TREATMENT
Clinical Predictors of Outcome from an Australian Pharmacological Relapse Prevention Trial

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Abstract — Aims: To assess which baseline characteristics of patients predict response to treatment with acamprosate (ACAMP) and naltrexone (NTX) in alcohol dependence. Methods: Outcome data from a 12-week randomized controlled trial of NTX, ACAMP and placebo for alcohol dependence were analysed by multiple logistic regression analyses to determine the predictive effects of gender and the baseline measures of dependence severity, craving, depression, anxiety and readiness to change in addition to NTX and ACAMP treatment. Moderators of the effect of each medication on outcomes were also examined. Results: Relapse was predicted by the interaction terms of ACAMP and alcohol dependence severity, NTX and depression as well as NTX and the readiness to change measure Taking Steps. Absinthe was similarly predicted by the interaction term ACAMP and alcohol dependence severity. Conclusion: The efficacy of NTX and ACAMP in reducing relapse or lapse is influenced by different clinical characteristics.

INTRODUCTION

Acamprosate (ACAMP) and naltrexone (NTX) are currently the most widely prescribed and extensively evaluated pharmacotherapies for the treatment of alcohol dependence. ACAMP is a synthetic gamma-aminobutyric acid (GABA) analogue that is thought to restore glutamatergic hyperexcitability following withdrawal from alcohol (Rammes et al., 2001; Spanagel and Ziegglansberger, 1997), whereas NTX is a μ-opioid receptor antagonist thought to reduce the reinforcing effects of alcohol (Swift et al., 1994). Several double-blind, randomized, placebo-controlled trials have demonstrated beneficial effects of each of these agents relative to placebo in alcohol-dependent individuals (Anton et al., 2005; Tempesta et al., 2000; Volpicelli et al., 1992; Whitworth et al., 1996). Meta-analyses conclude that NTX significantly delays time to relapse but is not associated with a significant modification in the abstinence rate, whereas ACAMP is associated with a significant improvement in the days of cumulative abstinence and abstinence rate (Rosset et al., 2008).

However, evidence for the efficacy of these medications is still not unequivocal with several studies failing to demonstrate any beneficial effect of NTX or ACAMP relative to placebo on measures of alcohol dependence (Anton et al., 2006; Chic et al., 2000; Gastpar et al., 2002; Krystal et al., 2001). Indeed, it has been observed that the efficacy data of alcohol pharmacotherapy are somewhat inconsistent and effect sizes are modest (Mann, 2004; Srisurapanont and Jarusuraisin, 2005). The heterogeneity of these findings points to the need for better characterization of patients who best respond to alcohol pharmacotherapy to guide treatment selection.

The possibility of a differential treatment response to alcohol pharmacotherapy is highlighted by several studies demonstrating the beneficial effects to occur in certain subpopulations over others, although many of these specificities have not been shown consistently. Predictors of response to ACAMP have included a typological differentiation of chronic alcoholism (Lesch et al., 2001) such as affiliation with Type I (Whitworth et al., 1996) and Type II (Kiefer et al., 2005; Whitworth et al., 1996), subgroups generally classified as those with a more severe dependence and greater withdrawal syndrome (type I) and anxiety (type II, Lesch and Walter, 1996). ACAMP has also been found to be preferentially effective in alcohol-dependent subjects that obtained low scores on somatic distress (Kiefer et al., 2005). However, Verheul et al. (2005) in a pooled analysis of seven European trials including 1485 patients found that ACAMP was not differentially associated with any predictor variables including physiological dependence, familial alcoholism, age-of-onset, anxiety symptomatology, severity of craving or gender. Another pooled analysis of European trials (Sass et al., 1995) similarly failed to find any predictors of efficacious response to ACAMP on any baseline characteristics.

