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Acamprosate supports abstinence, Naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes

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Abstract

Two pharmacological agents have repeatedly been shown to be efficacious for relapse prevention in alcohol dependence: The putative glutamate-antagonist *acamprosate* and the opioid-antagonist *naltrexone*. Clinical evidence for both drugs is based on various outcome criteria. Whereas for acamprosate primarily abstinence maintenance has been demonstrated, studies with naltrexone have mostly emphasised the prevention of heavy drinking. The remaining effects of both drugs are not always reported; accordingly the corresponding database is fragmentary. Thus, the primary objective of the present meta-analysis was to complete the efficacy profiles for acamprosate and naltrexone and to compare them with each other. Unreported results, requested from the study investigators and the drug manufacturers, were integrated in the computation of effect sizes. For the meta-analysis, emphasis was placed on the conceptual distinction between having a first drink and returning to heavy drinking. Naltrexone was found to have a significant effect on the maintenance of abstinence as well as the prevention of heavy drinking. Acamprosate was shown only to support abstinence; it did not influence alcohol consumption after the first drink. When the efficacy profiles of the two drugs were compared, acamprosate was found to be more effective in preventing a lapse, whereas naltrexone was better in preventing a lapse from becoming a relapse. The superiority of either one drug or over the other one cannot be determined as a general rule, it rather depends on the therapeutic target. Benefits in the treatment of alcohol dependence might be optimized by matching the efficacy profiles of specific antidipsotropics with the motivational status of alcohol-dependent patients.

Keywords

acamprosate, naltrexone, abstinence, relapse, meta-analysis, reporting bias, differential indication

Introduction

Relapse prevention in alcohol dependence was exclusively dominated by social and psycholocial treatments for many years. However, in the last decade, the benefits of pharmacological agents as an adjunctive therapy became increasingly evident. Two drugs were shown to be effective, not only on a primary but also on a meta-analytic level of evidence: The glutamate-antagonist *acamprosate* and the opioid-antagonist *naltrexone* (Schöchlin and Engel, 2000; Kranzler and van Kirk, 2001; Streeton and Whelan, 2001; Hopkins *et al*., 2002; Srisurapanont and Jarusuraisin, 2001; Berglund *et al*., 2003; Chick *et al*., 2003; Slattery *et al*., 2003; Mann *et al*., 2004; Bouza *et al*., 2004; Srisurapanont and Jarusuraisin, 2005). Acamprosate is available in 24 countries, mostly in Europe, Australia, South Africa and Latin America. It has been approved in the USA since 2004 after a first application was rejected by the Food and Drug Administration in 2002. Naltrexone has been approved in the United States for the treatment of alcohol dependence since 1994 and meanwhile used for this indication in many countries all over the world.

While the effectiveness of acamprosate and naltrexone is generally no longer questioned, developing strategies to optimize the treatment efficacy of antidipsotropics plays an increasingly important role in current research. Kiefer *et al*. (2003) showed that

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administering acamprosate and naltrexone together is a promising approach. Furthermore, similar to other medical and psychiatric disorders, alcohol-dependent patients may benefit from being individually allocated to receive either acamprosate or naltrexone according to their own characteristics and the specific efficacy profile of each drug. However, the comparison of efficacy profiles that is needed for an individual treatment allocation has been impeded by the fact that clinical research with acamprosate and naltrexone has been mostly limited to either one drug or the other.

Until recently, only two randomised controlled studies that included both drugs had been published (Kiefer *et al*., 2003; Anton *et al*., 2006). The remaining studies that examine either acamprosate or naltrexone have been based largely on different outcome criteria – a circumstance that is determined by cultural differences in therapeutic targets. Acamprosate studies, which have been conducted mainly in Europe, have emphasised the maintenance of abstinence as the main outcome, whereas naltrexone studies, which have occurred mainly in the United States, have focused on relapse prevention as the primary criterion for effectiveness. In this context it has to be considered that besides restrictions on the comparability of the two drugs, selective reporting of outcomes can lead to a substantial overestimation of treatment efficacy (Williams and Gamble, 2005; Chan *et al*., 2005).

Additional limitations may result from the common practice of calculating relapse rates by relating the number of relapsers to the complete study sample including both abstinent and non-abstinent patients. This is useful from a clinical perspective because it reflects the proportion of patients who benefit from treatment either by staying abstinent or by regaining control over drinking. In contrast, it does not exactly correspond to the theoretical definition of relapse as an inability to stop drinking once started (Keller, 1972), which applies only to situations in which alcohol is actually consumed. In Volpicelli *et al*.'s (1992) clinical study, where naltrexone showed a differential effect on the relapse rates of the entire sample and the subgroup of 'alcohol samplers' (alcohol-dependent patients who reported any drinking during treatment), the importance of a precise conceptualisation of relapse was pointed out.

Thus, the primary objective of the present study was to complete and to compare the efficacy profiles for acamprosate and naltrexone by including unpublished results that we requested from the study investigators and the drug manufacturers. Special attention was also given to the conceptual distinction between (a) the ability to refrain from taking the first drink after a period of abstinence and (b) the ability to stop drinking once it had started (Keller, 1972; Marlatt and Gordon, 1985).

Methods and materials

Identification of the study sample

Relevant clinical trials were identified through sequential search strategies. In the first step, an electronic literature search was performed using the Controlled Clinical Trials Register (Cochrane Collaboration) and PubMed (U.S. National Library of Medicine). The electronic search, last conducted in November 2004, was restricted to 'humans' and used the following key words and operators: (ACAM or NTX) and [(alcohol or alcoholism or drinking) or (relapse prevention or anti-craving)]. Sequentially, the reference sections of published studies and available meta-analyses were examined to identify additional trials. Unpublished studies were requested from drug manufacturers (Merck Lipha Santé, Lyon, France; Bristol-Myers Squibb Company, Princeton, New Jersey, USA; Dupont Pharmaceuticals, Wilmington, Delaware, USA).

Inclusion criteria

The meta-analysis was restricted to randomised placebo-controlled trials using placebo with acamprosate or naltrexone, or with both. Treatment duration had to be at least four weeks, and alcohol dependence had to be diagnosed by a standardised diagnostic system. For reasons of statistical power, at least ten participants per treatment group were required for inclusion.

