensity. The results of some studies [9,38] suggest that there is a clear interaction between naltrexone and type of psychosocial therapy, with naltrexone exerting more favourable effects on those subjects who receive a type of psychotherapy which is targeted at coping with situations of limited intake. In contrast, other authors [44,45] report no association between treatment with naltrexone and type of psychosocial therapy employed, pointing out that naltrexone's effectiveness is independent of psychosocial support, regardless of any possible interaction between the two forms of treatment.

Medium-term treatment (6 months). Landabaso *et al.*'s [43] results show naltrexone as having a favourable effect on both abstinence [OR (95% CI): 7, 49 (1.94, 32.52), $P = 0.004$] and relapse rates [OR (95% CI): 0.18 (0.04, 0.78), $P = 0.02$]. No significant differences were found between the naltrexone and control groups in terms of amount consumed [OR (95% CI): 1.1 (– 2.53, 0.33), $P = 0.13$] or degree of compliance [OR (95% CI): 0.52 (0.11, 2.54), $P = 0.4$].

Long-term treatment (≥12 months). The results reported by Krystal *et al.* [42] show no differences between naltrexone and placebo in terms of percentage of drinking days [WMD (95% CI): 3.00 (– 7.80, 1.80), $P = 0.2$] or number of drinks per drinking day [WMD (95% CI): 0.30 (– 1.35, 1.95), $P = 0.7$] at 12 months of treatment. In this study, no differences were observed similarly at 12 months, as between long- and short-term treatment with naltrexone (drinking days 15.1 ± 23 versus 19.4 ± 26; drinks per drinking day: 9.6 ± 10 versus 10.5 ± 8).

Safety

Side effects, although variable as between individual studies, were frequent overall. For analysis purposes, we took all those for which number and type were specified, regardless of duration of treatment or whether or not the comparison group had received placebo [9,33,35–44,46,48–51]. This analysis, in which 2564 subjects were included, showed a higher rate of adverse side

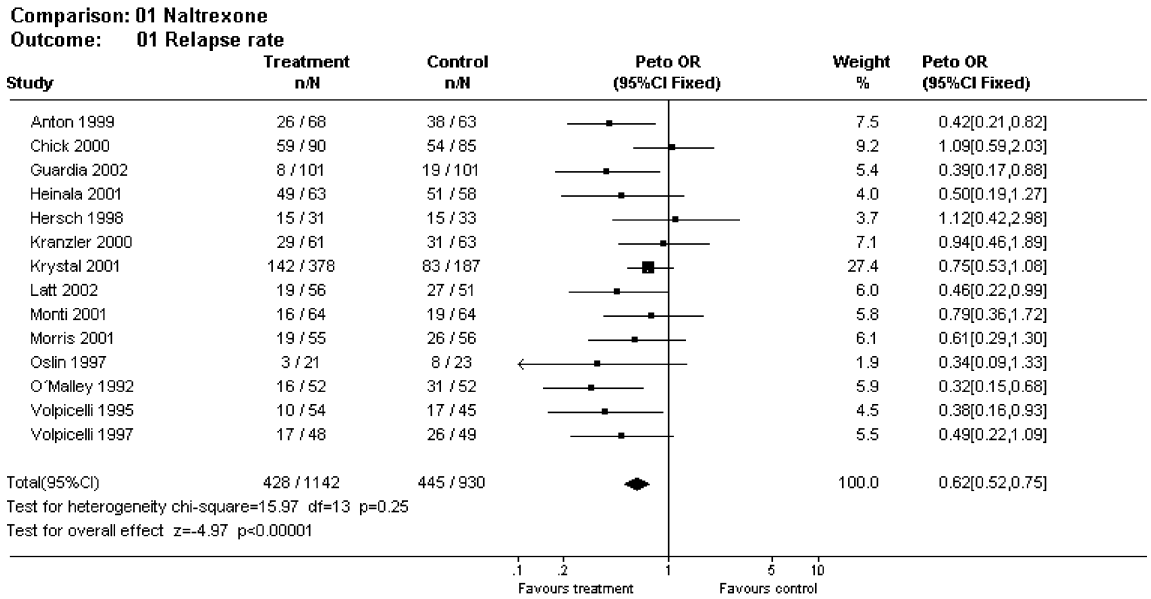

Figure 4 Short-term naltrexone versus placebo: results of the meta-analysis on relapse rate. Fixed-effects model. OR: odds ratio; CI: confidence interval