Several clinical predictors of NTX have been reported in the literature. Volpicelli et al. (1995) demonstrated that higher baseline somatic distress and anxiety predicted beneficial response to NTX. In addition, Kiefer et al. (2005) reported that alcohol-dependent subjects with Lesch type III, a syndrome thought to be characterized by affective disorders, displayed significantly longer abstinence exclusively during NTX treatment. They also observed that subjects displaying high depression scores demonstrated better outcomes to NTX relative to those with low depression scores. These results are inconsistent, however, with our observation that NTX significantly increases time to relapse relative to placebo only in subjects with presenting with no clinically relevant levels of baseline depression (Morley et al., 2006) and previous reports that NTX treatment exacerbates depression (Farren and O’Malley, 1999).

Furthermore, one study observed long-acting injectable NTX to be significantly more effective than placebo for men but not for women (Garbutt et al., 2005). Similarly, Hernandez-Avila et al. (2006) reported that only men showed greater reduction in measures of alcohol dependence following oral NTX treatment. In contrast, a recent analysis of two clinical trials observed the effect size of NTX relative to placebo to be similar in women and men (Baros et al., 2008). Finally, there is also evidence that higher levels of
craving at baseline predict favourable response to NTX relative to those subjects treated with placebo (Jaffe et al., 1996; Monterosso et al., 2001; Volpicelli et al., 1995).

There remains a lack of consistent evidence to suggest clearly which medication, NTX or ACAMP, is superior and whether there is consistent differential response across individuals. This has been due, in part, to the fact that most analyses of clinical predictors are from alcohol pharmacotherapy trials that do not directly compare the medications. To this degree, the current study aims to assess for the clinical predictors of response to ACAMP and NTX form a randomized, placebo-controlled, double-blind study (Morley et al., 2006). In line with previous studies, we examined the predictive value of gender and baseline craving, alcohol dependence severity, drinks per drinking day, depression, anxiety and stress on treatment outcome. In addition, we explored additional variables associated with readiness to change. Higher global motivation to change has been noted to indicate patient recognition and acknowledgement of escalating consequences and symptoms of dependence (DiClemente et al., 2009) and has been shown to predict alcohol consumption and time to lapse (Demmel et al., 2004; Heather et al., 1993; McMahon and Jones, 1996).

SUBJECTS AND METHODS

The analysis was conducted using subject data from 169 alcohol-dependent subjects enrolled in a placebo-controlled, double-blind, randomized trial of NTX and ACAMP (Morley et al., 2006). The study was a 12-week trial performed over a 24-month period at three sites in Australia. The methods are outlined briefly below.

Subjects
Subjects were men and women who had attended an inpatient detoxification programme, outpatient treatment or follow-up or who had responded to live or print advertising. Inclusion criteria consisted of being 18 and 65 years of age, a diagnosis of alcohol dependence or abuse (according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, DSM-IV), abstinence from alcohol for 3–21 days with resolution of any withdrawal symptoms, sufficient English comprehension skills to provide informed consent and complete questionnaires. Exclusion criteria were advanced liver disease (hepatocellular failure, variceal bleeding, ascites or encephalopathy), previous treatment with NTX or ACAMP within 3 months of randomization, any other drug dependence (other than nicotine) or severe current psychiatric disorder associated with psychosis and significant suicide risk. Women were excluded if they were pregnant or breastfeeding. All subjects were compensated $20 AUD for baseline and follow-up assessments. All subjects provided written informed consent. The study was approved by the Human Ethics Review Committee of Central Sydney Area Health Service, South Eastern Sydney Area Health Service and Wentworth Area Health Service.

Procedure
Before entry to the study, alcohol withdrawal (detoxification) treatment was offered if clinically indicated according to NSW detoxification guidelines. Following abstinence for a minimum of 3 days (maximum of 21 days), patients with alcohol dependence or abuse were randomized to receive either one tablet of NTX per day (50 mg), six tablets of ACAMP per day (1998 mg/day as two 333 mg tablets thrice daily), NTX placebo (tablets produced to have identical appearance to that of NTX) or ACAMP placebo (tablets produced to have identical appearance to that of ACAMP). Randomization was performed by placing a shuffled series of cards labelled with the four study groups into consecutively numbered envelopes.