Acquisition of unreported results

In a further step, the studies were reviewed to identify incomplete reporting of primary and secondary outcomes. Missing data were requested from both the study investigators and the drug manufacturer Merck Lipha Santé, to which some investigators referred. To avoid bias effects, results that were provided but which had not been explicitly requested were not included.

Outcome measures

The primary treatment outcomes that were used in the meta-analysis were a return to any drinking and a return to heavy drinking. Return to any drinking was defined as having the first drink after a period of continuous abstinence; return to heavy drinking was defined in accordance with the primary trial, usually defined as having more than five standard drinks per drinking occasion for men. Thereby different measures of standard drinks have been used in the primary studies, varying from 10 to 13.6 g of pure alcohol. In most acamprosate studies, patients were considered as continuously controlled when Percentage of Controlled Days (PCD) was 100%, whereby PCD was defined as the sum of time intervals during which the patient remained with a controlled consumption defined as a maximum of five standard drinks, divided by the expected duration of the trial.

Relapse rates were evaluated for the complete study sample and for the subgroup of non-abstinent patients. The former indicates the risk of relapse for all treated patients independently of their status of abstinence, whereas the latter indicates relapse only on the condition that alcohol had been consumed.

Secondary outcome measures were days drinking per week, quantity consumed per day, time to the first drink, time to first relapse and level of gamma-glutamyl transpeptidase. Time to first drink was defined as the number of days of continuous abstinence, whereas time to first relapse was the time interval before the first occurrence of heavy drinking.

Data extraction and coding

Patient characteristics, characteristics of the treatment, the study design, and primary and secondary treatment outcomes were coded onto data forms. The outcomes of a randomly selected 25% of all the trials were independently evaluated by two reviewers (SR and SL), which yielded an interclass correlation coefficient of $\kappa = 1.00$. One reviewer (SR) coded the remaining studies.

When results in the publications were given both graphically and numerically, the numerical values were extracted. Indicators of methodological quality (e.g. dropout and compliance rates, validity of outcome measures, and operationalisations) were rated separately. To increase the quality of the data extraction, the rules for assigning values were clearly defined in the instructions to the raters.

Data synthesis

For dichotomous outcomes, relative risk (RR) was calculated as the risk of an event in the intervention group divided by the corresponding risk in the control group, within a 95% confidence interval (95% CI). Analyses for dichotomous variables were performed exclusively as an intention-to-treat analysis, and dropouts were classified as treatment failures. Additionally, for the significant effects the number-needed-to-treat (NNT), defined as the reciprocal of the risk difference between the treatment and the placebo group, was examined. Continuous outcomes were analysed as standardised mean differences (SMD), i.e. the difference in means divided by the standard deviation (Hedges and Olkin, 1985).

Effect sizes were combined simultaneously for different outcomes and treatment interventions. The statistical model for effect integration was chosen in accordance with the statistical heterogeneity of the effect sizes: A fixed-effect model (Mantel and Haenszel, 1959) was used for homogenous effects; a random-effects model (DerSimonian and Laird, 1986) was used for data with significant heterogeneity. Heterogeneity was evaluated with the Q-statistic ($\alpha = 0.05$) and the I^2-statistic (Higgins *et al*., 2002). To evaluate the risk of a publication bias, funnel plots as described by Light and Pillemer (1984) and rank-order correlations between the estimated effect sizes and the variance (Begg, 1988) were used. The meta-analytic integration of effect sizes was performed with RevMan (Version 4.2; Cochrane Collaboration, 2005). The number needed to treat was calculated with STATA™ (Version 8.0) for Windows.

Results

Identified studies and provided outcomes

With the sequential use of search strategies, a total of 67 potentially relevant randomized placebo-controlled trials evaluating acamprosate and naltrexone were identified (acamprosate: 32; naltrexone: 35). In addition to the study publications, an internal report was obtained from the manufacturer of acamprosate (Lipha Pharmaceuticals, 2002), which includes a systematic presentation of study features and outcomes from 10 published acamprosate trials and one multi-centre trial that has only been released as an abstract at that time (Mason, 2006). Another unpublished acamprosate trial (Borg, 2003) was pointed out by the manufacturer Merck Lipha Santé and two naltrexone trials, which have exclusively been published as congress abstracts (Auriacombe *et al*., 2000; Rybakowski *et al*., 1997), were identified through the reference section of a systematic review (Berglund *et al.*, 2003). After applying our inclusion criteria, 26 trials had to be excluded because of marginal sample size, insufficient treatment durations, or the absence of a control group. Exclusion concerned 24 published and three unpublished trials. Finally, 21 randomized controlled trials using acamprosate and 20 randomized controlled trials using naltrexone were included in the meta-analysis (see Table 1).

Within the second step in the process of data research that addressed unreported results within published trials, a total of 32 investigators and Merck Lipha Santé (the manufacturer of acamprosate) were contacted. Results from 18 randomized controlled acamprosate trials and four randomized naltrexone studies were referred to the authors. Table 2 gives details about the trials that were included in the meta-analyses, showing the number of participants and the weighted proportion of unpublished results for primary and secondary treatment outcomes.

Studies with acamprosate

Among a total of 5280 alcohol-dependent men and women, 21 randomized controlled trials evaluated the safety and efficacy of acamprosate compared to placebo. Except for one study each from the United States (Mason, 2001), South Korea (Namkoong *et al*., 2003), and Brazil (Baltieri and de Andrade, 2003), all of the trials were conducted in Europe. Treatment duration varied from two months (Namkoong *et al*., 2003) to one year (Besson *et al*., 1998; Sass *et al*., 1996; Whitworth *et al*., 1996), with 6 months as the most common duration. Sample size ranged from $n = 26$ (Niederhofer and Staffen, 2003) to $n = 581$ (Chick *et al*., 2000a).

The mean age of the patients was between 40 and 50 years. However, Niederhofer and Staffen (2003) evaluated the safety and efficacy of acamprosate in a sample of adolescent patients. Besides DSM-III-R or DSM-IV (American Psychiatric Association, 1987, 1994) diagnostic criteria for alcohol dependence, the most common inclusion criteria were duration of dependence of at least one year and a mean corpuscular volume (MCV) greater than 96 fl. Treatment with acamprosate started between 5 and 14 days after alcohol detoxification. In one study, acamprosate was prescribed from the beginning of detoxification (Gual and Lehert, 2001).

