The effect of naltrexone and acamprosate on cue-induced craving, autonomic nervous system and neuroendocrine reactions to alcohol-related cues in alcoholics☆

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Abstract

Introduction: Naltrexone and acamprosate have been shown to be effective in relapse prevention of alcoholism. It is hypothesized that naltrexone exerts its effects primarily on cue-induced craving and neuroendocrine cue reactivity, whereas acamprosate exerts its effect primarily on autonomic nervous system reactions to alcohol-related cues.

Experimental procedures: In a randomized double-blind experiment, 131 abstinent alcoholics received either acamprosate (n=56), naltrexone (n=52) or placebo (n=23) for three weeks and participated in two cue-exposure sessions: the first the day before and the second at the last day of medication.

Results: Consistent with the hypotheses, naltrexone reduced craving more than acamprosate, and acamprosate reduced heart rate more than naltrexone. No medication effect was found on cue-induced cortisol.

Discussion: The findings provide some evidence for differential effects of naltrexone and acamprosate: naltrexone may exert its effect, at least partly, by the reduction of cue-induced craving, whereas acamprosate may exert its effect, at least partly, by the reduction of autonomic nervous system reactions to alcohol-related cues.

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KEYWORDS
Alcoholism; Naltrexone; Acamprosate; Efficacy; Craving; Cue reactivity
1. Introduction

Relapse prevention is among the most important treatments for alcohol dependence. Over the last 20 years, the role of pharmacotherapy in relapse prevention has become increasingly evident. There are two relatively new compounds that are proven effective (Kranzler, 2000) which are approved in both the United States and Europe, i.e. naltrexone and acamprosate. However, the effect size of these medications is moderate at best and their mechanism of action is not fully understood. The current study is the first randomized, double-blind, placebo-controlled study testing the main hypotheses regarding the assumed different mechanisms of action of the two compounds.

Naltrexone is an opioid antagonist that mainly acts at the mu opioid receptor (Littleton and Ziegglansberger, 2003). It is hypothesized to prevent relapse by attenuating the self-reported urge for alcohol's stimulating or rewarding properties (reward craving) in patients characterized by an opioidergic or withdrawal systems (relief craving), and is thus accompanied by autonomic nervous system reactions (Littleton, 1995; Koob and Le Moal, 2001, 2005). Several studies have shown that naltrexone is most effective in patients with strong self-reported baseline craving (Jaffe et al., 1996), and that craving can be reduced by naltrexone (e.g. Chick et al., 2000a; Anton et al., 1999; Volpicelli et al., 1992). It is generally believed that naltrexone reduces craving by blocking opioid receptors, which in turn leads to an attenuation of the rewarding effect of alcohol (Volpicelli et al., 1995).

Since its approval, several trials have been performed investigating naltrexone's efficacy in relapse prevention. However, the data are somewhat inconsistent and effect sizes are modest at best (see for reviews: Mann, 2004; Srisurapanont and Jarusuraisin, 2005a, b; Roozen et al., 2006). The most consistent finding has been an increase in time to first relapse, although not in all trials, including the largest with 627 veterans (Krystal et al., 2001). Negative findings may be accounted for by inadequate sample sizes, poor medication compliance (Mann, 2004) or inadequate patient treatment matching (Ooteman et al., 2005).