All subjects received medical care typically available at hospital-based drug and alcohol treatment services in Sydney, Australia. This consisted of attending one medical assessment (baseline) and four medical reviews with average duration of 15 min over the 12-week treatment period, held at Weeks 1, 2, 6 and 12. Medical follow-up appointments were optional at Week 26. Recent alcohol consumption, difficulties with taking medications such as side effects and compliance as measured by self-report and pill count were assessed in the medical reviews. At the initial baseline medical assessment, alcohol consumption in the previous 30 days was determined using the timeline follow back alcohol consumption form (Sobell et al., 1979). A blood sample was obtained to test for liver disease, renal dysfunction, calcium, electrolytes and full blood count. If subjects failed to attend the scheduled medical review, follow-up phone calls were made to arrange another appointment. A maximum of three contact attempts were made. Attempts were made to obtain drinking pattern information from all participants regardless of completion in the treatment protocol. All subjects also received four to six counselling sessions which aimed at improving medication compliance by addressing concerns about the medication, expectations for treatment and relapse prevention. Medication compliance was assessed by self-report, pill count of the packaging returned and a daily monitoring card adapted from that used by Chick et al. (2000).

Assessments
Levels of alcohol dependence, craving, physical and mental health were assessed at baseline, 12 weeks and at a 26-week follow-up. Clinical ratings performed at these visits included the Alcohol Dependence Scale (ADS; Skinner and Allen, 1982) the Penn Alcohol Craving Scale (PACS; Flannery et al., 1999), the Depression Anxiety Stress Scale (DASS; Lovibond and Lovibond, 1995), the Stages of Change Readiness and Treatment Expectancy Scale (SOCRATES; Miller and Tonigan, 1996). The 19-item SOCRATES is one of the most cited instruments for measuring motivation to change in adults with alcohol problems, determining three constructs: awareness of the problem (Recognition), ambivalence about the problem (Ambivalence) and taking steps to change the problem (Taking Steps).

Statistical analysis
The dependent variables were no relapse (relapse was defined as one instance of four or more drinks for women and six or more drinks for men on 1 day) and no lapse (abstinence) throughout treatment. Predictor variables were selected from those collated in the trial and previous research indicating their involvement in the treatment of alcohol dependence. Multiple logistic regression analyses were
carried out using a hierarchical method. Baseline variables were entered into Model 1, including gender; baseline drinking characteristics (scores on the ADS, drinks per drinking day and scores on the PACS scale); depression, anxiety and stress (scores on the DASS) and readiness for change (SOCRATES scores on Taking Steps, Ambivalence and Recognition). In Model 2, two variables representing medication group (NTX and ACAMP) were entered. In Model 3, interaction terms for baseline variables and medication group were entered to determine the moderating effect of these variables on medication. Continuous variables were centred to eliminate multicollinearity problems given the large number of interaction terms (Kraemer and Blasey, 2004). All analyses were two-tailed, with significance level at \( P < 0.05 \). Data were analysed using SPSS 16 for Macintosh.

**RESULTS**

Overall, 41 (67%) participants randomized to placebo, 36 (68%) randomized to NTX and 41 (75%) randomized to ACAMP completed the study in full. Alcohol consumption data for those participants (30%) that did not complete the treatment programme was obtained via contact with the subjects, their nominated contact person, treating clinician or hospital files. However, drinking information could not be obtained for five subjects, and these subjects were assumed to have relapsed to baseline from the last date of contact. The average days on medication for placebo was 60 ± 27, for NTX 57 ± 30 and ACAMP 61 ± 26, and these differences were not significant (\( F < 1 \)). Descriptive data for the predictor variables for each of the medication groups have previously been reported (Morley et al., 2006) and are presented as part of Table 1. Multiple logistic regression analyses for the final model (Model 3) of no lapse and no relapse are detailed in Tables 2 and 3, respectively (Models 1 and 2 not shown).