Aacamprosate was usually prescribed in a weight-dependent dosage of 1.332 mg per day for a body weight up to 60 kg and 1.998 mg per day for a body weight greater than 60 kg. Kiefer *et al*. (2003) compared acamprosate, naltrexone, and a combination of the two with placebo. All studies were conducted in outpatient settings that used psychosocial interventions. In all cases, continuous abstinence from alcohol was the primary treatment goal.

Studies with naltrexone

Among a total of 2182 alcohol-dependent men and women, 20 randomized controlled trials investigated the safety and efficacy of

Table 1 Characteristics of clinical trials included in the meta-analysis

Acamprosate				Naltrexone			
Author and date	Country	Trial duration (days)	Number of patients	Author and date	Country	Trial duration (days)	Number of patients
Baltieri & de Andrade (2003)	Brazil	90	75	Anton et al. (1999)	USA	90	131
Barrias et al. (1997)	Portugal	360	302	Balldin et al. (1999)	Sweden	168	118
Besson et al. (1998)	Switzerland	360	110	Chick et al.(2000b)	UK	90	164
Chick et al. (2000a)	UK	180	581	Gastpar et al. (2002)	Germany	90	171
Geerlings et al. (1997)	Benelux	180	262	Guardia et al. (2002)	Spain	90	202
Gual & Lehert (2001)	Spain	180	288	Heinälä et al. (2001)	Finland	90	121
Kiefer et al. (2003)	Germany	90	80	Hersh et al. (1998)	USA	56	64
Ladewig et al. (1993)	Switzerland	180	61	Kiefer et al. (2003)	Germany	90	80
Lhuintre et al. (1985)	France	90	70	Killeen et al. (2004)	USA	90	97
Lhuintre et al. (1990)	France	90	569	Kranzler et al. (2000)	USA	90	87
Mason (2001)[a]	USA	180	510	Krystal et al. (2001)	USA	360	627
Namkoong et al. (2003)	Korea	56	142	Latt et al. (2002)	Australia	51	107
Niederhofer & Staffen (2003)	Austria	90	26	Lee et al. (2001)	Singapore	90	53
Paille et al. (1995)	France	360	538	Monti et al. (2001)	USA	90	128
Pelc et al. (1992)	Belgium	180	102	Morris et al. (2001)	Australia	90	111
Pelc et al. (1997)	Belgium	90	188	O'Malley et al. (1992)	USA	90	104
Poldrugo (1997)	Italy	180	246	O'Malley et al. (2003)	USA	180	113
Rousseaux et al. (1996)	Belgium	90	127	Oslin et al. (1997)	USA	90	44
Sass et al. (1996)	Germany	360	272	Volpicelli et al. (1992)	USA	90	70
Tempesta et al. (2000)	Italy	180	330	Volpicelli et al. (1997)	USA	90	97
Whitworth et al. (1996)	Austria	360	448				

[a] unpublished

Table 2 Sample size and proportion of unpublished data

Acamprosate	Sample (total)		Proportion of unpublished data		
	Studies	Patients	Studies	Patients	Portion[a]
Outcome criteria	n	n	n	n	%
Abstinence	20	5280	1	518	10.8
Relapse	11	3172	9	2511	79.2
Time to first drink	6	1863	5	1561	83.8
Time to first relapse	1	142	1	142	100.0
Days drinking per week	14	3866	14	3866	100
Consumed amount per day	15	3945	14	3866	98.0
Gamma-Glutamyl Transpeptidase	6	1263	0.0	0	0.0
Naltrexone	Sample (total)		Proportion of unpublished data		
	Studies	Patients	Studies	Patients	Portion[a]
Outcome criteria	n	n	n	n	%
Abstinence	18	2182	3	869	33.8
Relapse	18	2182	3	738	0.0
Time to first drink	20	2475	0	0	0.0
Time to first relapse	5	770	1	111	4.4
Days drinking per week	5	1259	1	111	4.4
Consumed amount per day	11	1444	1	202	14.0
Gamma-Glutamyl Transpeptidase	6	675	1	111	16.4

[a]sample weighted portion

naltrexone. Most of the studies were conducted in the United States ($n = 11$), but there were also some in Europe ($n = 6$), Australia ($n = 2$) and Asia ($n = 1$). Treatment duration varied between 51 days (Latt *et al*., 2002) and one year (Krystal *et al*., 2001), but a duration of three months was most common. The largest trial included 15 treatment centres and 627 patients (Krystal *et al*., 2001).

The mean age of the patients was between 36 and 58 years. However, Oslin *et al*. (1997) evaluated the efficacy of naltrexone with military veterans whose age ranged from 50 to 70 years. Besides a DSM-III-R or DSM-IV (American Psychiatric Association, 1987, 1994) diagnosis of alcohol dependence, the most common inclusion criterion was consumption of at least five standard drinks of alcohol per day or excessive drinking on at least two days per week, or both. Hersh *et al*.'s (1998) trial evaluated the efficacy of naltrexone in the treatment of comorbid alcohol- and cocaine-use disorders.

O'Malley *et al*.'s (1992) and Heinälä *et al*.'s (2001) placebo-controlled trials compared the efficacy of naltrexone in combination with either supportive or coping-skills therapy. In combination with primary-care management and cognitive-behavioural therapy, O'Malley *et al*. (2003) compared naltrexone with placebo in combination with primary care management and cognitive behavioural therapy, using a nested sequence of three randomized-controlled trials.

Treatment with naltrexone was administered in a dose of 50 mg per day and always combined with a psychosocial intervention. Depending on the trial, either abstinence or controlled drinking was the primary treatment goal.

Relative risk of first drink after abstinence

As Fig. 1 shows, treatment with acamprosate significantly reduced the risk of having a first drink to 84% of the risk with a placebo treatment (RR = 0.84, 95% CI: 0.78–0.91). Eight patients must be treated to prevent one additional incidence of drinking (NNT = 7.7, 95% CI: 5.6–13.0). The 10.8% weighted proportion of unpublished data (see Table 2) can be attributed entirely to the inclusion of abstinence rates from the U.S. multi-centre trial (Mason, 2001).