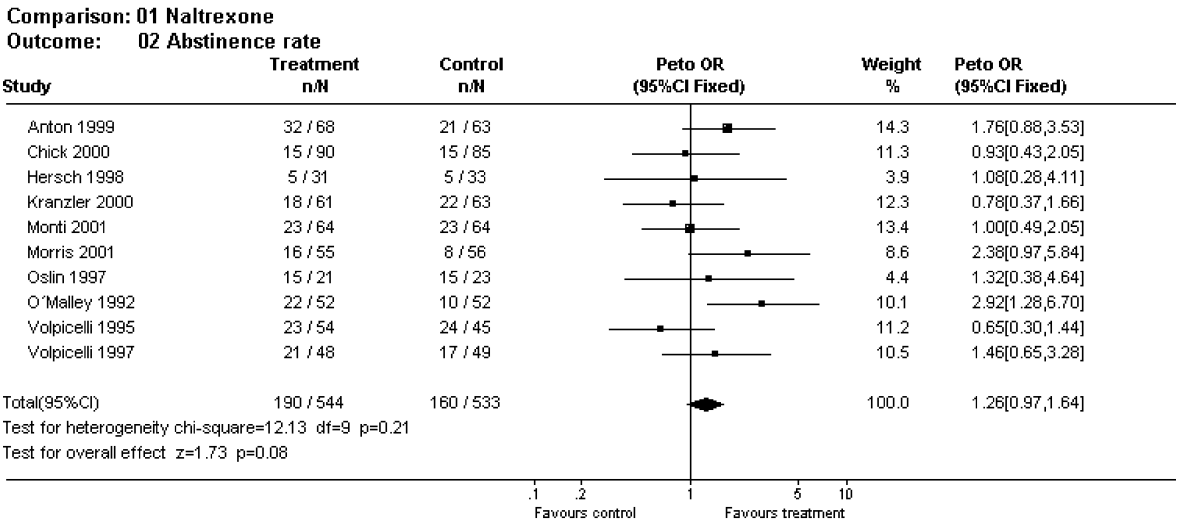

Figure 5 Short-term naltrexone versus placebo: results of the meta-analysis on abstinence rate. Fixed-effects model. OR: odds ratio; CI: confidence interval

Table 4 Effects of short-term naltrexone compared with placebo: overall results of the review for dichotomous variables on follow-up.

Outcome	*No. of studies contributing data*	*Total no. of patients*	*Test for heterogeneity*	*Mean effect size; Peto's (95% OR CI), P-value*
Relapse during follow- up	4 [34,38,45,47]	460	χ^2: 4.35; P = 0.23	0.65 (0.44, 0.97), 0.03
Abstinence during follow-up	2 [34,47]	211	χ^2: 0.0; P = 0.96	1.67 (0.92, 3.02), 0.09

Fixed-effects model.OR: odds ratio; CI: confidence interval.

effects, whether gastrointestinal (366 cases/1547 patients versus 160 cases/1017 patients) [OR (95% CI): 2.32 (1.95, 2.76); $P < 0.001$] or neuropsychiatric (659/1547 versus 380/1017) [OR (95% CI): 1.41 (1.16, 1.73); $P = 0.0008$], for the group treated with naltrexone, although in no case were these associated significantly with a higher rate of severe events, such as autolytic attack (1.4% and 1.2% in naltrexone and refer-

Table 5 Effects of short-term naltrexone compared with placebo: overall results of the review for secondary continuous outcomes.

Outcome	*Studies contributing data*	*Total no. of patients*	*Test for heterogeneity*	*Mean effect size; WMD (95% CI), P-value*
Time to relapse	4 [33,37,41,42]	1022	χ^2: 5.1; $P = 0.16$	9.29 (5.57,13.01), <0.001
Time to first drink	4 [33,37,39,41]	521	χ^2: 1.39; $P = 0.71$	0.26 (–0.41,0.93), 0.4
Drinking days	7 [9,39,41,42,44,46,51]	1172	χ^2: 12.1; $P = 0.07$	–4.49 (–5.22,–3.77), <0.001
Drinks/drinking day	5 [33,37,39,42,46]	718	χ^2: 9.4; $P = 0.052$	–0.75 (–1.20,–0.29), 0.001
Abstinent days	3 [33,37,46]	444	χ^2: 2.4; $P = 0.3$	5.94 (1.40,10.49), 0.01
Heavy drinking days	2 [41,45]	222	χ^2: 2.35; $P = 0.13$	–1.10 (–2.0,–0.21), 0.02
Total alcohol consumption (g/ week)	2 [35,46]	235	χ^2: 0.54; $P = 0.46$	–100 (–107,–93), <0.001
GGT(U/L)	6 [33,41,46,48,50,51]	604	χ^2: 4.14; $P = 0.53$	–19.9 (–24.28,–15.6), <0.001
AST (U/L)	3 [48,50,51]	308	χ^2: 0.98; $P = 0.61$	–6.99 (–8.23,–5.74), <0.001
CDT (%)	2 [33,37]	333	χ^2: 0.15; $P = 0.69$	–3.22 (–9.79,–3.36), 0.3
Craving				
Visual Analog Scale	3 [37,50,51]	398	χ^2: 2.62; $P = 0.27$	–0.3 (–0.44,–0.18), <0.001
OCDS*	2 [33,41]	255	χ^2: 3.02; $P = 0.08$	–0.99 (–1.97,–0.01), 0.05

Fixed-effects model. WMD: weighted mean difference;CI: confidence interval. GGT: gamma-glutamyltransferase. AST: aspartate aminotransferase. CDT: carbohydrate-deficient-transferrin level. OCDS*: Obsessive Compulsive Drinking Scale.

Table 6 Naltrexone versus placebo or reference group: results of the meta-analysis on compliance with treatment.