**Predictors of no lapse (abstinence)**

Model 1 (\( \chi^2 = 22.63, P < 0.05, -2LL = 171.45 \)) including the baseline characteristics revealed a significant association of previous drinks per drinking day and levels of Ambivalence with lapse (OR = 1.33, 95% CI = 1.07–1.65; OR = 1.09, 95% CI = 1.02–1.16, respectively). These variables remained significant (OR = 1.09, 95% CI = 1.03–1.16; OR = 1.34, 95% CI = 1.07–1.66, respectively) upon entering the treatment groups in Model 2 (\( \chi^2 = 22.90, P < 0.05, -2LL = 137.36, \chi^2 \) improvement = 0.27). Model 2 demonstrates that, consistent with main efficacy analysis (Morley et al., 2006), there was no significant effect of NTX (OR = 0.78, \( P = 0.65 \)) or ACAMP (OR = 0.79, \( P = 0.66 \)) on lapse after controlling for baseline covariates. The significant effect of previous drinks per drinking day and Ambivalence did not remain significant in Model 3 after including the interaction terms (\( \chi^2 = 48.17, P < 0.05, -2LL = 112.09, \chi^2 \) improvement = 25.27). In Model 3, a significant interaction of dependence severity and ACAMP treatment emerged whereby higher levels of dependence severity displayed a greater treatment effect (OR = 1.26, 95% CI = 1.01–1.56).

**Predictors of no relapse**

Neither Model 1 (\( \chi^2 = 14.71, P = 0.14, -2LL = 171.45 \)) nor Model 2 (\( \chi^2 = 15.74, P = 0.20, -2LL = 170.41 \)) was significant. Model 2 demonstrates that, consistent with main efficacy analysis (Morley et al., 2006), there was no significant effect of NTX (OR = 1.13, \( P = 0.79 \)) or ACAMP (OR = 0.71, \( P = 0.47 \)) on lapse after controlling for baseline covariates. In Model 3 (\( \chi^2 = 50.60, P < 0.02, -2LL = 135.56, \chi^2 \) improvement = 34.85), an interaction effect was observed between DASS Depression and NTX treatment (OR = 0.77, 95% CI = 0.63–0.95) whereby, in NTX-treated subjects, lower levels of depression were associated with no relapse. An interaction effect also occurred between dependence severity and ACAMP treatment (OR = 1.28, 95% CI = 1.02–1.62) such that higher levels of dependence severity at baseline predicted a beneficial response to ACAMP. In addition, a significant association of Taking Steps and no relapse was revealed (OR = 1.28, 95% CI = 1.03–1.60) along with a significant interaction of Taking Steps and NTX treatment (OR = 0.67, 95% CI = 0.49–0.93), such that lower baseline levels of Taking Steps were associated with favourable treatment outcomes for those treated with NTX.

**DISCUSSION**

This study aimed to identify factors that protect against relapse and lapse (abstinence) in the treatment of alcohol dependence. In the total sample, the significant predictors of no lapse and no relapse were depression, anxiety, stress and ambivalence. In the treatment groups, NTX was associated with a significant reduction in lapse and relapse compared to placebo, whereas ACAMP was not. The interaction effect between NTX and depression severity suggests that NTX is more effective in reducing lapse for those with higher levels of depression. Conversely, ACAMP was associated with a significant reduction in relapse for those with lower levels of ambivalence, indicating a protective effect. These findings support the importance of targeting these factors in the development of future treatments for alcohol dependence.
dependence. Specifically, we aimed to assess the clinical predictors of response to ACAMP and NTX treatment in a double-blind, randomized, controlled trial.