Naltrexone significantly increased abstinence from alcohol. The risk of having a first drink by taking naltrexone was reduced to 93% of the risk in the control group (RR = 0.93, 95% CI: 0.88–0.99, see Fig. 2). To prevent one additional incidence of drinking, 17 patients must be treated with naltrexone (NNT = 17.4, 95% CI 9.7–111.0). The sample-weighted proportion of unpublished data is 33.8% (see Table 2).

Relative risk of heavy drinking

The relative risk of relapse to heavy drinking in the complete sample was lowered significantly by acamprosate from that achieved with placebo (RR = 0.82, 95% CI: 0.73–0.92; see Fig. 3;

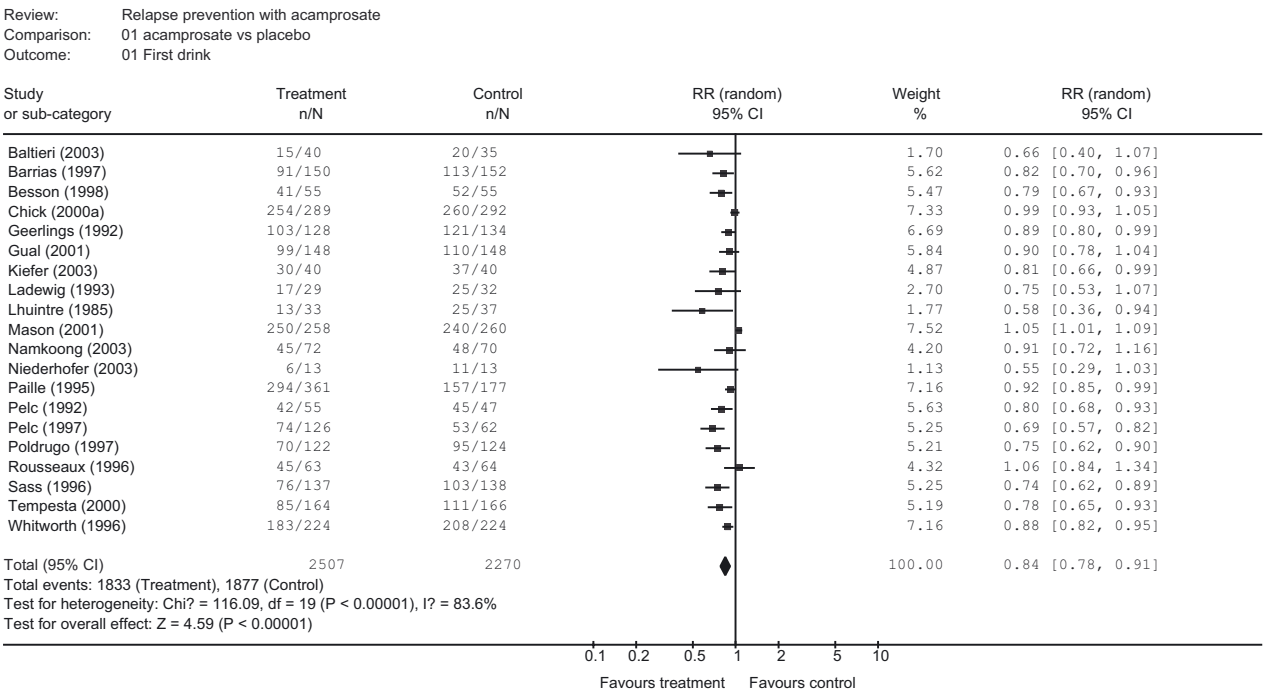

Figure 1 Relative risk ratio from acamprosate

NNT = 8.6, 95% CI: 5.7–18.7). The proportion of unpublished results is 79.2% (see Table 2).

As Fig. 4 shows, naltrexone significantly lowered the risk of heavy drinking in the complete sample to 80% over that achieved with placebo (RR = 0.80, 95% CI: 0.71–0.91; NNT = 8.1, 95% CI: 5.5–16.5). All of the results related to relapse were reported in the trial publications.

Within the subgroup of non-abstinent patients, acamprosate had no significant effect on the risk of heavy drinking (RR = 0.98, 95% CI: 0.94–1.02; see Fig. 5). Similar to the relapse rates in the com-

