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Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients

Received: 15 December 2003 / Accepted: 19 February 2004 / Published online: 19 August 2004
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Abstract *Rationale:* Acamprosate is a proven effective intervention in the treatment of alcohol dependence. However, acamprosate prevents lapses or relapses only in a minority of patients. An important question, therefore, is whether there is a specific subgroup of patients who respond particularly well to acamprosate. *Objectives:* To identify predictors of acamprosate efficacy. Based upon the available evidence and hypotheses about the mechanisms underlying acamprosate's effects on drinking behavior, the following variables were considered to be potential positive predictors: high physiological dependence at baseline, negative family history of alcoholism, late age-of-onset, serious anxiety symptomatology at baseline, severe craving at baseline, and female gender. *Method:* Potential predictors of acamprosate's efficacy were

analyzed in a pooled analysis of data from seven randomized placebo-controlled trials involving a total of 1485 patients with alcohol dependence. Outcome is measured in terms of cumulative abstinence duration (CAD), continuous abstinence (ABST), and time to first relapse (TFR). *Results:* CAD and ABST were predicted by baseline measures of craving and anxiety, as well as by study and treatment condition. Acamprosate efficacy was not differentially associated with any of the predictor variables. Importantly, the hypotheses were rejected despite the large sample size and sufficient statistical power. *Comment:* The most straight-forward clinical implication of this study is that acamprosate can be considered as a potentially effective pharmacotherapy for all patients with alcohol dependence. The effect size of acamprosate alone is, however, moderate. Some evidence indicates that the combination of acamprosate with naltrexone or disulfiram leads to substantially better outcomes.

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Keywords Campral · Acamprosate · Efficacy ·
Effectiveness · Predictors · Patient-treatment matching

Introduction

The efficacy of oral acamprosate given to alcohol-dependent patients after detoxification has been investigated in several well designed double-blind randomized placebo-controlled trials (RCTs) (Sass et al. 1996; Whitworth et al. 1996). In these trials, acamprosate was consistently found to be more effective than placebo in preventing alcohol relapse. In a pooled analysis of data from 11 RCTs involving a total of 3,338 patients with alcohol dependence, abstinence rates after 6–12 months were significantly greater with acamprosate than with placebo (35% versus 24% and 33% versus 21%, respectively) (Sass 1995). Thus, although clearly efficacious in some patients, acamprosate has been shown not to prevent lapses or relapses in the majority. Given this observation, the question is whether there is a specific

subgroup of patients who will respond particularly well to acamprosate (Schuckit 1996; Wilde and Wagstaff 1997). Cumulative evidence supports the idea that matching can improve outcome in other pharmacotherapies for alcohol dependence. For example, it has been found that the selective 5-HT₃ antagonist ondansetron is an effective treatment of alcohol dependence only in early-onset alcoholics (Johnson et al. 2000). Furthermore, naltrexone works better in alcohol-dependent patients with a positive family history (Monterosso et al. 2001), and adds to the effectiveness of ondansetron only in early-onset alcoholics (Ait-Daoud et al. 2001). The current meta-analytic study is the first that specifically addresses potential predictors of acamprosate's efficacy, which might be useful for matching.

Although the precise mechanism of acamprosate's efficacy remains unknown, the available evidence suggests that acamprosate moderates some of the neurochemical changes (e.g. GABAergic and/or glutamatergic dysregulation) resulting from chronic ethanol exposure. More precisely, it is suggested that acamprosate most likely interferes with the negative reinforcing effects of alcohol via a reduction of the neuronal hyperexcitability that occurs during withdrawal and post-withdrawal periods, as well as via inhibition of conditioned withdrawal or physiological reactivity induced by stimuli that are repeatedly paired with the state of withdrawal, an action which might also reduce craving (Littleton 1995; Spanagel and Zieglänsberger 1997; Wilde and Wagstaff 1997). The following variables can be considered potential predictors of acamprosate's efficacy (Verheul et al. 1999):