A significant interaction effect of ACAMP and dependence severity in predicting abstinence and relapse was observed. That is, for subjects randomized to ACAMP, those with high baseline severity of dependence were less likely to lapse and relapse compared with those with low severity of dependence. This result is somewhat consistent with previous research showing differential response to ACAMP treatment with type and severity of alcohol dependence. Indeed, previous research has found ACAMP to be more effective in patients classified as Lesch type I (greater withdrawal and severity of dependence) and type II (greater anxiety) patients compared with those classified as type III or IV (affective or organic disorder; Lesch and Walter, 1996). In addition, Kiefer et al. (2005) reported that ACAMP was mainly effective in type I patients. The current results suggest that the severity of baseline dependence may particularly moderate the effect of ACAMP on treatment outcomes. Interestingly, the current results suggest that, in the current sample, this moderating effect occurs at a greater degree than to that of NTX. It is possible this occurs through ACAMP’s specific mechanism of action modulating glutamatergic and GABA-ergic dysregulations of systems relating to withdrawal and therefore greater severity of dependence (Littleton, 1995; Verheul et al., 1999).

In addition, we observed a significant interaction effect of DASS Depression scores and NTX on relapse. That is, for subjects randomized to NTX, a beneficial treatment response occurred in those patients with lower levels of baseline depression relative to those with higher baseline depression. This corresponds with the observation from our initial main effects analysis that NTX delayed time to relapse relative to placebo in those subjects with low levels of depression (Morley et al., 2006). Such results are noteworthy given that alcohol-dependent patients suffering from comorbid depression experience greater disability, greater health service use and higher rates of relapse during treatment (Burns and Teesson, 2002; Greenfield et al., 1998). These findings are also somewhat consistent with preclinical studies demonstrating the ability of NTX to block alcohol-induced reinstatement but not stress-induced reinstatement (Le et al., 1999). Interestingly, we failed to observe any evidence of a moderating effect of depression and ACAMP on treatment outcome.

A relationship between NTX treatment and depression has been increasingly reported, although the direction of this association is yet to be consistently ascertained. Early studies have noted depression or dysphoria associated with the use