Many studies have examined the effect of naltrexone on craving in non-experimental settings (see for reviews: Srisurapanont and Jarusuraisin, 2005a, b; Roozen et al., 2006). However, only a limited number of studies have included cue-induced craving or measures of autonomic nervous system reactions to alcohol-related cues in the laboratory as outcome measures. Alcohol-related cues (e.g. negative mood, the sight and smell of alcohol) are generally believed to act as triggers for craving and/or autonomic nervous system reactions to alcohol-related cues (e.g. Cooney et al., 1997; Kaplan et al., 1985; Niaura et al., 1988). Therefore, cue-induced craving and autonomic nervous system reactions to alcohol-related cues may be important intermediate outcome measures for naltrexone's efficacy as well. With respect to the effect of naltrexone on cue-induced craving, the limited number of studies showed inconsistent results. Some studies (Rohsenow et al., 2000; O'Malley et al., 2002; Palfai et al., 1999) found a reduction in the level of cue-induced craving after naltrexone treatment, whereas other studies (Modesto-Lowe et al., 1997; Monti et al., 1999) did not. It should be noted, however, that Monti et al. (1999) did find an effect on the number of patients reporting cue-induced craving. The number of studies about naltrexone's effect on autonomic nervous system reactions to alcohol-related cues is even smaller. Monti et al. (1999) did not find an effect of naltrexone treatment on measures of autonomic nervous system reactions to alcohol-related cues (blood pressure and heart rate) in alcoholics. In fact, they found a smaller decrease in blood pressure after naltrexone treatment than after placebo treatment. Others hypothesized that naltrexone's effect on craving may be related in part to naltrexone's ability to stimulate the HPA axis and to normalize its suppressed basal activity and blunted response to a number of functional tests (Adinoff et al., 2005; Kiefer et al., 2002; O'Malley et al., 2002).

Acamprosate or calcium-acetyl-homotaurinate is a glutamate-antagonist and possible GABA-agonist. In general, acamprosate is believed to maintain abstinence primarily by reducing craving. Some investigators hypothesize that acamprosate specifically acts on craving that is mediated through glutamatergic and GABA-ergic dysregulations of stress, anxiety or withdrawal systems (relief craving), and is thus accompanied by autonomic nervous system reactions (Littleton, 1995; Koob and Le Moal, 2001, 2005; Verheul et al., 1999).

Since its approval, several trials have been performed investigating acamprosate's efficacy. In most clinical trials, continuous abstinence rather than relapse or craving has been the primary outcome measure, with a beneficial effect of acamprosate on continuous abstinence rates with a modest effect size (see for a review: Mann, 2004; see for a meta-analysis: Mann et al., 2004). The effects of acamprosate on craving are less consistent. Several trials showed a significant reduction of craving compared to placebo (e.g. Chick et al., 2000b; Peic et al., 1997; Pailie et al., 1995), but other studies did not (Roussaux et al., 1996; Tempesta et al., 2000). Only few studies included cue-induced craving and/or autonomic nervous system reactions to alcohol-related cues as outcome measures. Weinstein et al. (2003) presented some preliminary results of an uncontrolled pilot study suggesting that acamprosate does alter cue-induced self-reported craving and reaction time to an alcohol-related stimulus. In addition, Agelink et al. (1998) showed improved autonomic neurocardiac balance in abstinent alcoholics treated with acamprosate, i.e. following treatment with acamprosate patients showed less disturbances in neurocardiac vagal function.

In summary, it seems that acamprosate and naltrexone exert their effect on relapse via different mechanisms and relate to different aspects of drinking behaviour. However, until now, the literature lacks sufficient empirical evidence on the differential effect of naltrexone and acamprosate on both cue-induced craving and autonomic nervous system and neuroendocrine reactions to alcohol-related cues. The aim of the current study is, therefore, to investigate possible mechanisms of action on craving of naltrexone and acamprosate. The primary hypothesis is that naltrexone and acamprosate exert their effect through different mechanisms: naltrexone will primarily exert its effect on cue-induced craving and endocannabinoid cue-reactivity measures of the HPA axis (cortisol), whereas acamprosate will primarily exert its effect on cue-induced autonomic nervous system parameters associated with withdrawal symptoms or anxiety (heart rate, skin conductance). The secondary hypothesis is that both naltrexone and acamprosate result in a larger reduction of cue-induced craving and/or autonomic nervous system and neuroendocrine reactions to alcohol-related cues than placebo.
2. Experimental procedures