1. *Physiological dependence (PD)*: it is widely accepted that withdrawal symptoms result from brain neurochemistry that is more or less opposite to the presumed neurochemical effects of acamprosate (Samson and Harris 1992; Tsai et al. 1998). Therefore, it is suggested that those in whom withdrawal accounts (partly) for the maintenance of drinking, are most likely to benefit from acamprosate treatment. A recent study provided some support for this hypothesis (Lesch and Walter 1996).
2. *Familial alcoholism*: assuming that non-familial alcoholics drink alcohol primarily for its self-medicating properties and that they are motivated to drink because of negative reinforcement-based craving, it can be postulated that the absence of familial alcoholism is a differential predictor of efficacy. Consistently, in a randomized trial of acamprosate and fluoxetine, it was shown that acamprosate was differentially effective among non-familial alcoholics, while familial alcoholics responded only to fluoxetine treatment (Gerra et al. 1992).
3. *Age-of-onset (AO)*: substantial evidence indicates that non-familial alcoholics who drink to self-medicate psychological symptoms develop their drinking problems at a higher age than those characterized by genetic vulnerability (e.g. Cloninger 1987). Therefore, we expect that age-of-onset is associated with the

severity of negative reinforcement-based craving and, thus, that late age-of-onset is a differential predictor of the efficacy of acamprosate.

4. *Anxiety symptomatology*: it is reasonable to postulate that anxiety symptomatology might be a psychological predictor for the efficacy of acamprosate. Substantial evidence suggests that trait anxiety is closely related to an inherited tendency towards decreased inhibitory (or GABAergic) and/or increased excitatory (or glutamatergic) neurotransmission. For example, it has been shown that the function of the GABAergic system is impaired only in heroin addicts with co-morbid anxiety disorders or personality disorders from the anxious cluster and not in heroin addicts uncomplicated by axis I and axis II disorders, suggesting that there is a GABAergic deficiency independently of previous substance abuse (Gerra et al. 1998). Other suggestive evidence can be derived by Lesch and Walter (1996).
5. *Severity of craving*: it has been postulated that acamprosate is an anti-craving agent which might be particularly effective against the type of craving that has been called "conditioned pseudo-withdrawal" (Littleton et al. 1996), suggesting that those who experience high levels of craving are more likely to benefit from acamprosate than those in whom craving is not a major factor maintaining the alcohol dependence.
6. *Gender*: female gender might be associated with efficacy because females are more frequently characterized by type 1 alcoholism than males (Cloninger 1987).

The primary objective of this study is to identify potential predictors of acamprosate's efficacy in a pooled analysis of data from seven RCTs involving a total of 1485 patients with alcohol dependence. All RCTs had similar research designs and included a largely overlapping set of predictor variables, thereby providing a unique opportunity to explore predictors of acamprosate's efficacy in a very large sample.

Materials and methods

Sample

The efficacy of acamprosate has been investigated in 12 randomized clinical trials. Five trials were excluded from this meta-analysis because they provided measurements of a limited number of predictor variables. Therefore the sample consists of 1485 patients who participated in seven trials conducted throughout Europe (Ladewig et al. 1993; Geerlings et al. 1997; Pelc et al. 1997; Poldrugo 1997; Besson et al. 1998; Tempesta et al. 2000; Gual and Leher 2001). Recruitment and selection of patients are described in the original papers and results are reviewed elsewhere (Kranzler and Van Kirk 2001; Mason 2001). All trials have been approved by the appropriate ethics committees

and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the studies. Taken together, a total of 1485 were randomized to either acamprosate ($n=765$) or placebo ($n=720$). Comparison of both treatment groups in terms of the predictor variables did not reveal any statistically significant differences.