### Table 2. Predictors of abstinence (no lapse) at Week 12 of subjects treated with compliance therapy and either naltrexone, acamprosate or placebo by logistic regression analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictor</th>
<th>Wald X</th>
<th>OR</th>
<th>P-value</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Gender (male)</td>
<td>0.06</td>
<td>1.27</td>
<td>0.82</td>
<td>0.17</td>
<td>9.56</td>
</tr>
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<td></td>
<td>Dependence severity</td>
<td>2.37</td>
<td>0.90</td>
<td>0.12</td>
<td>0.80</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>Drinks per drinking day</td>
<td>3.33</td>
<td>1.13</td>
<td>0.07</td>
<td>0.99</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>Craving</td>
<td>0.24</td>
<td>0.96</td>
<td>0.63</td>
<td>0.82</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>0.85</td>
<td>1.06</td>
<td>0.36</td>
<td>0.94</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>0.077</td>
<td>1.02</td>
<td>0.78</td>
<td>0.89</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>0.02</td>
<td>0.99</td>
<td>0.89</td>
<td>0.88</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>Taking Steps</td>
<td>0.75</td>
<td>1.10</td>
<td>0.39</td>
<td>0.89</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>Ambivalence</td>
<td>3.81</td>
<td>1.53</td>
<td>0.51</td>
<td>0.10</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>Recognition</td>
<td>0.18</td>
<td>0.94</td>
<td>0.67</td>
<td>0.71</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>NTX</td>
<td>1.06</td>
<td>0.25</td>
<td>0.30</td>
<td>0.02</td>
<td>3.58</td>
</tr>
<tr>
<td></td>
<td>ACAMP</td>
<td>0.49</td>
<td>0.46</td>
<td>0.49</td>
<td>0.05</td>
<td>4.03</td>
</tr>
<tr>
<td></td>
<td>NTX × gender (male)</td>
<td>0.56</td>
<td>3.35</td>
<td>0.46</td>
<td>0.14</td>
<td>79.95</td>
</tr>
<tr>
<td></td>
<td>ACAMP × gender (male)</td>
<td>0.63</td>
<td>3.78</td>
<td>0.43</td>
<td>0.14</td>
<td>99.55</td>
</tr>
<tr>
<td></td>
<td>NTX × dependence severity</td>
<td>0.33</td>
<td>0.94</td>
<td>0.57</td>
<td>0.76</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>ACAMP × dependence severity</td>
<td>4.29*</td>
<td>1.26</td>
<td>0.04</td>
<td>1.01</td>
<td>1.56</td>
</tr>
<tr>
<td></td>
<td>NTX × drinks per drinking day</td>
<td>0.31</td>
<td>1.06</td>
<td>0.58</td>
<td>0.86</td>
<td>1.32</td>
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<td>ACAMP × drinks per drinking day</td>
<td>0.41</td>
<td>0.94</td>
<td>0.52</td>
<td>0.78</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>NTX × craving</td>
<td>0.23</td>
<td>1.06</td>
<td>0.64</td>
<td>0.84</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>ACAMP × craving</td>
<td>0.14</td>
<td>1.04</td>
<td>0.71</td>
<td>0.84</td>
<td>1.34</td>
</tr>
<tr>
<td></td>
<td>NTX × depression</td>
<td>3.70</td>
<td>0.78</td>
<td>0.05</td>
<td>0.60</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>ACAMP × depression</td>
<td>0.37</td>
<td>0.95</td>
<td>0.54</td>
<td>0.81</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>NTX × anxiety</td>
<td>0.19</td>
<td>1.06</td>
<td>0.66</td>
<td>0.83</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td>ACAMP × anxiety</td>
<td>0.51</td>
<td>0.92</td>
<td>0.48</td>
<td>0.74</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>NTX × stress</td>
<td>1.24</td>
<td>1.12</td>
<td>0.27</td>
<td>0.92</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>ACAMP × stress</td>
<td>0.20</td>
<td>1.05</td>
<td>0.66</td>
<td>0.86</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>NTX × Taking Steps</td>
<td>2.60</td>
<td>0.73</td>
<td>0.11</td>
<td>0.50</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>ACAMP × Taking Steps</td>
<td>0.03</td>
<td>0.97</td>
<td>0.85</td>
<td>0.74</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>NTX × Ambivalence</td>
<td>0.73</td>
<td>0.78</td>
<td>0.39</td>
<td>0.43</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>ACAMP × Ambivalence</td>
<td>0.08</td>
<td>1.15</td>
<td>0.78</td>
<td>0.44</td>
<td>3.03</td>
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<tr>
<td></td>
<td>NTX × Recognition</td>
<td>3.86</td>
<td>1.98</td>
<td>0.05</td>
<td>1.00</td>
<td>3.93</td>
</tr>
<tr>
<td></td>
<td>ACAMP × Recognition</td>
<td>0.52</td>
<td>0.81</td>
<td>0.47</td>
<td>0.45</td>
<td>1.45</td>
</tr>
</tbody>
</table>

Parentheses indicate the group coded as 1 for dummy variables, models were obtained by enter method. Craving: as measured by the PACS Craving Scale; dependence severity: as measured by the ADS; depression, anxiety and stress: as measured by the DASS; Taking Steps, Recognition and Ambivalence: measured by the SOCRATES.

ACAMP, acamprosate; NTX, naltrexone; SOCRATES, Stages of Change Readiness and Treatment Expectancy Scale.