2.1. Participants

The study population consisted of both treatment-seeking and non-treatment-seeking alcoholics, that were recruited either at the Jellinek addiction treatment center in Amsterdam or through advertisement in newspapers and radio-interviews. Inclusion criteria were: primary DSM-IV diagnosis of alcohol dependence; minimum age of 18; and no heavy drinking days (≥ 5 units) for a minimum of one week and a maximum of six months. Exclusion criteria were: co-morbid cocaine or heroine dependence; cocaine or heroine use in the last 30 days before intake; current use of naltrexone, acamprosate or disulfiram; severe cognitive deficits; insufficient demand of the Dutch language; disturbed renal function (creatinine > 120 μmol/l); acute hepatitis (ASAT/ALAT ≥ 3 × normal value); severe liver insufficiency; hypersensitivity for acamprosate and/or naltrexone; pregnancy; lactation; expected medical interventions including pain relief with opioids; severe medical illnesses; active psychosis; current use of anti-psychotic medication; and suicidality.

2.2. General design

All clients filled out self-report questionnaires on demographics, immediately after inclusion in the study. To assess the severity of their alcohol problems all participants self-administered the Alcohol Use Disorders Identification Test (AUDIT; Baber et al., 1992). All participants were instructed to quit drinking one week before start of the medication period. They were then prepared for a cue-exposure challenge. Based on a Drinking Triggers Interview (Monti et al., 1993a), individualized audio-taped mood induction scripts were prepared (Cooney et al., 1997). The aim of the script was to induce the mood in which the subject was most likely to experience craving.

One day before the start of the medication period, every subject was exposed to a cue-exposure challenge, in which craving and autonomic nervous system reaction to alcohol-related cues were measured. All subjects then participated in a randomized, double-blind, placebo-controlled protocol: 40% of the subjects received acamprosate, 40% naltrexone and 20% placebo for 21 days, under supervision of a physician. The placebo group was smaller than the medication groups because the effect of naltrexone and acamprosate compared to placebo was not the main focus of this study, but part of our secondary research question. The dosages of naltrexone and acamprosate were given according to current treatment recommendations. For acamprosate, 2.0 g/day was given to patients with bodyweight >60 kg, and 1.3 g/day in patients with bodyweight ≤60 kg. The recommended dose of naltrexone is 50 mg/day. All tablets (placebo, naltrexone and acamprosate) were identical in appearance. Based on data about the pharmacokinetics of the compounds, 21 days of administration should be sufficient to exclude the possibility that no effect is detected due to a potential latency period for the effect of acamprosate (Wilde and Wagstaff, 1997) or naltrexone (Mason et al., 2002; Yuen et al., 1999). After three weeks of placebo or medication, all subjects were exposed to a second cue-exposure session according to exactly the same protocol as the first session, with an additional retrospective assessment of medication compliance of the past three weeks. After debriefing and unblinding, a treatment advice was given by the physician. All subjects received three vouchers with a total value of 35 Euro.

2.3. Procedure

The cue-exposure paradigm was based on procedures developed by Cooney et al. (1997) and Monti et al. (1993b). First, subjects were screened for alcohol use by a breathalyzer, connected to electrodes and acclimatized for 30 min. Each subject was then asked to relax for 4 min. The subject’s favourite beverage was then poured in the glass in front of the subject. While the pre-recorded mood induction script was played over the headphone for 5 min, the subject was instructed to sniff the beverage four times (one time at the start of the script and three times at the end of the script). During exposure, craving was assessed four times on a VAS scale ranging from 0 to 10 (at the 1st, 3rd, 4th and 5th minute). At the end, a self-report craving questionnaire (JACQ-now; Ooteman et al., 2006a) was filled out and a final assessment with the VAS scale was taken before bringing the participant back to a relaxed state.

