CLINICAL PREDICTORS OF RESPONSE TO NALTREXONE IN ALCOHOLIC PATIENTS: WHO BENEFITS MOST FROM TREATMENT WITH NALTREXONE?

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Abstract — Aims: To determine the clinically ascertained variables that are related to satisfactory response to naltrexone (NTX) treatment of alcohol dependence after detoxification. Methods: The use of intake and outcome variables were measured in a randomized 3-month open-controlled trial comparing the effects of naltrexone plus psychotherapy treatment versus psychotherapy treatment alone on the maintenance of abstinence in the final 28 days (n = 336, all male). Results: Predictors of a positive response to NTX treatment were family history of alcoholism (P = 0.010), early age at onset of drinking problems (P = 0.014) and comorbid use of other drugs of abuse (P < 0.001). Among the subjects not treated with NTX, the greater the number of predictor variables, the lower the final 28 days abstinence rates (P = 0.00003), but this was not the case in patients treated with NTX (P = 0.844). Conclusions: Patients with these features, suggesting biological vulnerability overall have poorer outcomes, but this can be reduced with NTX treatment. The type of alcoholism should be considered before deciding on the pharmacological strategy.

INTRODUCTION

Pharmacotherapy is widely used in the treatment and prevention of alcohol withdrawal symptoms, but its role in the prevention of alcoholic relapse remains limited. The main drugs used in the treatment of alcohol dependence are naltrexone (NTX) (O’Malley et al., 1992; Volpicelli et al., 1992) and acamprosate (Paille et al., 1995; Sass et al., 1996). NTX has proved, in several double-blind clinical trials, to be more effective than placebo as an adjunct to psychosocial treatments for alcohol dependence, in both short- and long-term studies (Anton et al., 1999; Chick et al., 2000; Morris et al., 2001; Rubio et al., 2001; Guardia et al., 2002; Latt et al., 2002; Baldin et al., 2003). However, some clinical trials have failed to find significant drug–placebo difference for several outcome variables, such as drinking days during treatment, or days of abstinence until first alcohol intake (Krystal et al., 2001; Gastpar et al., 2002).

NTX is an opioid-receptor antagonist which is believed to act in alcoholism by blocking the putative effects of endogenous opioids release after alcohol consumption, and thus blocking the pleasurable effects or “high” of alcohol (Volpicelli et al., 1995a; O’Malley et al., 1996; Na and Lee, 2002). Using this effect, naltrexone might reduce the quantity and frequency of drinking among alcoholics who relapse (O’Malley et al., 1992; Volpicelli et al., 1992, Jimenez-Arriero et al., 1998). However, its effectiveness varies among patients, and not everyone who drinks alcohol shows evidence of a “high” or an increase in endogenous opioids (Gianoulakis et al., 1989). This has led to a research aimed at identifying the alcoholic subtype that most benefits from treatment with it. Given the heterogeneity of alcohol dependence, it has been of interest to investigate the potential predictors of response. The post-hoc analysis of the original sample in which Volpicelli et al. (1992) studied the efficacy of naltrexone concluded that

the drug may be useful for subjects presenting high levels of craving and somatic symptoms (Volpicelli et al., 1995a). In another study, the same research group found that patients with high levels of alcohol craving or a substantial family history of alcoholism were more likely to benefit from naltrexone treatment (Monterosso et al., 2001). Kranzler et al. (2003) have recently reported the efficacy of naltrexone in the treatment of early problem drinkers.

Alcoholism is a multifactorial disorder involving biological and psychosocial interactions, and with substantial heritability (Goodwin, 1985). Some clinical traits, used for classifying alcoholic subsets, have been proposed as clinical markers of potential special biological vulnerability (Cloninger et al., 1988; Babor et al., 1992). The purpose of our current study was to determine whether family history of alcoholism (FHA+) was related to a satisfactory outcome in our clinic’s alcoholic patients treated with naltrexone, and also to examine the predictive power of other clinical variables.

SUBJECTS AND METHODS

Design

We performed a randomized 3-month open-controlled trial comparing the effects of naltrexone plus psychotherapy treatment with those of psychotherapy treatment alone on the maintenance of abstinence from alcohol after detoxification. This type of trial was chosen for the following reasons: (i) the aim of the study was not to determine the efficacy of naltrexone in the treatment of alcohol dependence, but rather to identify the potential predictors of response to treatment; (ii) physician and patient being open to the study medication, with accompanying psychotherapy more closely mirrors routine clinical practice in Spain, than a double-blind study; (iii) an open study permitted the study of diverse clinical situations that may predict different response to treatment, such as that of severely ill patients, homeless, multisubstance abusers or patients with either behavioural or affective disorders. We considered that clinicians should maintain...
control over the treatment prescribed at all times, providing therapeutic intervention in case of complications.