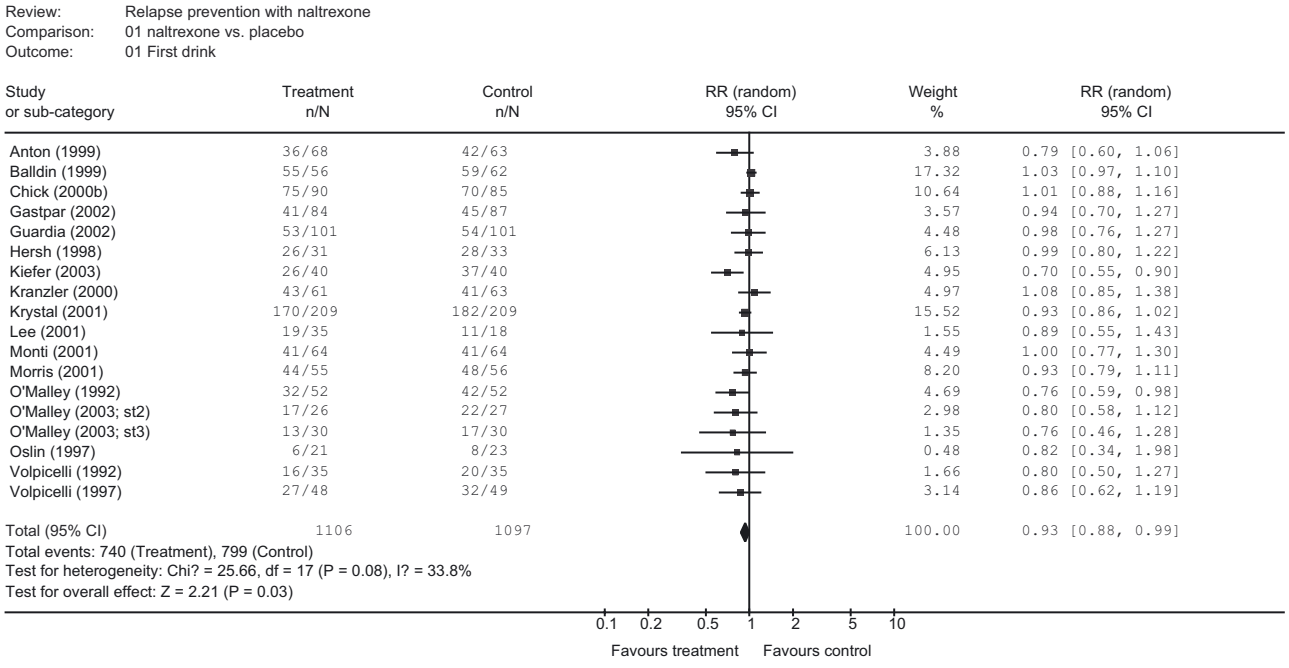

Figure 2 Relative risk ratio from naltrexone

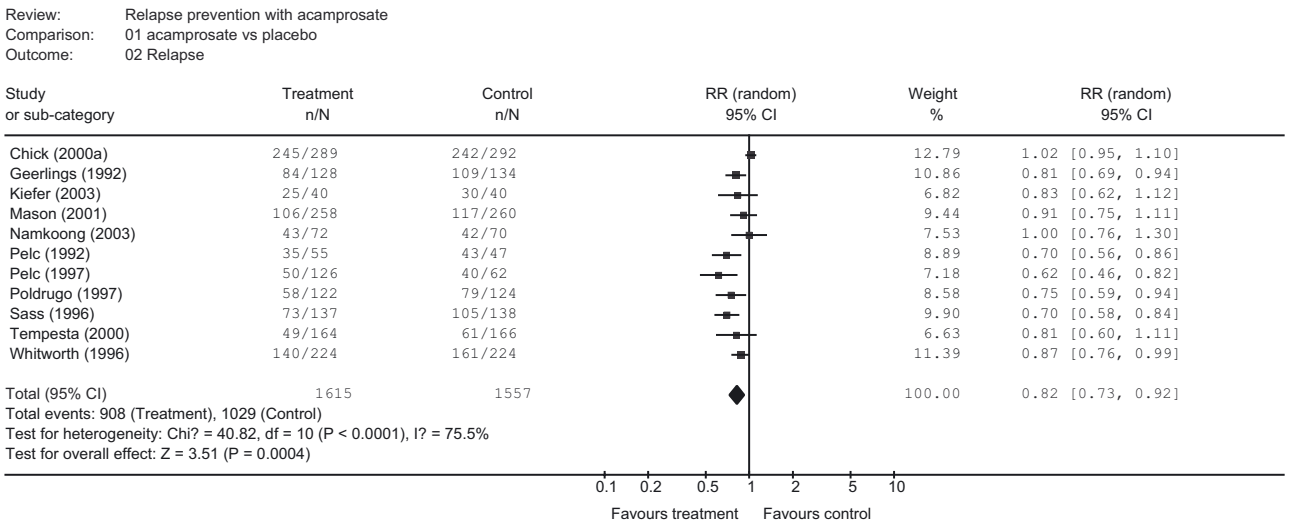

Figure 3 Relative risk ratio from acamprosate

plete sample, the proportion of unpublished results was 79.2% (see Table 2).

Naltrexone produced a significant reduction in heavy drinking compared to placebo (RR = 0.88, 95% CI: 0.80–0.96; see Fig. 6) in the subgroup of non-abstinent patients. Nine non-abstinent patients must be treated with naltrexone to prevent one additional occurrence of relapse. No unpublished data were included in the analysis.

Secondary outcomes

The secondary outcomes for acamprosate and naltrexone are shown in Table 3. Acamprosate significantly prolonged the time to first drink (SMD = 0.22, 95% CI: 0.05–0.38), but naltrexone did not (SMD = 0.06, 95% CI: −0.10–0.21). Time to first heavy drinking was not examined in clinical trials for Acamprosate; the corresponding effect of naltrexone was marginally significant ($p = 0.052$). Drinking frequency was significantly reduced by acamprosate (SMD = −0.19, 95% CI: −0.26 to −0.13, $p < 0.001$) and naltrexone (SMD = −0.14; 95% CI: −0.25 to −0.03, $p < 0.05$). Gamma-glutamyl transpeptidase (GGT) was significantly reduced by naltrexone (SMD = −0.37, 95% CI: −0.51 to −0.22), and the effect of acamprosate on GGT (SMD = −0.34, 95% CI: −0.69 to −0.01) was marginally significant (n.s., $p = 0.057$). Naltrexone's largest effect was on the amount of alcohol consumed (SMD = −0.89, 95% CI: −1.88–0.10), but this effect did not reach significance because of the high heterogeneity of effects.

Publication bias

Figure 7 shows the funnel-plot for the logarithm of the relative risks of having a first drink plotted against the standard error. Asymmetry is caused by missing effect sizes in the area of high standard errors in the top right field of the plot. The corresponding funnel-plot for relapse rates shows a similar asymmetry (data not shown). Using Kendall's test, corrected z-values (first drink: $z = -1.02$; $p = 0.31$; relapse: $z = -1.68$, $p = 0.09$), examined according to Begg (1988), indicated no significant correlations.

Discussion

The problem of publication bias has received a comparatively large amount of attention in the scientific community; however, the issue of selective reporting (i.e. selecting a subset of outcomes within published studies) has not been discussed until recently (Williamson and Gamble, 2005). It has been shown that within-study selective reporting of outcomes can have a substantial impact on the results of meta-analytic integrations (Chan *et al*., 2005; Williamson and Gamble, 2005). Besides the risk of overestimating 'true' effects, non-reporting of results also decreases the accuracy and generalizability of meta-analyses and predetermines the verification of research hypotheses to a restricted selection of published outcomes.

Considering these limitations, unreported results from clinical trials with acamprosate and naltrexone were requested from study investigators and drug manufactures. In this way, published and unpublished outcomes from 41 randomized controlled studies were identified and included in meta-analytic integration of treatment effects. Thus, the present meta-analysis probably allows the most comprehensive evaluation of acamprosate and naltrexone that has been published so far.