2.4. Subjective outcome measures

At baseline and during cue exposure, craving was measured on a 10-point VAS scale that measured craving “right now” (VASa) (“How strong is your urge or need to drink right now?”). Immediately after cue exposure, subjects were retrospectively asked to give a rating of their craving during the session on a 10-point VAS scale (VASb) (“How strong was your strongest urge or need to drink alcohol during the session?”). In addition, they were asked to administer the 24-item Jellinek Alcohol Craving Questionnaire (JACQ-now; Ooteman et al., 2006a), a questionnaire with four subscales that measure the core aspects of craving. After the second cue-exposure session, an evaluation form was filled out and medication compliance (defined as the percentage of pills taken by the subject) was retrospectively assessed by self-report.

2.5. Autonomic nervous system and neuroendocrine outcome measures

2.5.1. Autonomic nervous system reaction to alcohol-related cues outcome measures

The following physiological measures were continuously recorded during both cue-exposure challenges: (1) heart rate (HR); (2) skin conductance level (SCL); (3) skin conductance response (SCR). Based on these assessments, mean values of HR, SCL and SCR as well as Δ peak values (see statistical analysis) were calculated, since subjects may peak at different moments in time in which case mean values may mask the cue-exposure (and medication) effect.

For HR assessment, ECG electrodes were placed on either side of the participant’s chest. A Contact Precision Instruments analogue-digital converter (ADC) sampled the ECG signal at a rate of 300 Hz and calculated the number of interbeat intervals (IBIs) during 10-s sampling periods (range 2 mV, High Pass 10 Hz, Low Pass 200 Hz). For the assessment of SCL and SCR, electrodes were taped to the middle phalanx of the forefinger and the middle finger of the participant’s non-dominant hand. The skin conductance signal was amplified by a Contact Precision Instruments skin conductance coupler, sampled at a fixed 40 Hz. SCL and SCR count were averaged across a 10-s sampling period. The response criterion for SCR was an increase of 0.0015625 μS.

2.5.2. Neuroendocrine cue-reactivity outcome measure

Cortisol production was measured in saliva and sampled ten times during the cue-exposure session. The first baseline sample was taken directly following the resting period, and a second baseline sample was taken 5 min after the resting period. A further eight samples were taken 15, 20, 25, 30, 35, 40, 45, and 50 min after start of the cue exposure. Saliva was collected using Sarstedt salivettes with a dental cotton roll, frozen at −20°C and cortisol analyses were performed at the Department of Psychology, TU Dresden, Germany, (Laboratory Dr. Kirschbaum) using a commercial immunoassay with chemiluminescence detection. The lower sensitivity of the assays is 0.44 nmol/l, intra-assay and inter-assay coefficients of variation are less than 10%.

2.6. Statistical analysis

Despite some drop-outs after randomization, there were no significant (p<0.05) differences in baseline characteristics between the
three groups, with the exception of more years of education in the placebo condition. However, in order to improve the power of the study and to prevent residual confounding, AUDIT (Alcohol Use Disorders Identification Test) scores, gender and benzodiazepine use will be used as covariates in all analyses.

Responses at each cue-exposure session on the autonomic nervous system and endocrinological measures were operationalized as Δ peak values. For craving, two different Δ peak scores were calculated: the first by subtracting the baseline VAS score from the highest VAS score filled out during cue exposure (Δ peak VASa), the second by subtracting the baseline VAS score from the retrospective VAS score ‘how strong was your strongest urge?’ filled out immediately after cue exposure (Δ peak VASb). For HR, SCL and SCR, Δ peaks were calculated by subtracting the average of the last minute of the baseline-period from the maximum value during the 5-min lasting cue-exposure period. Cortisol Δ peak scores were calculated by subtracting the mean of two baseline values (sample 1a and 1b were regarded as baseline values since it takes approximately 15–25 min before the cortisol reaction becomes apparent following the cue) from the highest cortisol value after cue exposure.

The effect of naltrexone and acamprosate for each of the autonomic nervous system and neuroendocrinological measures was estimated using univariate ANCOVA (General Linear Model module, SPSS 12), with the difference score in Δ peak value between the first and second cue exposure as dependent variable, medication condition (naltrexone, acamprosate and placebo) as independent variable and Δ peak of the first cue-exposure session, baseline AUDIT scores, benzodiazepine use and gender as covariates.