Medication

Treatment with acamprosate was initiated approximately 1–4 weeks after the start of detoxification and was continued for 3–12 months (median 6 months). The dose was adjusted for body weight (1998 mg/day ≥ 60 kg; 1332 mg/day < 60 kg) in all studies except for Tempesta et al. (2000), who used a standard dose of 1998 mg/day, and Pelc et al's (1997) dose ranging study (1332 mg/day in $n=63$; 1998 mg/day in $n=63$).

Assessments

Predictors In general, each of the six predictor variables was rated at baseline by the research physicians. PD (or severity of withdrawal symptoms) was rated on a 4-point Likert scale. To assess familial alcoholism, all eight trials included a dichotomous YES/NO question about possible alcohol problems among family members. Age-of-onset was not measured directly, but was derived from other variables. Some studies included a direct question on duration of alcohol dependence (Geerlings et al. 1997; Pelc et al. 1997; Gual and Lehert 2001). For these studies, age-of-onset was computed by subtracting duration of alcohol problems from current age. In other studies, the patient was asked to indicate the first year during which drinking became problematic to him/her (Ladewig et al. 1993; Poldrugo 1997; Besson et al. 1998; Tempesta et al. 2000). For these studies, age-of-onset was computed by subtracting year of birth from year of first problems. Regarding anxiety symptomatology, all eight trials have administered the Hamilton Depression scale which consists of questions about several psychiatric symptoms including depression and anxiety symptom. The Hamilton scale was recoded from 0 to 10. Severity of craving (or psychological dependence) and physiological dependence were rated on visual analogue scales (VAS; 0–100). Finally, gender was one of the standard demographic variables.

Outcome Outcome analyses are based on cumulative abstinence duration (CAD), continuous abstinence (ABST), and time to first relapse (TFR). CAD encompasses all patients at all time points during their study participation and allows for minor lapses in abstinence without categorical assessment as a treatment failure. By considering the trial divided into time periods separated by visits, CAD is estimated as the sum of the durations of

periods where complete abstinence was observed. This constitutes a worst case estimate of CAD. For example, while a patient may have relapsed during one period for only 1 day, the whole period is considered as total relapse. ABST is a binary (success–failure) variable, where success is attributed to a patient who remains continuously and completely abstinent throughout the entire course of the study. In this definition, a patient leaving the trial sooner than expected, irrespective of the reason, is no longer considered to be abstinent. ABST is a simple but conservative outcome parameter and does not depend on arbitrary definitions of what constitutes relapse to drinking. Furthermore, it has the advantage that it can be calculated in the same way for every study. Finally, TFR enhances ABST evaluations in allowing to model response in time, and not just the binary success–failure endpoint.

Statistical analysis

Selection of patients All the randomized patients were considered eligible for the analysis; thus the full sample was studied in conformity with the intention-to-treat (ITT) principle. Even patients without at least one key variable after baseline entered the analysis and were systematically considered to be a failure, due to classical missing data allocation in this pathology (Lehert 1994).

Missing data There were very few missing data for the predictor variables. Much effort was exerted in the collection of these missing values from the original CRFs. With respect to follow-up, less than 3% of the data were missing. Missing values are considered missing at random (MAR; Little and Rubin 1987) and therefore systematically imputed following the full information maximum likelihood technique (Anderson 1957).

Statistical techniques and models To investigate whether acamprosate has a differential effect on particular subgroups of patients, the nullity of the first-order interaction term between all the known predictors at baseline and treatment (acamprosate versus placebo) was assessed. With respect to CAD, the significance of each predictor was assessed separately, by using a mixed analysis of variance model (Winer 1989), where treatment and study block factors were considered as fixed and random factors, respectively. Instead of assuming the equality between category means of the study factor and the treatment by study interaction, we tested and estimated the unknown variances associated with these two terms throughout a variance component model: (1) as a first step, we used an unweighted mean balanced two-way mixed ANOVA, in testing the unique treatment by study interaction effect. The main study effect was considered a potential determinant of efficacy, because of differences in nationality, medical practices, and treatment duration. Treatment duration is less important as most of these studies have a duration of 6 months, with the only exception of the Pelc study with a duration of 4 months,