*P < 0.05.
of NTX treatment in healthy volunteers (Hollister et al., 1981; Mendelson et al., 1978) and deterioration of comorbid major depression has been described in some alcohol-dependent patients following NTX treatment (Schurks et al., 2005). However, Kiefer et al. (2005) revealed that NTX displayed a tendency to be more effective in patients with higher levels of depression. More recently, Walsh et al. (2008) demonstrated that the efficacy of NTX in smoking cessation was moderated by depressive symptoms wherein NTX was related to superior quit rates at higher levels of depressive symptoms. It is relevant to note, however, that subjects in the Kiefer trial were excluded if they had a current mental impairment that required psychotropic medication. In our sample, a substantial proportion of subjects were observed to have a depressive or anxiety disorder and/or taking psychotropic medication. Such delineation is important given that several antidepressants have been found to alter the binding of μ-opioid receptors in some regions of the brain (Chen and Lawrence, 2004; Giaroni et al., 2008).

A recent secondary analysis of an alcohol pharmacotherapy trial by Krystal et al. (2008) reported that the presence of comorbid mood/anxiety disorder predicted poor outcomes overall, but that NTX was associated with a reduction in the percent drinking days compared with placebo only among those patients receiving antidepressants. In contrast to our results, the authors conclude that NTX may have a greater efficacy for reducing drinking among the depressed. However, it is possible that timely assessment of and monitoring depressive symptoms in relation to antidepressant adherence may be necessary in determining the casual direction in such cases. Furthermore, their results are incongruous with studies that have failed to find any added benefit of the antidepressant sertraline to NTX treatment in alcohol-dependent patients with comorbid depression (O’Malley et al., 2008; Oslin, 2005). Certainly the treatment of alcohol-dependence patients with comorbid depression remains intricate. It is possible to conclude that this subgroup may respond differentially to NTX treatment to some degree and that the presence of negative mood states should act as a marker for patients requiring additional care.

The current results demonstrate that baseline levels of readiness to change (Taking Steps) as measured by the SOCRATES predict relapse overall. Similarly, Demmel et al. (2004) found that the measure Taking Steps was the only SOCRATES subscale related to treatment outcome in a group of alcohol-dependent patients. Interestingly, we observed that NTX yielded a greater treatment effect for those subjects with lower baseline levels of Taking Steps. The Taking Steps dimension of the SOCRATES is thought to measure the ‘action’ stage of motivational change that...
Accordingly, these results do not support previous studies that investigation.

with lower rates of relapse. The interaction of active medi-
dependence severity may thus be helpful in selecting differ-

lected by lower levels of depression, whereas

analysis was not designed to examine the comparable efficacy
to the absence of any treatment effect in the trial and that the

did not observe any differential medication effect of ACAMP
to be determined in predicting treatment response to alcohol

explained by the final models, suggesting there remains much

treatment outcome is moderated by different baseline clinical

differences in response to NTX (Baros et al., 2008) and in

instance may be due to inconsistent statistical design.

It was observed that the efficacy of NTX and ACAMP on
treatment outcome is moderated by different baseline clinical
characteristics. It is relevant to note, however, that approxi-

only 40% of the variance in treatment outcome is

explained by the final models, suggesting there remains much to

determine in predicting treatment response to alcohol
pharmacotherapy. Meta-analyses have indicated that ACAMP
has more efficacy in preventing a lapse, whereas NTX pre-

a lapse becoming a relapse (Rosner et al., 2008). We did not observe any differential medication effect of ACAMP or NTX on abstinence and relapse. However, this may be due to the absence of any treatment effect in the trial and that the analysis was not designed to examine the comparable efficacy of the two medications between these outcomes.

CONCLUSION

The current study observed that the efficacy of NTX and ACAMP in reducing relapse or lapse is influenced by different clinical characteristics. Beneficial treatment response to NTX was predicted by lower levels of depression, whereas those with higher severity of dependence responded more favourably with ACAMP. Baseline levels of depression and dependence severity may thus be helpful in selecting differential treatment for patients.

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REFERENCES


Chen F, Lawrence AJ. (2004) Chronic antidepressant treatment causes a selective reduction of mu-opioid receptor binding and functional coupling to G Proteins in the amygdala of fawn-