Subjects

Once subjects had completed the detoxification period, either in the hospital or as an outpatient, they were informed about the therapeutic options (with and without naltrexone), but told that the treatment (drug/no drug) they would receive would be chosen at random. They were informed that neither a relapse nor failing to follow the prescribed treatment would lead them to be asked to leave the trial. However, they would be taken out of the trial if they failed to make contact with the psychiatrist in a period of over 15 days (i.e. two consecutive visits). They were also informed that they could drop out of the study at any time. After receiving full information about the study they were asked for their consent to take part.

Of the 407 alcoholic patients approached, 52 were excluded because of medical problems that contraindicated the use of naltrexone (e.g. AST and ALT >3 times normal values), and 19 later refused to participate because of problems related to reporting with the frequency required by the study. Thus, 336 subjects participated. Participants were alcohol-dependent males, aged between 18 and 65 years, who had requested detoxification in the Addictive Behaviour Unit of the ‘Doce de Octubre’ hospital (Madrid). At intake, the patients met the DSM-IV criteria for alcohol dependence (APA, 1994). In addition, we applied the following exclusion criteria: (i) opiate use during the year before inclusion in the trial; (ii) presence of another psychiatric disorder diagnosed by the DSM-IV (SCID) at baseline evaluation (Firsts et al., 1995); and (iii) a medical condition that could contraindicate the use of naltrexone.

Of the 336 participating subjects, 268 were detoxified with diazepam over a period of 5–10 days (138 in the NTX-group and 130 in the non-NTX group). They had been abstinent for a mean of 14.5 days (SD 7.2), before starting the medication.

Treatments offered

Patients in the naltrexone group were prescribed 50 mg/day. (No placebo was used in this study). Supportive group therapy was offered to all patients, once a week, throughout the entire study period. Therapy was less structured than in classical relapse prevention programmes. Basic relapse prevention techniques were used (for dealing with situations of risk, craving and negative emotional states). Abstinence was positively reinforced. When the psychiatrist found that the patient, in either of the groups, met the clinical criteria for depressive or anxiety disorder, sertraline (100–200 mg/day) was added. Insomnia was treated with hydroxyzine, an H1 receptor antagonist, for insomnia (50–100 mg/day h.s.). In cases of alcohol intake or of high level of subjective craving, or when both clinician and patient considered it appropriate, disulfiram was added to the treatment.

Assessments

Alcohol dependence level was defined according to DSM-IV criteria (SCID-IP, Firsts et al., 1995); the Addiction Severity Index (ASI) (McLellan et al., 1980) and the Severity of Alcohol Dependence Scale (SADS) (Stockwell et al., 1979; Rubio et al., 1998). Craving was evaluated with three analogue scales (frequency, duration and intensity) (Miller, 1996). During follow-up assessments, participants were evaluated each week on the basis of the participant’s self data on alcohol intake and consumption pattern (Miller, 1996). In addition, the following biological parameters of alcohol use were used: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and carbohydrate-deficient transferrin (CDT). Other substance-use disorders were defined according to the DSM-IV criteria (SCID-IP, Firsts et al., 1995)

Family history of alcoholism was assessed by interviewing first-degree relatives (parents, siblings, offspring). Subjects were classified as family history positive (FH+) if they had a first-degree relative with a history of alcohol dependence. Where necessary, the diagnosis was made by applying the Research Diagnostic Criteria-Family History (RDC-FH) (Bueno et al., 1989).

The following outcome variables were computed: number of drinking days, number of heavy drinking days (defined as the consumption of >5 drinks or 40 g ethanol/day), abandonment of treatment, days of continued abstinence and final abstinence defined as absolute and continuous abstinence in the final 28 days of the follow-up period.

Patients visited their psychiatrists every week (±3 days) until the end of the study. In the event of relapse, frequency of visits was increased in order to help curtail the relapse and to offer the patient assistance, if required. At each visit, entries in the diary of alcohol consumption they had been asked to complete at home were checked, along with craving, and compliance with the treatment. Consumption and compliance data were compared with the information given by the family. Where there was a clear contradiction, we opted to use the information suggesting the most consumption. Biological parameters were not used for determining the amount of consumption or relapse, as it may be that occasional consumption of alcohol fails to have an influence on plasma levels of AST, ALT, GGT and CDT.