The integrated effects of the meta-analysis that are based on reported outcomes correspond to the drug's primary mechanisms of action. Even though not completely clarified yet, the efficacy of acamprosate is presumably based on its ability to regulate withdrawal-induced glutamatergic hyperexcitability, whereas the efficacy of naltrexone is mediated primarily by its antagonistic properties in the endogenous opioid system (Volpicelli *et al*., 1995; Spanagel *et al*., 2005). Consequently, maximum efficacy for

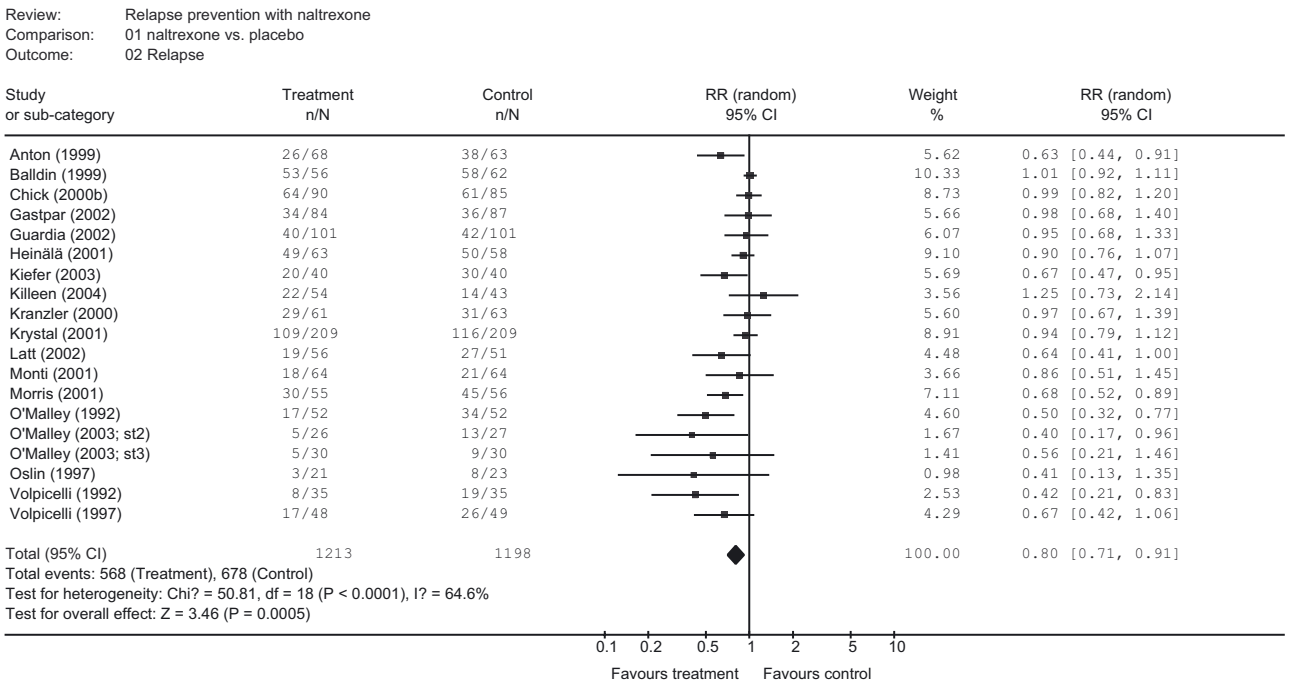

Figure 4 Relative risk ratio from naltrexone

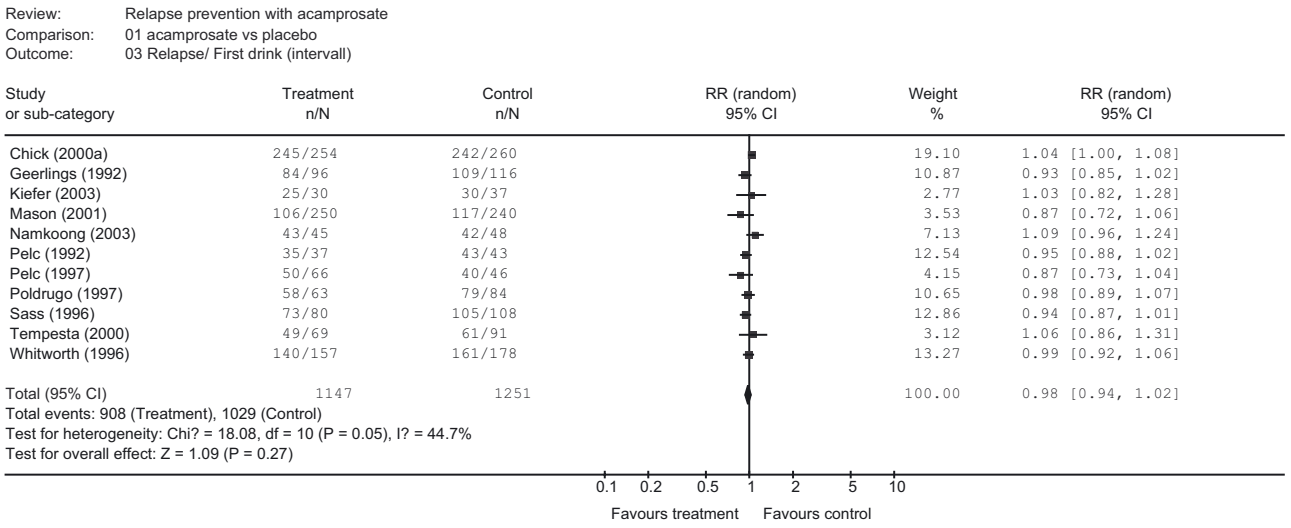

Figure 5 Relative risk ratio from acamprosate

each drug is expected under different conditions: Acamprosate presumably works best in controlling the desire to drink after a period of abstinence (Littleton and Zieglgängsberger, 2003), and naltrexone is expected to be most efficacious while the person is still drinking (Sinclair, 2001). In the meta-analysis, the corresponding components of efficacy have been demonstrated: Acamprosate reduced the risk of having a first drink after abstinence to 84%, whereas naltrexone reduced the risk of heavy drinking in non-abstinent patients to 88% compared to the control groups.