Outcome	*Studies contributing data*	*Naltrexone (cases/total of patients)*	*Comparison group (cases/total of patients)*	*Test for heterogeneity*	*Mean effect size; Peto's OR (95% CI), P-value*
Discontinuation due to side-effects	11 [9,33,35–37,38,43,44,46,48,51]	112/1089	29/803	χ^2: 17; $P = 0.06$	2.59 (1.82,3.71), <0.001
Retention rate	13 [9,33,35–37,39,41–44,46,48,51]	773/1554	586/1081	χ^2: 17.06; $P = 0.15$	0.94 (0.80,1.1), 0.5

Fixed-effects model.OR: odds ratio; CI: confidence interval.

ence group, respectively) or deterioration of hepatic function (0.9% and 0.3% in naltrexone and reference group, respectively). The most frequent side effects of naltrexone were basically nausea (14% of patients), sensation of dizziness (12% of patients) and asthenia (10% of patients). Headaches were common in both naltrexone and the comparison group (15% and 16% of patients, respectively). Taking all the studies included as a whole, only three deaths were described, one affecting a patient treated with naltrexone and two in the reference group, and all three occurred in the same study [43].

As Table 6 shows, a significantly higher number of naltrexone-treated patients withdrew from the studies prematurely because of intolerance, attributable in most instances to the development of nausea. Nevertheless, joint analysis of 13 trials indicates that naltrexone was not associated significantly with lower adherence to treatment (Table 6), although in these same studies the rate of compliance ranged from 40% [36] to 87% [33]. Although the study by Croop *et al.* [36] is a non-randomized controlled trial it was considered appropriate to include it in the meta-analysis after performing a sensitivity analysis that showed no appreciabe differences between the pooled effect sizes obtained.

Analysis of the results of the studies by Anton [33,34], Heinala [38] and Hersh [39], in which naltrexone was administered without any preceding detoxification or abstinence phase, reproduces the general results, with no substantial differences being observed *vis-à-vis* the overall position in terms of adverse effects (data not shown).

Acamprosate versus naltrexone

These drugs were compared in a multi-centre, single-blind study involving 157 males with DSM-III-R alcohol dependence and a stable family environment [49] (Table 3). The results of this trial, which shows good methodological quality as assessed by Jadad's scale, significantly favoured naltrexone in the intention-to-treat analysis of the following outcomes: rates of abstinence [Peto's OR (95% CI): 2, 90 (1.53, 5.48), $P < 0.001$] and relapse, defined as intake of over five standard drinks or 40 g of ethanol per day [Peto's OR (95% CI): 0.32 (0.16, 0.63), $P = 0.001$]; cumulative abstinence [WMD (95%

CI): 63 (24.80, 101.20), $P = 0.001$]; time to relapse [WMD (95% CI): 21.00 (9.99, 32.01), $P < 0.001$]; number of drinks per drinking day [WMD (95% CI): −5.00 (−7.04, −2.96), $P < 0.001$]; degree of craving [WMD (95% CI): −4.00 (−7.48, −0.52), $P = 0.02$] and retention rate [Peto's OR (95% CI): 2.39 (1.03, 5.53), $P = 0.04$]. No notable differences were in evidence between the two drugs in time to first intake [WMD (95% CI) 5.00 (−5.11, 15.11), $P = 0.3$].

Adverse side effects, both gastrointestinal (41 versus 12 cases) and neuropsychiatric (25 versus two cases), were higher in the group that received naltrexone, and two patients withdrew from treatment due to intolerance.

DISCUSSION

This review, which covered 33 studies published from 1990 to 2002, found evidence pointing to the effectiveness, albeit with a moderate effect size, of naltrexone and acamprosate as adjuvant treatments for alcohol dependence in adults. Similarly, it indicates that both drugs are safe and acceptably tolerated. However, the high degree of non-compliance with therapy may limit their effectiveness in clinical practice.

Acamprosate has been evaluated in studies having minimal methodological differences, a substantial number of participants, rigorous design and considerably consistent results. Joint analysis of such studies shows that this drug raises the continuous abstinence rate with a NNT of about 10 and doubles the days of cumulative abstinence, not only during the treatment phase but also in the follow-up period. Furthermore, acamprosate improves adherence to treatment and is observed to have a good safety pattern. In our opinion, the results obtained in this analysis, results which, moreover, coincide with those obtained by other authors [52–55], provide consistent evidence of the safety and efficacy of using acamprosate in tandem with different psychosocial interventions in the treatment of alcohol dependence. However, although acamprosate is usually described as an anti-craving agent, we cannot ensure this effect given the impossibility of assessing its mean effect on this particular outcome and the discrepancy in the results of the individual studies.

Although more numerous, naltrexone-based studies display a greater number of methodological limitations, which tends to hinder evaluation. Despite this, however, joint analysis shows that short-term administration of naltrexone significantly reduces the relapse rate to excessive and destructive drinking as well as outcomes linked to frequency of drinking and amount consumed, but does not substantially enhance abstinence. Naltrexone exerts a clearly favourable effect on the relapse rate (the definition of which, albeit with variations, is acceptably uniform) during the active treatment phase, which is maintained into the follow-up period, although the number of patients evaluated in this case is relatively small. Results show that during the active treatment phase with naltrexone the number needed to treat was nine, with 95% CI 6–14, for relapse avoidance. Furthermore, naltrexone significantly prolongs time to relapse and reduces the frequency of drinking, as reflected by either percentage of drinking days or number of drinks per drinking day and overall consumption, results that are comparable to those reported in earlier studies [53–59]. Similarly, in line with other authors [59], naltrexone would appear to reduce craving although, owing to the diversity of the instruments employed for measurement, there is less evidence to support the results obtained.