Table 1  Sample characteristics and alcohol-related variables

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=23)</th>
<th>Naltrexone (n=52)</th>
<th>Acamprosate (n=56)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Subject characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean age in years (SD)</td>
<td>45.3 (9.6)</td>
<td>47.2 (10.1)</td>
<td>48.1 (9.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>% men</td>
<td>78.3</td>
<td>78.8</td>
<td>66.1</td>
<td>0.27</td>
</tr>
<tr>
<td>% Dutch ethnicity</td>
<td>87.0</td>
<td>88.5</td>
<td>76.8</td>
<td>0.23</td>
</tr>
<tr>
<td>% inpatients</td>
<td>17.4</td>
<td>32.7</td>
<td>25.0</td>
<td>0.36</td>
</tr>
<tr>
<td>% in treatment</td>
<td>73.9</td>
<td>69.2</td>
<td>64.3</td>
<td>0.68</td>
</tr>
<tr>
<td>% higher education</td>
<td>50.0</td>
<td>28.0</td>
<td>38.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean years education (SD)</td>
<td>15.8 (5.0)</td>
<td>13.6 (4.3)</td>
<td>13.4 (3.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>% employed</td>
<td>54.5</td>
<td>58.0</td>
<td>57.4</td>
<td>0.96</td>
</tr>
<tr>
<td>% married</td>
<td>22.7</td>
<td>32.0</td>
<td>16.7</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Alcohol-related variables</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean AUDIT score (SD)</td>
<td>20.5 (4.2)</td>
<td>21.3 (5.1)</td>
<td>20.8 (5.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean age of onset (SD)</td>
<td>32.8 (8.2)</td>
<td>35.9 (10.3)</td>
<td>35.2 (9.7)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Other substance use</strong></td>
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<tr>
<td>% using benzodiazepines</td>
<td>27.3</td>
<td>12.0</td>
<td>13.0</td>
<td>0.21</td>
</tr>
<tr>
<td>% using cannabis</td>
<td>18.2</td>
<td>8.0</td>
<td>18.5</td>
<td>0.26</td>
</tr>
<tr>
<td>% using nicotine</td>
<td>86.4</td>
<td>84.0</td>
<td>92.6</td>
<td>0.39</td>
</tr>
<tr>
<td>% using anti-depressives</td>
<td>40.9</td>
<td>26.0</td>
<td>31.5</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Physiological baseline values of HR and SCL at T1</strong></td>
<td></td>
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</tr>
<tr>
<td>HR (SD)</td>
<td>78.8 (22.2)</td>
<td>78.9 (26.3)</td>
<td>73.9 (11.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>SCL (SD)</td>
<td>2.8 (1.2)</td>
<td>2.1 (1.2)</td>
<td>3.1 (4.2)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation, AUDIT = Alcohol Use Disorders Identification Test, HR = heart rate, SCL = skin conductance level.
Standardized effect sizes are presented as Cohen’s $d$ values. For the primary research question, relatively large samples were included to compare the acamprosate and naltrexone group. For both research questions, significance was tested at the 0.05 level. However, given the relatively small sample size of the placebo group, $p$-values smaller than 0.1 were regarded as trends for the secondary research question.

3. Results

3.1. Study population

A total of 524 subjects were screened (see Fig. 1). Of these, 188 subjects refused to participate at intake and 139 subjects had to be excluded (most important reasons for exclusion: various medical conditions and current use of anti-craving compounds). Of the remaining 197 subjects, 41 subjects filled out baseline questionnaires, but refused further participation before randomization leaving 156 subjects for the current study. Of these 156 subjects, 25 subjects (16%) (7 in the acamprosate group, 11 in the naltrexone group, and 7 in the placebo group) dropped out after the first cue-exposure session, leaving 131 subjects (84%) who completed the entire study: 56 in the acamprosate group, 52 in the naltrexone group, 23 in the placebo group.