and the Besson study with a longer duration. However, the Besson study was censored at 6 months for this particular re-analysis; (2) as a second step, we improved the first analysis by taking simultaneously into account the other available predictors: (a) to decrease the intrinsic block effect by entering main heterogeneous effects between studies, (b) to take into account the second-order interactions between predictor variables, treatment, and study, (c) accounting for the unbalanced constrained design with very different sample sizes. In this respect, CAD was analyzed throughout a variance components general linear model (GLM, type III model was considered as the appropriate sum of squares decomposition), with study block as a random factor (associated with an unknown variance), and the other categorical and continuous predictors associated as fixed covariates. As CAD may be censored and is expected to be somewhat skewed, it might not match initial assumptions on normality and homoscedasticity. GLM was used both on untransformed and rank-transformed data to assess the significances. Because of the large number of candidate effects (main and interactions), we carried out a stepwise selection by starting from all the candidate effects. Finally, ABST was studied by a binary logistic regression, and TFR as a right-censored variable by a Cox proportional hazard regression.

Power analysis Statistical power of the tests was important, given the generally expected low power associated with interaction terms (Fleiss 1985). The power was calculated taking into account the mixed model (see above) with study factor considered as random. In a first approximation, the different sample sizes of studies were assimilated to their harmonic mean for this calculation. The magnitude of the alternative hypothesis for the interaction is the non-centrality parameter λ (generalizing the simple true difference for two treatment groups) calculated as the quadratic mean of the difference between treatment groups for each predictor category and was logically fixed to 5%. The true standard deviation was estimated as the mean residual square obtained on all the separate analysis $\sigma \cong 25\%$. In these general conditions, the beta risk (thus the power) was estimated from the non-central F cumulative distribution (use of Patnaik approximation; Winer 1989), although it has been shown that this calculation is only approximated for mixed models (Koele 1982). Associated with each ANOVA, the power of detecting such a mean difference of at least 5% was found to be 0.87. For the estimate of power for GLM model, a direct expression is not available, given the large number of assumptions to know for all the predictors. The power has been systematically estimated by a Monte Carlo simulation, i.e. (a) assuming a rank distribution, (b) carrying out a crossed design in simulating each effect following a normal distribution given by its observed mean and SD, and (c) assuming the variance component of study block factor. On the basis of the same value of the non-centrality parameter, a mean power of 0.93 (SD=0.07) was found, thus with a slightly improved power as compared to the simple bivariate ANOVA. Similarly,

power was calculated for ABST in using adapted calculations of power for logistic models (Choi 1998). With the same conditions as above, the power to detect interaction effects $>4.15\%$ was 0.95, associated with $\alpha=0.05$, and a percentage of explained variability (measured by deviance) of 45%. In conclusion, the current sample size ($n=1,485$) allows us to perform adequately powered tests on interaction based on a clinically relevant of a global difference between treatment groups of 5% across all the categories of all predictors.

Results

Separate analysis for each predictor

Physiological dependence High PD or severe withdrawal symptomatology at baseline is postulated to be differentially associated with higher efficacy of acamprosate as compared to low PD. When the mean CAD was calculated for each PD category, the change in CAD as a function of PD appeared to be non-linear, with middle range PD being associated with the highest CAD values (see Table 1). There seems to be an effect of treatment that is rather constant for each PD subgroup, except for the highest severity of PD (4th category), but the small number of patients makes interpretation difficult. GLM on CAD exhibits a highly significant effect of the treatment ($P<0.001$), a highly significant study effect ($P<0.001$), but no significant effects of PD or the interactions between PD, treatment, and study. Because the relationship between CAD and PD was not linear, it seemed reasonable to also fit the influence of PD with a quadratic model. The linear and quadratic components of PD are close to significant ($P=0.06$, $P=0.057$), but the interactions remain non-significant. Finally, logistic regression was used to study ABST. The results were very similar to GLM on CAD. The estimated odds ratio was 1.42 [95% CI (1.19–1.69)]. The main effects for the linear and quadratic components of PD become even more significant with this analysis, than with CAD. However, again no significant interactions were detected.