With respect to its effect on the abstinence rate, while our results coincide with those obtained by Agosti [60] and West [59], they do not agree with those of other authors [54,57,58]. In our case, analysis of the data on 1077 patients from 10 studies shows that, despite an upward trend in the abstinence rate for naltrexone versus placebo, this increase lacks statistical significance. The consistency of studies that have relied on methodology of a similar nature and comparable quality, which have been conducted over an equivalent time period and have used the same outcome measure definition, is confirmed by the homogeneity of the data. Moreover, the fixed-effects model used by us would appear to be suitable for calculation of the joint effect estimator [61]. Among the possible causes that might explain the difference in results, we feel that the designated search period coupled with the inclusion and exclusion criteria employed together dictate a different selection of studies, in terms both of number and characteristics, and onsequently of patients analysed. It should perhaps be said here that, to our knowledge, this review has included the greatest number of studies to date, studies which are not only published and therefore scientifically verified but also largely homogeneous. Furthermore, they are all recent studies, a factor that prevents any possible bias arising from date of publication [54,62].

Only few studies administered naltrexone with fixed medication and time for a period longer than 12 weeks. Apart from conducting different comparisons—with naltrexone being compared in two of these against a placebo or reference group, and in Rubio's study against acamprosate—these studies employ different outcome variables and report divergent results. Hence, whereas Krystal evaluates percentage of drinking days and number of drinks per drinking day at 12 months, without observing any favourable effect whatsoever for naltrexone, Landabaso reports an improvement in the abstinence rate, the relapse rate and other secondary outcomes after 6

months of treatment. It should be stressed, however, that analysis of the results of the latter study exhibits important limitations, prominent among which were the small sample size and absence of explicit references to the type of aversive medication allowed. Furthermore, only in the study by Rubio *et al*. were naltrexone and acamprosate compared. Although naltrexone proved more effective than acamprosate for all outcomes examined in this multi-centre good-quality study, the results none the less need to be replicated before naltrexone's superiority can be claimed with any certainty. Accordingly, we feel that assessment of efficacy of naltrexone administered over more than 12 weeks versus placebo or reference group is still subject to a considerable degree of uncertainty, and that its possible superiority over acamprosate ought to be verified in a greater number of patients before being considered evident.

All the studies incorporated a certain type of psychosocial therapy, although the structure and intensity of same were very different. It was therefore not possible to establish with any degree of certainty which of them might be best or which might be best suited to the therapeutic profile of acamprosate or naltrexone, even if there might be any interaction between both forms of treatment. However, the results of some individual studies coincide with those reported recently by some authors who point out that the case for formal psychosocial therapy has not been absolutely made [55], and that the widely held belief that pharmacotherapy for alcohol dependence should always be combined with psychosocial interventions is debatable and merits further research [63].

Our results indicate that approximately only half of patients receiving acamprosate or naltrexone complete the treatment. This figure, which coincides with that of previous publications [52,57,64], is clearly a cause for concern as adherence to treatment had shown itself to be a fundamental factor in the remission of alcohol dependence [4,51]. In addition, compliance is generally acknowledged to be higher within the context of controlled clinical trials than in usual care settings and, as such, is a major contributory factor to the reduction of a drug's efficacy when used in different environments [65].

In the case of naltrexone, the lower degree of compliance with treatment has been attributed to its poor tolerability and hepatic toxicity [51,64]. However, in the light of our results, a number of considerations are called for. First there is the fact that, in our analysis, similar and equally small percentages of compliance were observed in the comparison groups. In the second place, the compliance figures varied widely between studies, ranging from 40% to just under 90% of patients, something that suggests the importance of some identifiable factors, such as the demographic characteristics of the population and degree of motivation, and even others thus far unidentified. In the third place, although there are few studies that describe clearly the reasons for lack of compliance, such studies nevertheless report that only 10% of patients treated with naltrexone fail to complete the treatment due to the presence of one or more adverse drug effects, which is why we, like Streeton and Whelan [58], feel that, on the whole, naltrexone is safe and tolerated acceptably. In addition, our results show that at the currently used dose of 50 mg daily, hepatic toxicity is very unlikely. Indeed, meta-analysis shows that compared with placebo or a control group, naltrexone significantly reduces GGT and AST levels, thereby confirming its efficacy in terms of reducing alcohol consumption for which both are objective markers generally not open to bias [66].

At this precise moment in time, insufficient data exist to confirm any claim asserting the superiority of one drug over the other because the studies which assess their efficacy systematically use different outcome measures, yet the data presented in this paper nevertheless suggest a different practical application for each of the drugs. Thus, while acamprosate seems to fit in well with a classic therapeutic approach aimed at achieving total abstinence, naltrexone would appear to be more useful in a therapeutic approach geared to a lower and perhaps more controlled consumption, something that has also been shown capable of reducing the harmful consequences of alcohol dependence [4]. Moreover, it seems plausible that naltrexone may be administered safely and effectively without any preceding phase of abstinence or detoxification, which would afford indubitable advantages for clinical practice. None of the acamprosate studies has envisaged this eventuality.