3.2. Baseline characteristics

Table 1 shows that most study participants were Dutch, male, unemployed, unmarried and with low education. In the total group, 26.7% of the participants were inpatients, 41.2% were outpatients and 32.1% was currently non-treatment-seeking. Most subjects had moderate to severe levels of alcohol dependence. With the exception of the mean years of education, there were no significant ($p<0.20$) differences between the groups in baseline characteristics; mean years of education was higher in the placebo than in the active medication conditions. With respect to the baseline values of the subjective craving scores or the autonomic nervous system parameters during the first cue-exposure session, there were no significant differences between the medication conditions (see Table 1 for the baseline data of heart rate and skin conductance level; baseline data for skin conductance response, cortisol and subjective craving are not shown).

3.3. Medication compliance

Self-reported medication compliance in study completers was good. The mean percentage of taken pills was 98.1% in the placebo group, 99.1% in the naltrexone group, and 96.5% in the acamprosate group. These findings were confirmed by data on medication (metabolites) in randomly taken urine samples: 95% of the patients were urine positive for naltrexone or acamprosate at the second test session.

3.4. Effect of naltrexone and acamprosate on craving

For all craving measures, and for each active medication group, a significant increase in $\Delta$ peak value was found during both cue-exposure sessions ($p<0.05$). In line with our expectations, the reductions in $\Delta$ peak craving scores between the sessions in the naltrexone group were significantly larger than the reductions in $\Delta$ peak craving scores between the sessions in the acamprosate group for VASb [$p<0.05$, $d=0.29$]. No significant effects were found for the other craving indicators (VASa and the (sub)scales of the JACQ). In contrast to our expectations, reductions in $\Delta$ peak craving scores between the sessions in both the acamprosate and naltrexone group were not significantly larger than in the placebo group (see Fig. 2).
3.5. Effect of naltrexone and acamprosate on autonomic nervous system reactions to alcohol-related cues

For all physiological parameters, and for each medication group, a significant increase in Δ peak value was observed during both cue-exposure sessions (p < 0.05). In line with our expectations, the decrease in Δ peak HR in the acamprosate was significantly larger than the decrease in Δ peak HR in the naltrexone group [p < 0.05, d = 0.15]. However, in contrast to our expectations, no significant medication effect was found in the reduction of Δ peak SCL between the sessions and a trend was found for a smaller reduction between the sessions for both active medications compared to the placebo group on Δ peak SCL [p = 0.08, d = 0.06 for acamprosate; p = 0.05, d = 0.27 for naltrexone]. In addition, reductions in Δ peak on all physiological measures between the sessions in the naltrexone group were not significantly larger than in the placebo group. However, a trend was found for a larger decrease in Δ peak HR in the acamprosate group compared to placebo [p = 0.07, d = 0.40] (see Fig. 3).

3.6. Effect of naltrexone and acamprosate on endocrinological cue reactivity

No significant cue-induced cortisol Δ peak values were found at the first and second cue-exposure session in each medication group. In contrast to our expectations, no significant effects of naltrexone and acamprosate on reductions in Δ peak cortisol levels were observed. In addition, no significant differences between placebo and active medications were found in basal cortisol levels or in cortisol Δ peaks (see Fig. 3d).

4. Discussion

In summary, the effect of naltrexone on cue-induced craving was significantly larger than the effect of acamprosate [p < 0.05; d = 0.29], although this effect was not statistically significant for the comparison of naltrexone with placebo.

With respect to autonomic nervous system reaction to alcohol-related cues, a small but significant effect was seen for acamprosate versus naltrexone [p < 0.05; d = 0.15], and a trend for a moderate reduction in Δ peak HR was found in the acamprosate group compared to placebo [p = 0.07; d = 0.40].

No significant medication effects were observed with regard to cortisol responses to cue exposure.