Table 1 The impact of physiological dependence at baseline on CAD

CAD	Placebo		Acamprosate	
	Mean±SD	<i>n</i>	Mean±SD	<i>n</i>
Physiological dependence				
No sign of weaning	37.0±38.7	281	50.7±41.9	306
Minor signs	44.4±43.0	295	57.0±42.6	314
Important signs	47.6±42.4	134	59.9±43.0	133
Very important signs	35.8±41.4	10	43.8±44.3	12
Total	42.0±41.4	720	54.8±42.5	765

ANOVA: physiological dependence, $P=0.155$; treatment, $P=0.015$; interaction, $P=0.975$

Familial history of alcoholism (FH) A negative family history of alcoholism (FH⁻) is postulated to be differentially associated with higher efficacy of acamprosate as compared to FH⁺. When the mean CAD was calculated for each FH group, the main treatment effect appeared to be significant. This effect tends to be higher for FH⁺ patients although the difference does not reach statistical significance (interaction FH×treatment, $P=0.294$) (see Table 2). GLM on CAD yields a significant effect of treatment ($P<0.001$) and study ($P<0.001$), but no significant main effect of FH, and no significant interactions between FH, treatment, and study. A logistic regression on ABST exhibits highly significant main effects of treatment ($P<0.001$), and study ($P<0.001$), but no significant main effect of FH, and no significant interactions between FH, treatment, and study.

Age-of-onset Later AO is postulated to be differentially associated with higher efficacy of acamprosate as compared to earlier AO. The mean CAD was calculated for each AO group (by increments of 10 years). There are very small, non-significant differences among categories ($P=0.677$). The main treatment effect is significant, and this effects seems stronger for patients with a later AO, but the difference does not reach statistical significance (interaction FH×treatment, $P=0.599$) (see Table 3). GLM on CAD shows a highly significant effect of treatment ($P<0.001$), a significant AO effect ($P=0.016$), but no significant interactions between AO, treatment, and study. A logistic regression on ABST exhibits a highly significant effect of the treatment ($P<0.001$), a close to significant AO effect ($P=0.066$), but no significant interactions between AO, treatment, and study.

Anxiety symptomatology High scores on anxiety are postulated to be differentially associated with higher efficacy of acamprosate as compared to low scores. The mean CAD was calculated for each anxiety group (classes correspond to quartiles, thus are equidistributed), revealing a strong association between anxiety and CAD ($P=0.000$). However, this association is evident among both treatment groups (interaction anxiety×treatment, $P=0.705$) (see Table 4). GLM on CAD exhibits a highly significant effect of treatment ($P<0.001$) and anxiety ($P=0.024$), but no significant interactions between anxiety, treatment, and study. A logistic regression on ABST exhibits a highly significant effect of treatment ($P<0.001$), anxiety

Table 2 The impact of earlier familial problems of alcohol on CAD

CAD	Placebo		Acamprosate	
	Mean±SD	<i>n</i>	Mean±SD	<i>n</i>
Earlier familial problems				
No	41.9±41.5	330	52.8±43.3	360
Yes	41.9±41.3	383	57.4±41.5	314
Total	41.9±41.4	713	55.2±42.4	759

ANOVA: familial problems, $P=0.301$; treatment, $P=0.000$; interaction, $P=0.294$

Table 3 The impact of age-at-onset on CAD

CAD	Placebo		Acamprosate	
	Mean±SD	<i>n</i>	Mean±SD	<i>n</i>
Age-of-onset				
10–19 years	11.1±19.3	3	56.3±42.7	4
20–29 years	41.4±42.9	75	48.8±40.1	88
30–39 years	43.8±40.8	194	54.8±42.1	205
40–49 years	39.5±39.4	149	59.2±42.5	157
50–59 years	49.3±42.3	61	62.0±41.7	76
60–69 years	37.0±42.4	8	60.0±48.6	10
Total	42.5±40.8	490	56.2±42.0	540

ANOVA: age-of-onset, $P=0.519$; treatment, $P=0.003$; interaction, $P=0.599$

($P=0.011$), and study ($P<0.001$), but no significant interactions between anxiety, treatment, and study.