Limitations

Although the available literature is, on the whole, consistent and of good methodological quality, its analysis revealed a number of problems that hinder extrapolation of the results to clinical practice. First, there is the fact that almost all the studies use strict selection criteria, thereby favouring a socially and medically stable population group that suffers from no other comorbidities or dependencies and is, in general, not averse to undergoing previous treatment: a profile that is not fully representative of patients with alcohol dependence. Secondly, the related psychosocial interventions are widely varied with regard to both orientation and to structure and intensity. Furthermore, in many studies such interventions are described inadequately, thereby hampering evaluation of the specific effect of the drugs *per se*. Thirdly, some naltrexone studies in particular have a scant sample size, which renders assessment of results

much more difficult. Fourthly, most of the studies have a relatively short duration, something that is far more evident in the case of the naltrexone studies, and fail to analyse the effects of the drugs *vis-à-vis* other outcomes, such as alcohol-related morbidity or degree of satisfaction of participants.

In addition, the meta-analysis was rendered difficult for several reasons, chief among which were: not all studies analyse the same outcomes of interest; not all describe the results quantitatively and in a comparable manner; and not all the papers furnish the measure of the degree of dispersion of the continuous variables. The outcome variables are multiple in number, are at times not systematized, whether in terms of their definition or in terms of the instrument employed for their measurement and, in some instances, may even prove somewhat inappropriate. Hence, continuous abstinence may prove too strict and perhaps somewhat unrealistic as an outcome measure, given the chronic and recurrent nature of alcohol dependence.

Another concern regards the strict criteria applied for selecting studies that may lead to publication bias, given the fact that our analysis is entirely dependent on published literature [67]. Although we recognize that the results of unpublished studies might be different from those of published studies, inclusion of unpublished data in scientific reviews remains controversial [68,69]. Some studies have shown that about 28–31% of published meta-analysis include unpublished studies and many of the systematic reviews or meta-analysis exclude explicitly unpublished studies or abstracts because they are not peer-reviewed and are therefore considered unreliable [68–70]. We also agree with recent reports indicating that the inclusion of non-full-journal publications entails important methodological problems that may lead to confounding results in the estimation of effects. The results of studies presented as abstracts usually report greater effectiveness and less adverse effects than those published as full papers and the analysis of these data is often difficult, because much of the material is incomplete [69,71,72]. In addition, some other studies have mentioned the difficulties encountered in obtaining unpublished information from industry and it is known that the use of unpublished data may not necessarily reduce the bias in meta-analysis, particularly if the unpublished data are provided by interested sources such as pharmaceutical companies [71,72]. Thus, the potential for publication bias cannot be solved satisfactorily by locating these trials [69].

Faced with these facts, in this systematic review we have attempted to reduce the possibility of publication and location bias. Therefore, in accordance with some recommendations [69,73,74] we have made a broad search of literature using at least three database sources supplemented by other search strategies. Also, in accordance with Oxman & Guyatt [73] we believe that our search for evidence was reasonably comprehensive. In addition, we have particularly included randomized studies that are less vulnerable to publication bias [69]. We have also tried to reduce the possible impact of publication bias using the fixed-effect model to combine the results of individual studies in the meta-analysis. This procedure has the advantage of reducing bias impact, as less weight is given to smaller studies which are associated with a greater risk of publication bias [75]. Concerning other statistical and modelling methods used for dealing with publication bias, such as funnel plots and sensitivity analysis, we have to say that in our case sensitivity analysis by excluding smaller and poorer quality studies did not change our results. Conversely, in line with recent reports indicating that publication bias cannot ruled out safely in the meta-analysis by means of funnel plots [16,69] we decided not to use them in our work.

In summary, although we recognize that the risk of some degree of publication bias may not have been ruled out entirely, we have tried to reduce its possible impact by some documented effective means. Further, the stringent inclusion and exclusion criteria established, the exhaustive evaluation of all references by two independent and experienced reviewers, the minimum sample size and the intention-to-treat analysis of the results make for a conservative approach to the effect of the drugs studied, rendering it rather improbable that these would appear to be effective when in reality they were not.

CONCLUSIONS

Notwithstanding its limitations, this review serves to confirm the safety and efficacy of acamprosate and naltrexone as treatments for alcohol dependence. There are insufficient data available to establish with any certainty the superiority of one drug over the other. Acamprosate seems especially useful in a therapeutic approach targeted at achieving abstinence, whereas naltrexone seems more indicated in programmes geared to controlled consumption. Although both drugs are safe and acceptably tolerated, the high degree of non-compliance with therapy may limit their effectiveness in clinical practice. In addition, there are still numerous areas of uncertainty needing further research, among which the following warrant special mention: the need for these drugs to be combined with formal psychosocial therapy and the type of psychosocial intervention best suited to each; the interaction between the therapeutic profile of these drugs and the characteristics of the participants; the optimal duration of treatment; the identification of factors that predict

poor compliance; and the search for measures that enhance patients' adherence to treatment.

Acknowledgements

We would like to thank Michael Benedict for his help with the English version of the manuscript.