First, it seems that naltrexone has a moderate effect on cue-induced craving compared to acamprosate. This was most strongly present on the VASb-scale [p < 0.05, d = 0.29]. The VASb scale may therefore be the most sensitive scale in the current study to detect a reduction in cue-induced craving. An explanation for this may be that the VASb scale is administered directly following the experience of cue-induced craving, combining the advantages that a) the craving experience is very recent, and that b) it concerns the highest craving score of the entire cue-exposure period and therefore reduces the risk that the highest score is missed.
Since the effect of naltrexone on cue-induced craving is only moderate, it is questionable whether naltrexone exerts its main therapeutic effect on relapse through the reduction of cue-induced craving. This would be in line with studies showing low correlations between craving and relapse (Rothenberg and Monti, 1999). Although we did not find an effect of acamprosate on cue-induced craving at three weeks of medication, acamprosate may exert its effects on cue-induced craving after more than three weeks of medication.

Second, in line with our prediction, a small but significant effect on Δ peak HR was seen for acamprosate versus naltrexone \( p < 0.05; \ d = 0.15 \). In addition, although it did not reach statistical significance, acamprosate showed a trend for a moderate effect on one of the physiological measures (heart rate) compared to placebo \( p = 0.07, \ d = 0.40 \), whereas naltrexone did not. Sympathetic autonomic nervous system reactions to alcohol-related cues may therefore be a sensitive parameter for acamprosate’s mechanism of action. This is in line with our hypothesis that acamprosate is differentially effective in reducing physiological reactions that are mediated through glutamatergic and GABA-ergic dysregulations of stress, anxiety or withdrawal systems (Littleton, 1995; Verheul et al., 1999; Koob and Le Moal, 2001, 2005). It is also in line with a study showing improved neurocardiac balance (Agelink et al., 1998) and a pilot study showing an effect of acamprosate on another cue-reactivity measure (reaction time) (Weinstein et al., 2003). However, despite of a moderate effect size for acamprosate compared to placebo \( d = 0.31 \), we did not find a significant medication effect on SCL. Moreover, in sharp contrast to our predictions, we found a trend for smaller reductions in cue-induced SCR in both medication groups compared to the placebo group \( p < 0.1; \ \ d = 0.06 \) for acamprosate and \( d = 0.27 \) for naltrexone. It may be that not all sympathetic outcome measures in our study are sensitive to the dampening effect of acamprosate. In the current study, naltrexone did not significantly decrease any physiological indicators of cue reactivity. This is partly in line with Monti’s study, showing a smaller decrease of cue-induced arterial pressure in the naltrexone group compared to placebo (Monti et al., 1999). Our finding, however, is not in line with McCaul’s study in heavy drinkers, showing alcohol-induced heart rate reductions after naltrexone (McCaul et al., 2001). This discrepancy may result from the fact that McCaul’s study alcohol was actually consumed and heavy drinkers instead of alcohol dependent subjects were studied.

Third, no significant effects of naltrexone on baseline cortisol and Δ peak cortisol after cue exposure were observed. Our findings, therefore, do not support the hypothesis that naltrexone exerts its therapeutic effect by restoring the blunted basal activity and reactivity of the HPA system in alcohol dependent subjects. Our finding is not in line with the study of O’Malley et al. (2002) showing a stimulating effect of naltrexone on cortisol (O’Malley et al., 2002). However, in that particular study subjects were exposed to real alcohol (elevating cortisol levels) and cortisol was measured by an invasive method (in serum), which may explain the discrepancies with the current study. Another explanation why we did not find an effect of naltrexone on cortisol might be the poor temporal resolution of the cortisol reaction and subsequently the difficulty of attributing cortisol responses to the cue-exposure period. Since the literature is scarce and not very consistent, further investigation of the effect of naltrexone on the HPA-axis in the regulation of craving and relapse is warranted.