A more controversial issue is whether the efficacy of each drug is restricted to these conditions. In other words, in addition to preventing excessive drinking, does naltrexone also improve abstinence? And besides preventing a lapse, does acamprosate also

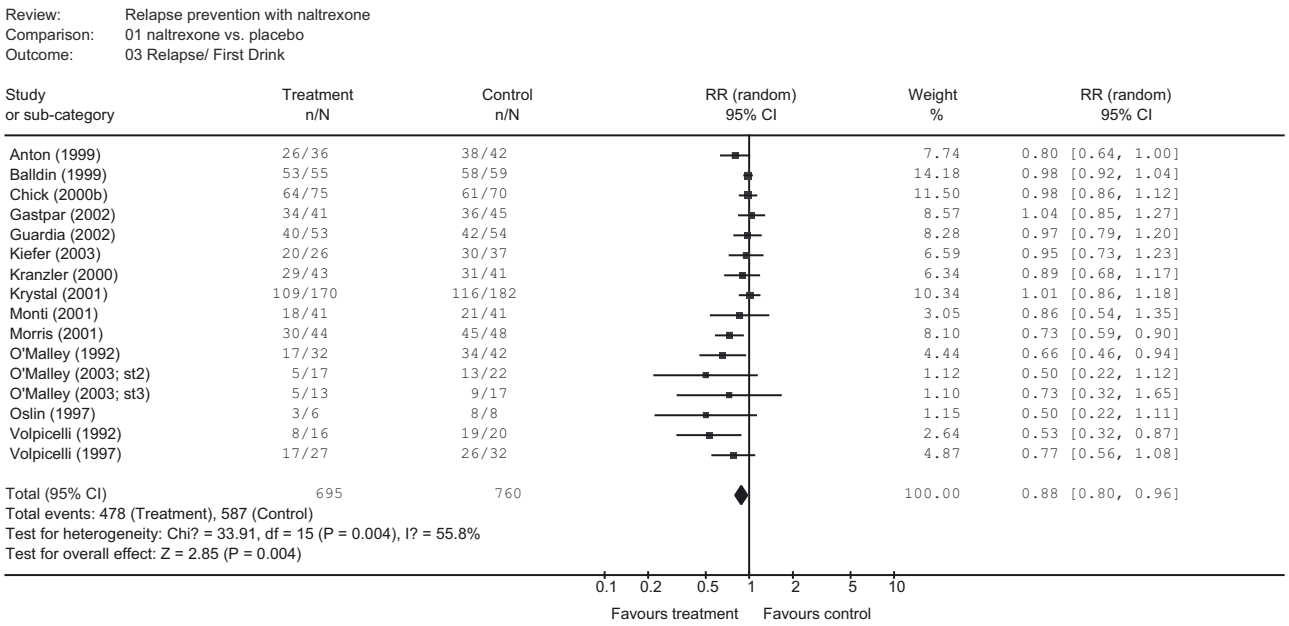

Figure 6 Relative risk ratio from naltrexone

Table 3 Effects of acamprosate and naltrexone on secondary outcomes

Outcome criteria	Acamprosate				Naltrexone			
	SMD	95% CI		p	SMD	95% CI		p
Time to first drink	0.22	0.05	0.38	< 0.01	0.06	20.10	0.21	n. s.
Time to first relapse					0.97	−0.01	1.94	n. s.
Drinking days per week	−0.19	−0.26	−0.13	< 0.001	−0.14	−0.25	−0.03	< 0.05
Consumed amount per day	−0.22	−0.29	−0.16	< 0.001	−0.89	−1.88	0.10	n. s.
Gamma-Glutamyl Transpeptidase	−0.34	−0.69	0.01	n. s.	−0.37	−0.51	−0.22	< 0.01

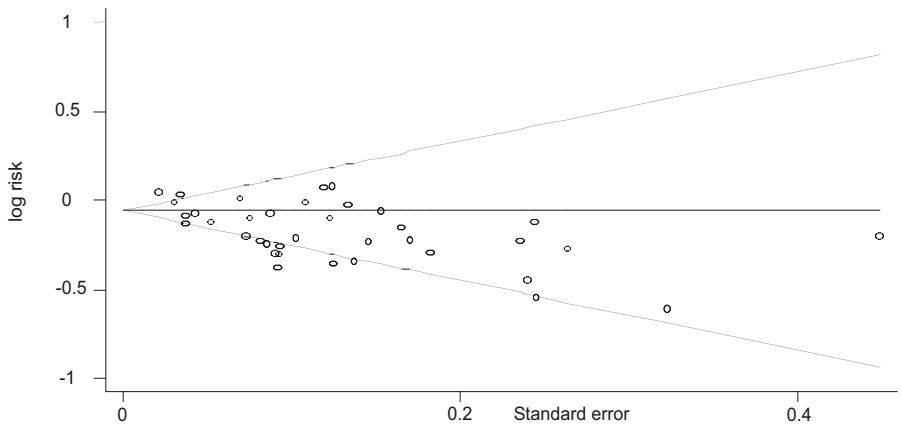

Figure 7 Funnel-plot for the relative risk of having a first drink

reduce the risk of a lapse becoming a relapse? Sinclair (2001) assumes that 'if there's no alcohol consumed, there's no alcohol-induced opioids to be blocked by naltrexone'. In that case, an opioid antagonist would not work when taken during abstinence. Similarly, it would be expected that if withdrawal-induced hyperexcitability were already reduced by alcohol, there would be no withdrawal symptoms to be regulated by a glutamate antagonist. Consequently, acamprosate would not work when taken during drinking episodes.

The meta-analysis confirms the latter expectation but not the former one. Contrary to Sinclair's hypothesis, naltrexone was shown to have a significant effect on the maintenance of abstinence, although with a lower magnitude than for the prevention of excessive drinking. These results support O'Malley and Froehlich's (2003) hypothesis that naltrexone blocks both the immediate effects of alcohol and responses to conditioned reinforcing cues, which otherwise would induce a 'conditioned high' and trigger a relapse.

In contrast, no relapse preventing effect was shown for acamprosate if the computation of relapse rates was restricted to alcohol samplers. Accordingly efficacy of acamprosate only occurs during periods of abstinence. Similar evidence has been found in clinical studies (Chick *et al*., 2000a; Namkoong *et al*., 2003) in which acamprosate was found not to be efficacious for patients who had resumed drinking before the medication was started (Chick *et al*., 2000a; Namkoong *et al*., 2003).