References

1. Chick, J. & Erickson, C. K. (1996) Conference summary: consensus conference on alcohol dependence and the role of pharmacotherapy in its treatment. *Alcoholism: Clinical and Experimental Research*, **20**, 391–402.
2. Fuchs, C. S., Stampfer, M. J., Colditz, G. A., Giovannucci, E. L., Manson, J. E., Kawachi, I., Hunter, D. J., Hankinson, S. E., Hennekens, C. H. & Rosner, B. (1995) Alcohol consumption and mortality among women. *New England Journal of Medicine*, **332**, 1245–1250.
3. Ashworth, M. & Gerada, C. (1997) ABC of mental health: addiction and dependence-II: Alcohol. *BMJ*, **315**, 358–360.
4. Swift, R. M. (1999) Drug therapy for alcohol dependence. *New England Journal of Medicine*, **340**, 1482–1490.
5. O'Malley, S. S. (1998) *Naltrexone and alcoholism treatment. Treatment Improvement Protocol (TIP) Series 28.* NCADI, 15-10-1998. Rockville, MD: US Department of Health and Human Services. http://www.health.org/govpubs/BKD268. Accessed 21 December 2002.
6. Boening, J., Lesch, O. M., Spanagel, R., Wolffgramm, J., Narita, M., Sinclair, D., Mason, B. & Wiesbeck, G. A. (2001) Pharmacological relapse prevention in alcohol dependence: from animal models to clinical trials. *Alcoholism: Clinical and Experimental Research*, **25**, 127–131.
7. Sinclair, J. D. (1990) Drugs to decrease alcohol drinking. *Annals of Medicine*, **22**, 357–362.
8. Holder, H. D., Cisler, R. A., Longabaugh, R., Stout, R. L., Treno, A. J. & Zweben, A. (2000) Alcoholism treatment and medical care costs from Project MATCH. *Addiction*, **95**, 999–1013.
9. O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E. & Rousanville, B. (1992) Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Archives of General Psychiatry*, **49**, 881–887.
10. Volpicelli, J. R., Alterman, A. I., Hayashida, M. & O'Brien, C. P. (1992) Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry*, **49**, 876–880.
11. Sinclair, J. D. (2001) Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol and Alcoholism*, **36**, 2–10.
12. Hunt, W. A. (1993) Neuroscience research: how has it contributed to our understanding of alcohol abuse and alcoholism? A review. *Alcoholism: Clinical and Experimental Research*, **17**, 1055–1065.
13. Littleton, J. M. (1995) Acamprosate in alcohol dependence: how does it work? *Addiction*, **90**, 1179–1188.
14. Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J. & McQuay, H. J. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*, **17**, 1–12.
15. Hadorn, D. C., Baker, D., Hodges, J. S. & Hicks, N. (1996) Rating the quality of evidence for clinical practice guidelines. *Journal of Clinical Epidemiology*, **49**, 749–754.
16. Tang, J. & Liu, J. L. (2000) Misleading funnel plot for detection of bias in meta-analysis. *Journal of Clinical Epidemiology*, **53**, 477–484.
17. Modesto-Lowe, V., Burleson, J. A., Hersh, D., Bauer, L. O. & Kranzler, H. R. (1997) Effects of naltrexone on cue-elicited craving for alcohol and cocaine. *Drug and Alcohol Dependence*, **49**, 9–16.
18. Jaffe, A. J. & Rounsaville, B. (1996) Naltrexone, relapse prevention, and supportive therapy with alcoholics. An analysis of patient treatment matching. *Journal of Consulting and Clinical Psychology*, **64**, 1044–1053.
19. Pettinati, H. M., Volpicelli, J. R., Pierce, J. D. & O'Brien, C. P. (2000) Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *Journal of Addictive Diseases*, **19**, 71–83.
20. Besson, J., Aeby, F., Kasas, A., Lehert, P. & Potgieter, A. (1998) Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. *Alcoholism: Clinical and Experimental Research*, **22**, 573–579.
21. Chick, J., Howlett, H., Morgan, M. Y. & Ritson, B. (2000) United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol and Alcoholism*, **35**, 176–187.
22. Geerlings, P. J., Ansoms, C. & Van den Brink, W. (1997) Acamprosate and prevention of relapse in alcoholics. Results of a randomized, placebo-controlled, double-blind study in out-patient alcoholics in the Netherlands, Belgium and Luxembourg. *European Addiction Research*, **3**, 129–137.
23. Gual, A. & Lehert, P. (2001) Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol and Alcoholism*, **36**, 413–418.
24. Ladewig, D., Knecht, T. & Lehert, P. (1993) Acamprosate—a stabilizing factor in long-term withdrawal of alcoholic patients. *Therapeutische Umschau*, **50**, 182–188.
25. Lhuintre, J. P., Moore, N., Tran, G., Steru, L., Langrenon, S., Daoust, M., Parot, P., Ladure, P., Libert, C. & Boismare, F. (1990) Acamprosate appears to decrease alcohol intake in weaned alcoholics. *Alcohol and Alcoholism*, **25**, 613–622.
26. Paille, F. M., Guelfi, J. D., Perkins, A. C., Royer, R. J., Steru, L. & Parot, P. (1995) Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol and Alcoholism*, **30**, 239–247.
27. Pelc, I., Verbanck, P., Le Bon, O., Gavrilovic, M., Lion, K. & Lehert, P. (1997) Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. A 90-day placebo-controlled dose-finding study. *British Journal of Psychiatry*, **171**, 73–77.
28. Poldrugo, F. (1997) Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. *Addiction*, **92**, 1537–1546.
29. Roussaux, J. P. & Hersh, D. (1996) Does acamprosate diminish the appetite for alcohol in weaned alcoholics? *Journal de Pharmacie de Belgique*, **51**, 65–68.
30. Sass, H., Soyka, M., Mann, K. & Zieglgansberger, W. (1996) Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. *Archives of General Psychiatry*, **53**, 673–680.
31. Tempesta, E., Janiri, L., Bignamini, A., Chabac, S. & Potgieter, A. (2000) Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. *Alcohol and Alcoholism*, **35**, 202–209.