Our findings raise the question whether acamprosate and naltrexone are highly effective in the reduction of cue-induced craving and autonomic nervous system reactions to alcohol-related cues in the short term. In summary, it seems that naltrexone may only moderately reduce cue-induced craving (specifically when measured by use of a VAS scale) and that acamprosate may only moderately reduce arousal of the sympathetic nervous system (specifically heart rate). Cue-reactivity measures may not be sensitive enough to elucidate pharmacologic mechanisms of action, or alternatively, naltrexone and acamprosate may exert their effect by acting on other brain systems. Finally, it is possible that the observed moderate effects on cue-induced parameters may reflect the moderate clinical effects on relapse.

The moderate effect sizes in this and other studies on the efficacy of acamprosate and naltrexone are most likely a consequence of inefficient patient–treatment matching, resulting in subgroups of non-responders who mask the effect of the medication (Verheul et al., 1999; Ooteman et al., 2005). In line with this post-hoc explanation, we found large standard deviations of the mean group values for all outcome measures. Subgroups of alcoholics may differentially respond to acamprosate or naltrexone. One part of the patients may benefit with reasonably large effect sizes, whereas another part may even show an effect in the opposite direction. More research is needed on the characteristics of these responders and non-responders at the phenotypic level (e.g. clinical characteristics), the endophenotypic level (e.g. brain functioning) as well as at the genetic level (e.g. gene polymorphisms) (see also: Gottesman and Gould, 2003; Ooteman et al., 2005).

Despite the various strengths of the current study (e.g. explicit hypothesis driven approach; inclusion of two competitive medications; cue-induced craving and autonomic nervous system reaction to alcohol-related cues as the outcome measures), the current study also has several limitations. First, the study has a relatively small placebo group, which may have masked existing effects of acamprosate and naltrexone when compared to placebo. Second, our study focussed on effects after only three weeks of medication. Long-term medication challenges may show different results. For example, in Weinstein’s pilot study a reduction in cue reactivity was found after six weeks of treatment (Weinstein et al., 2003). Perhaps, acamprosate’s immediate effect on autonomic nervous system reactions to alcohol-related cues is followed by a delayed effect on cue-induced craving. Third, since exactly the same cue-exposure protocol was repeated at the second session, it cannot be excluded that habituation masked existing differences in cue-reactivity measures between groups. Fourth, although the participants were instructed not to drink during the medication period, some of the patients may have been drinking alcohol. Although this may account for the non-responders only, drinking itself has also been hypothesized to affect specifically naltrexone’s mechanism of action (see for a review: Sinclair, 2001). Fifth, in the current study, the reductions in sympathetic arousal are hypothesized to be related to withdrawal and anxiety. However, sympathetic indices are conservatively interpreted as general measures of arousal. For example, cue-reactivity theorists have suggested that sympathetic arousal can reflect...
either appetitive, aversive or cognitive aspects of craving. Our hypothesis, predicting that acamprosate primarily acts on autonomic nervous system reactions to alcohol-related cues, may therefore be too simple. Sixth, in the current study we attempted to differentiate medications according to their unique effects on reward and relief aspects of cue reactivity (craving scores and actual physiological reactions respectively). It may have been better to differentiate relief and reward aspects of cue reactivity by using the Alcohol Craving Questionnaire (ACQ) that includes anticipations of positive outcome and relief from negative outcome (Singleton et al., 1994). However, it must be noted that, until now, attempts to differentiate relief and reward concepts at the phenotypic level have been rather disappointing (e.g. Cooper et al., 1995; Ooteman et al., 2006b).

In conclusion, this study shows some evidence for moderate and differential effects of naltrexone and acamprosate on cue-induced craving and autonomic nervous system reactions to alcohol-related cues respectively. The results of this study only partly support the efficacy of naltrexone and acamprosate in the reduction of cue-induced craving and autonomic nervous system reaction to alcohol-related cues. More research is needed on the mechanisms of action of acamprosate and naltrexone on craving, patient–treatment matching, alternative mechanisms of naltrexone and acamprosate, the implications of these findings for the treatment of alcoholism, the effects of long-term treatment on cue-induced craving and autonomic nervous system reactions to alcohol-related cue measures and the effects of combined pharmacotherapy.

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Conflict of interest

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