Severity of craving Severity of craving is postulated to be differentially associated with higher efficacy of acamprosate. The mean baseline craving was calculated for each study and craving group (by increments of 25 points). Although there is an inverse association between baseline craving levels and CAD ($P=0.000$), the relationship is not monotonous (see Table 5). This table is pooled for all studies, but craving was not uniformly measured (some with VAS, others with a categorical scale). It is thus useful to add in the model the term study and its interactions with craving and treatment. GLM on CAD reveals significant effects of treatment ($P<0.001$), craving ($P=0.002$), and the interaction between study and craving, but no significant effects of the interactions craving by treatment, treatment by study, or craving by treatment by study. Finally, a logistic regression on ABST exhibits significant effects of the treatment ($P<0.001$), no effect of craving ($P=0.449$), a significant study×craving effect, but again no significant effects for the interactions craving by treatment, treatment by study, or craving by treatment by study.

Gender Female gender is postulated to be differentially associated with higher efficacy of acamprosate as compared to male gender. The mean CAD was calculated

Table 4 The impact of anxiety symptomatology at baseline on CAD

CAD	Placebo		Acamprosate	
	Mean ±SD	<i>n</i>	Mean ±SD	<i>n</i>
Anxiety symptomatology				
No sign of anxiety (1st quartile)	47.8±43.5	145	60.8±42.9	150
Minor signs (2nd quartile)	39.7±39.9	138	53.7±41.5	171
Important signs (3rd quartile)	27.5±34.4	137	47.4±42.8	146
Very important signs (4th quartile)	37.0±41.7	147	49.9±43.5	148
Total	38.1±40.6	567	53.0±42.8	615

ANOVA: anxiety symptomatology, $P=0.000$; treatment, $P=0.000$; interaction, $P=0.705$

Table 5 Impact of the severity of craving at baseline on CAD

CAD	Placebo		Acamprosate	
	Mean±SD	<i>n</i>	Mean±SD	<i>n</i>
Severity of craving				
0–25	43.6±42.4	264	55.3±43.5	276
25–50	35.9±40.4	132	50.8±43.5	122
50–75	48.7±41.8	133	53.0±42.3	135
75–100	30.7±37.4	83	47.7±43.3	69
100–125	54.8±41.6	44	62.0±39.5	32
Total	42.2±41.6	656	53.5±43.0	634

ANOVA: severity of craving, $P=0.000$; treatment, $P=0.000$; interaction, $P=0.626$

for each study and gender categories (see Table 6). No marked (and significant) differences were observed between male and female subjects, and the difference in efficacy between the two drugs remain constant in each gender category (interaction $P=0.979$). GLM on CAD reveals a significant effect of treatment ($P<0.001$) and study ($P<0.001$), but no significant interactions between craving, treatment and study. Finally, a logistic regression on ABST yields a significant effect of treatment ($P<0.001$) and study ($P<0.001$), but no significant interactions between craving, treatment and study.