32. Whitworth, A. B., Fischer, F., Lesch, O. M., Nimmerrichter, A., Oberbauer, H., Platz, T., Potgieter, A., Walter, H. & Fleischhacker, W. W. (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet*, **347**, 1438–1442.
33. Anton, R. F., Moak, D. H., Waid, L. R., Latham, P. K., Malcolm, R. J. & Dias, J. K. (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. *American Journal of Psychiatry*, **156**, 1758–1764.
34. Anton, R. F., Moak, D. H., Latham, P. K., Waid, R., Malcolm, R. J., Dias, J. K. & Roberts, J. S. (2001) Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *Journal of Clinical Psychopharmacology*, **21**, 72–77.
35. Chick, J., Anton, R., Checinski, K., Croop, R., Drummond, D. C., Farmer, R., Labriola, D., Marshall, J., Moncrieff, J., Morgan, M. Y., Peters, T. & Ritson, B. (2000) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol and Alcoholism*, **35**, 587–593.
36. Croop, R. S., Faulkner, E. B. & Labriola, D. F. (1997) The safety profile of naltrexone in the treatment of alcoholism. Results from a multi-centre usage study. The Naltrexone Usage Study Group. *Archives of General Psychiatry*, **54**, 1130–1135.
37. Guardia, J., Caso, C., Arias, F., Gual, A., Sanahuja, J., Ramirez, M., Mengual, I., Gonzalvo, B., Segura, L., Trujols, J. & Casas, M. (2002) A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multi-centre clinical trial. *Alcoholism: Clinical and Experimental Research*, **26**, 1381–1387.
38. Heinala, P., Alho, H., Kiianmaa, K., Lunnqvist, J., Kuoppasalmi, K. & Sinclair, J. D. (2001) Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology*, **21**, 287–292.
39. Hersh, D., Van Kirk, J. R. & Kranzler, H. R. (1998) Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology*, **139**, 44–52.
40. Knox, P. C. & Donovan, D. M. (1999) Using naltrexone in inpatient alcoholism treatment. *Journal of Psychoactive Drugs*, **31**, 373–388.
41. Kranzler, H. R., Modesto-Lowe, V. & Van Kirk, J. (2000) Naltrexone versus nefazodone for treatment of alcohol dependence. A placebo-controlled trial. *Neuropsychopharmacology*, **22**, 493–503.
42. Krystal, J. H., Cramer, J. A., Krol, W. F., Kirk, G. F. & Rosenheck, R. A. for the Veterans Affairs Naltrexone Cooperative Study 425 Group (2001) Naltrexone in the treatment of alcohol dependence. *New England Journal of Medicine*, **345**, 1734–1739.
43. Landabaso, M. A., Iraurgi, I., Sanz, J., Calle, R., Ruiz de Apodaka, J., Jimenez-Lerma, J. M. & Gutierrez-Fraile, M. (1999) Naltrexone in the treatment of alcoholism: two-year follow up results. *European Journal of Psychiatry*, **13**, 97–105.
44. Latt, N. C., Jurd, S., Houseman, J. & Wutzke, S. E. (2002) Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. *Medical Journal of Australia*, **176**, 530–534.
45. Monti, P. M., Rohsenow, D. J., Swift, R. M., Gulliver, S. B., Colby, S. M., Mueller, T. I., Brown, R. A., Gordon, A., Abrams, D. B., Niaura, R. S. & Asher, M. K. (2001) Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. *Alcoholism: Clinical and Experimental Research*, **25**, 1634–1647.
46. Morris, P. L., Hopwood, M., Whelan, G., Gardiner, J. & Drummond, E. (2001) Naltrexone for alcohol dependence: a randomized controlled trial. *Addiction*, **96**, 1565–1573.
47. O'Malley, S. S., Jaffe, A. J., Chang, G., Rode, S., Schottenfeld, R., Meyer, R. E. & Rousanville, B. (1996) Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Archives of General Psychiatry*, **53**, 217–224.
48. Oslin, D., Liberto, J. G., O'Brien, J., Krois, S. & Norbeck, J. (1997) Naltrexone as an adjunctive treatment for older patients with alcohol dependence. *American Journal of Geriatric Psychiatry*, **5**, 324–332.
49. Rubio, G., Jimenez-Arriero, M. A., Ponce, G. & Palomo, T. (2001) Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. *Alcohol and Alcoholism*, **36**, 419–425.
50. Volpicelli, J. R., Clay, K. L., Watson, N. T. & O'Brien, C. P. (1995) Naltrexone in the treatment of alcoholism: predicting response to naltrexone. *Journal of Clinical Psychiatry*, **56**, 39–44.
51. Volpicelli, J. R., Rhines, K. C., Rhines, J. S., Volpicelli, L. A., Alterman, A. I. & O'Brien, C. P. (1997) Naltrexone and alcohol dependence. Role of subject compliance. *Archives of General Psychiatry*, **54**, 737–742.
52. Wilde, M. & Wagstaff, A. (1997) Acamprosate, a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs*, **56**, 1038–1053.
53. Hoes, M. (1999) Relapse prevention in alcoholics: a review of acamprosate versus naltrexone. *Clinical Drug Investigation*, **17**, 211–216.
54. Kranzler, H. R. & Van Kirk, J. (2001) Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. *Alcoholism: Clinical and Experimental Research*, **25**, 1335–1341.
55. Berglund, M., Andreasson, S. & Franck, J. (2002) *Treatment of alcohol and drug abuse—an evidence-based review*. http://www.sbu.se/admin/Docs/PUB/833/drugslut.htm. Accessed 21 January 2003.
56. Agosti, V. (1995) The efficacy of treatments in reducing alcohol consumption: a meta-analysis. *International Journal of the Addictions*, **30**, 1067–1077.
57. Srisurapanont, M. & Jarusuraisin, N. (2002) Opioid antagonists for alcohol dependence (Cochrane Review). *Cochrane Library*, **issue 1**.
58. Streeton, C. & Whelan, G. (2001) Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. *Alcohol and Alcoholism*, **36**, 544–552.
59. West, S. L., Garbutt, J. C. & Carey, T. S. (1999) Pharmacotherapy for alcohol dependence. Summary, evidence report/technology assessment. *Agency for Health Care Policy and Research*, **3**. AHCPR Publication No. 99-E004. http://www.ahcpr.gov
60. Agosti, V. (1994) The efficacy of controlled trials of alcohol misuse treatments in maintaining abstinence: a meta-analysis. *International Journal of the Addictions*, **29**, 759–769.
61. Fleiss, J. (1994) Measures of Effect Size for Categorical Data. In: Cooper, H. & Hedges, L. V., eds.*The Handbook of Research Synthesis*. New York: Russell Sage Foundation.
62. Hopayian, K. (2001) The need for caution in interpreting high quality systematic reviews. *BMJ*, **323**, 681–684.