It has to be considered that the demonstrated failure of acamprosate to prevent heavy drinking exclusively relates to drinking within the sampling-situation. In accordance with the results of a meta-analyses performed by Chick *et al*. (2003), significant effects were shown for the entire sample including non-abstinent as well as abstinent patients. Additionally the non-significant results do not indicate that the substance is losing its efficacy in the course of further treatment. It might be possible that acamprosate will support abstinence after a second, third or even later attempt in an undiminished way. The development of acamprosate's effectiveness after treatment failures needs to be evaluated in further clinical trials.

In summary, the comparative evaluation of acamprosate and naltrexone pointed to specific therapeutic advantages of each drug. Acamprosate is the medication of choice if the goal is complete abstinence, whereas naltrexone can be used to prevent excessive drinking in non-abstinent patients. Given that both drugs are available, discrepancies in efficacy profiles could be used for differential indications. Based on the assumption that: (a) different therapeutic goals are appropriate for different patients and (b) continuous abstinence is generally associated with the highest benefit in the treatment of alcohol dependence, patients who are motivated to achieve complete abstinence could be allocated to an abstinence-oriented treatment that uses acamprosate, whereas patients with a long history of treatment failures and a low motivation for abstinence could be allocated to a harm-reduction treatment in which naltrexone is used. In this way, individually allocating patients to treatments according to their motivational status could further enhance the effectiveness of treatments for alcohol dependence.

In comparison to other mental disorders, a risk reduction that varies between 7% and 20% (depending on the treatment outcome and sample of patients) might seem low (Kranzler and Kirk, 2001). However, it should also be considered that systematic variations in study designs and treatment implementations potentially influence the magnitude of effects. For example, low treatment compliance and high dropout rates reduce the statistical power of addiction-research studies probably more than in most other kinds of psychiatric research. In addition, effect sizes obtained with acamprosate and naltrexone are based entirely on clinical trials that use antidipsotropics only as an adjunct to psychosocial and psychotherapeutic interventions. Accordingly, effect sizes do not reflect the therapeutic advantages of acamprosate and naltrexone compared to placebo; rather, they reflect an additional effect over that obtained with psychosocial treatment alone – a fact that often leads to misleading interpretations. Effect sizes in studies that use only placebo would be expected to exceed the effects that are demonstrated in studies that additionally use psychosocial treatment.

The present meta-analysis also indicates the importance of explicitly differentiating between relapses for an entire group of patients and those for a subgroup of non-abstinent patients. Whereas standardization based on a sample of all treated patients is a useful way to evaluate treatment efficacy in general, the influence of a substance on relapse and excessive drinking can only be examined if the computation of relapse rates is restricted to the subgroup of patients who are not abstinent. The adequacy of this calculation is also made clear when one considers that a relapse can occur only if alcohol is consumed.

Results of the meta-analytic integration have to be evaluated against the background of some methodological limitations, which mainly concern the comparative evaluation of acamprosate and naltrexone. Because the study design of trials with acamprosate and naltrexone differ systematically from each other (e.g. in treatment duration, inclusion criteria, the use of psychosocial interventions), effect sizes that are obtained cannot be attributed exclusively to the treatment intervention. Differences in patient recruitment as well as criteria of in- and exclusion have been discussed in the literature as factors that might limit the comparability between studies with acamprosate and naltrexone (Anton *et al*., 2006; Lipha Pharmaceuticals, 2002). Patient recruitment by advertisement, which was applied in US naltrexone trials, might determine a lower grade of patient's dependence than the recruitment from inpatient settings, conducted in European acamprosate studies. On the other hand, some US trials also include patients with psychiatric comorbidity as well multiple substance use, whereas these patient groups have been excluded in most trials with acamprosate. Above all, the potential effects of the treatment goal (abstinence versus harm reduction) must be taken into consideration. Perhaps acamprosate was shown to be better in helping to maintain abstinence because abstinence was the exclusive goal of the psychosocial intervention and not because of the drug's pharmacological effects. And perhaps naltrexone was shown to be better in preventing excessive drinking because the cognitive-behavioural strategies that were used were focused more on preventing heavy drinking than on maintaining abstinence. This might also be a reason for the non-significant effects shown for acamprosate on drinking in the COMBINE study

(Anton *et al*., 2006), a large multi-centre trial that was recently conducted in the United States and a current study from Australia (Morley *et al*., 2006). One difference compared to most of the previous studies was the comprehension of cognitive behavioural strategies that teach how to cope with a lapse (Kadden *et al*., 1999). Negative effects on a patient's commitment to abstinence caused by techniques that consider the possibility of treatment failures have been demonstrated in other fields of addition therapy (Supnick and Colletti, 1984; Wassermann *et al*., 1998). Because treatment goals do not systematically vary within studies using acamprosate and naltrexone, their influence cannot be examined on a meta-analytic level. Thus, this question must be addressed in future clinical trials.

Further limitations may derive from the fact that controlled drinking is not the main outcome criteria in acamprosate studies. Thus, the outcome was not focussed in primary research and classifications of patients as controlled drinkers or relapsers were done after study completion for the purpose of the meta-analysis. Thereby classification of patients as relapsers in acamprosate studies are based on mean values related to certain time intervals, thus data evaluation of uncontrolled drinking in these studies is less accurate than in most naltrexone studies. Thus, further clinical studies for acamprosate that explicitly examine controlled drinking, are needed.

Additionally, a large range of effect sizes was shown for all primary outcomes, illustrating the diverse nature of the studies in terms of design and methodology. Because the sources of variance are not entirely clear, threats to the internal validity of meta-analytic integrations cannot be entirely excluded.

Finally, comparisons between acamprosate and naltrexone should optimally be derived from randomized clinical trials that include both drug treatments as well as different types of treatment outcomes. The study by Kiefer *et al*. (2003) and Project COMBINE (Anton *et al*., 2006) meet these criteria. As long as such trials are rare, meta-analytic comparisons of acamprosate and naltrexone can be a useful method to further characterize the efficacy profiles of both drugs and to additionally deduce strategies and hypotheses for further research.

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M. Soyka and P. Lehert have worked as consultants for Lipha Pharmaceuticals and Forest Laboratories.

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