General multivariate model

A simultaneous multifactorial analysis—taking into account all previous significant terms—was conducted in order to control for high correlations between predictors and thus for potential confounding. Although analysis of individual predictors included all patients, the multifactorial assessment only included 983. This is because all predictors were available in only 983 patients. With respect to CAD, the analysis detected four significant main effects: craving ($P<0.001$), anxiety ($P=0.005$), study ($P<0.0001$), and treatment condition ($P<0.0001$). In addition, the multifactorial analysis confirmed the non-significance of the interactions between predictors and treatment ($P=0.347$, $P=0.829$, $P=0.892$, respectively). Similarly, a logistic regression was carried out on exactly the same predictors and associated interactions on ABST. The results show a similar picture. Finally, Cox proportional hazard regression analysis was used to confirm the

Table 6 Impact of gender on CAD

CAD	Placebo		Acamprosate	
	Mean±SD	<i>n</i>	Mean±SD	<i>n</i>
Gender				
Male	42.3±41.6	566	55.1±42.7	609
Female	40.9±40.5	154	53.6±41.8	156
Total	42.0±41.4	720	54.8±42.5	765

ANOVA: gender, $P=0.610$; treatment, $P=0.000$; interaction, $P=0.979$

above results. The results are rather similar to the previous results, except that only craving and treatment appeared to be significant. Anxiety was no longer a significant predictor.

Discussion

This pooled analysis of seven European randomized controlled trials comparing acamprosate with placebo revealed that outcome measured by three different endpoints (CAD, ABST, TFR) was predicted by craving, anxiety, study, and treatment. However, acamprosate efficacy was not differentially associated with any of the predictor variables. Importantly, the hypotheses are rejected despite the large sample size and sufficient statistical power in this pooled analysis ($n=1010-1485$).

This study does not corroborate findings from other studies such as Gerra et al. (1992) and Lesch and Walter (1996), which provide suggestive data in favor of matching patients to acamprosate treatment based on their clinical characteristics. It is important to note that these other studies used different methodologies to detect individual differences, were not placebo-controlled and had very small sample sizes. Furthermore, our findings call into question recent theories about potential predictors based on data about acamprosate's mechanism of action (e.g. Spanagel and Zieglgänsberger 1997; Wilde and Wagstaff 1997; Verheul et al. 1999). One possible reason for these inconsistencies is that clinical characteristics may be poorly associated with the neurochemistry affected by acamprosate. To the extent that this explanation is viable, a matching trial using neurobiological predictors (e.g. glutamate-induced excitotoxicity, allelic variations [Oslin et al. 2003]) and standardized measures of psychological and psychophysiological measures should be considered. However, it is also possible that acamprosate's putative effects on particular neurochemical systems are less specific than originally thought, perhaps because of interactions between neurotransmitter systems. In that case, it might be very difficult to identify matching variables based upon current knowledge and available methodologies.

This study has some clear strengths and limitations. Strengths include (1) sufficient statistical power to detect interaction (and thus matching) effects due to the large sample size, and (2) high external validity due to the inclusion of multiple trials from several countries. The most important limitation is the lack of standardized assessments for the predictor variables, except for the severity of anxiety symptomatology (Hamilton scale). The measures of withdrawal symptoms, familial alcoholism, age-of-onset, and craving were based on clinical assessments, and perhaps meaningful clinical heterogeneity among alcoholics was not fully covered by these simple variables. Two factors mitigate this concern to some extent: (1) variables such as gender and age-of-onset are rather straightforward and can be easily determined, and (2) our measurement strategy is the one that is most often

applied in daily clinical practice. So at least it can be concluded that these simple clinical assessments do not help the clinician to identify those alcoholics who are most likely to benefit from acamprosate.

The most straightforward clinical implication of this study is that acamprosate can be prescribed to all patients. At this moment there is only weak evidence for matching strategies. Although acamprosate is not effective in all patients, recent evidence suggests two clinical strategies to improve the effectiveness of acamprosate: a combination of acamprosate with naltrexone (Kiefer et al. 2003) or with disulfiram (Besson et al. 1998). Studies investigating the added effect of a combination of acamprosate with different types and intensities of psychotherapy have produced contradicting results and therefore this strategy is of questionable validity (Van den Brink 2003).

Acknowledgements Merck-Lipha, France, provided data and statistical support, and covered the costs for meetings between the researchers. The clinical trials included in this meta-analysis comply with the current laws in the respective countries in which they were conducted.

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