63. De Wildt, W. A. J. M., Schippers, G. M., Van den Brink, W, Potgieter, A. S., Deckers, F. & Bets, D. (2002) Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? *Alcohol and Alcoholism*, **37**, 375–382.
64. Oncken, C., Van Kirk, J. & Kranzler, H. R. (2001) Adverse effects of oral naltrexone: analysis of data from two clinical trials. *Psychopharmacology*, **154**, 397–402.
65. Hughes, D. A., Bagust, A., Haycox, A. & Walley, T. (2001) The impact of non-compliance on the cost-effectiveness of pharmaceuticals. A review of the literature. *Health Economics*, **10**, 601–615.
66. Allen, J. P., Litten, R. Z., Strid, N. & Sillanaukee, P. (2001) The role of biomarkers in alcoholism medication trials. *Alcoholism: Clinical and Experimental Research*, **25**, 1119–1125.
67. Egger, M. & Davey Smith, G. (1998) Bias in location and selection of studies. *BMJ*, **316**, 61–66.
68. Cook, D. J., Guyatt, G. H., Ryan, G., Clifton, J., Buckingham, L., Willan, A., McIlroy, W. & Oxman, A. D. (1993) Should unpublished data be included in meta-analysis? Current convictions and controversies. *Journal of the American Medical Association*, **269**, 2749–2753.
69. Song, F., Eastwood, A. J., Gibody, S., Duley, L. & Sutton, A. J. (2000) Publication and related biases. *Health Technology Assessment*, **4**, 1–105.
70. Egger, M., Juni, P., Bartlett, C., Holestein, F. & Sterne, J. (2003) How important are comprehensive literature searches and the assessment of trial quality in systematic reviews. Empirical study. *Health Technology Assessment*, **7**, 1–75.
71. Davey Smith, G. & Egger, M. (1998) Meta-analysis: unresolved issues and future developments. *BMJ*, **316**, 221–225.
72. Ferguson, D., Laupacis, A., Salmi, L. R., McAlister, F. A. & Huet, C. (2000) What should be included in meta-analysis? An exploration of methodological issues. *International Journal of Technology Assessment in Health Care*, **16**, 1109–1119.
73. Jadad, A. R., Moher, D. & Klassen, T. P. (1999) Guides for reading and interpreting systematic reviews. II. How did the authors find the studies and assess their quality. *Archives of Pediatrics and Adolescent Medicine*, **152**, 812–817.
74. Oxman, A. D. & Guyatt, G. H. (1991) Validation of an index of the quality of review articles. *Journal of Clinical Epidemiology*, **44**, 1271–1278.
75. Greenland, S. (1994) Invited commentary: a critical look at some popular meta-analytic methods. *American Journal of Epidemiology*, **140**, 290–296.