‘Blind’ assessors

Outcome data were collected by assessors who saw patients once a week, after the weekly group therapy session. Attempts were made to keep them blinded to the drug taken by the patients. They used the following sources of data: (i) the patient’s self-assessment (patients were asked not to talk about the pharmacological treatment); (ii) the psychiatrist assigned to the case, who provided any data required from the clinical records and results of biochemical analyses (but did not disclose the treatment prescribed); and (iii) the patient’s family, who provided information about drinking and any attempts by the patient to cease the pharmacological treatment.

Statistical analysis

Comparison of qualitative and quantitative variables was made using chi-squared test with the Yates continuity correction and analysis of variance (ANOVA), respectively. The sample was divided according to the selected variables associated with final abstinence, and the logistic regression model was used to determine the influence of treatment with naltrexone on the final state for each subgroup. Present age was used as a covariate for analysis. We also included the rest of the predictors in this model. Finally, we used the chi-squared tendency model to determine the influence of number of predictors on outcome among those treated with and without...
naltrexone. The statistical package used was SPSS 9.0. A $P$-value $< 0.05$ was considered significant.

RESULTS

Sample characteristics
The two treatment groups did not differ with respect to sociodemographic and clinical data, such as pattern of alcohol consumption, amount of alcohol habitually consumed, and age (Table 1). The mean values were: age 43.68 years, alcohol consumption per occasion 219.33 g of ethanol; age at onset of habitual consumption 16.52 years, and beginning of alcohol problems 22.84 years. Fifty-two (15.48%) patients had antecedents of treatment for depressive-anxiety disorders; 216 (61.9%) were FHA+; 78 (23.21%) had a family history of other psychiatric disorders; and 73 (21.73%) presented other substance-use disorders, either currently or in the past. There was no difference between the groups in the concomitant use of disulfiram or sertraline during the study.

Outcome measures
Table 2 shows the overall outcome for the total sample according to the treatment. The proportion of patients that

### Table 1. Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone $(n = 168)$</th>
<th>Non-naltrexone $(n = 168)$</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (M and SD)</td>
<td>41.34 (8.01)</td>
<td>41.77 (9.2)</td>
<td>0.691</td>
<td>0.489</td>
</tr>
<tr>
<td>Pattern of alcohol consumption before trial (M and SD)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amount of alcohol/day (g/d)</td>
<td>221.8 (52.6)</td>
<td>215.1 (63.1)</td>
<td>1.057</td>
<td>0.290</td>
</tr>
<tr>
<td>Heavy drinking days/28 days</td>
<td>25.3 (9.2)</td>
<td>24.8 (9.1)</td>
<td>0.489</td>
<td>0.625</td>
</tr>
<tr>
<td>Serum markers (IU/l) (M and SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>119 (82)</td>
<td>114 (97)</td>
<td>0.510</td>
<td>0.609</td>
</tr>
<tr>
<td>AST</td>
<td>88 (24)</td>
<td>91 (22)</td>
<td>1.194</td>
<td>0.232</td>
</tr>
<tr>
<td>ALT</td>
<td>65 (37)</td>
<td>68 (32)</td>
<td>0.794</td>
<td>0.427</td>
</tr>
<tr>
<td>CDT</td>
<td>25 (19)</td>
<td>24 (21)</td>
<td>0.457</td>
<td>0.647</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone $(n = 168)$</th>
<th>Non-naltrexone $(n = 168)$</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antecedents of depressive/anxiety disorders</td>
<td>27 (16.07)</td>
<td>25 (14.88)</td>
<td>0.023</td>
<td>1</td>
<td>0.880</td>
</tr>
<tr>
<td>Family history of alcoholism</td>
<td>104 (61.90)</td>
<td>112 (66.66)</td>
<td>0.635</td>
<td>1</td>
<td>0.425</td>
</tr>
<tr>
<td>Other substance use disorders (excluded nicotine)</td>
<td>40 (23.80)</td>
<td>33 (19.64)</td>
<td>0.630</td>
<td>1</td>
<td>0.427</td>
</tr>
<tr>
<td>Use of disulfiram</td>
<td>41 (24.40)</td>
<td>42 (25.00)</td>
<td>$\chi^2 = 0.02$</td>
<td>1</td>
<td>0.89</td>
</tr>
<tr>
<td>Use of sertraline</td>
<td>40 (23.80)</td>
<td>42 (25.00)</td>
<td>$\chi^2 = 0.06$</td>
<td>1</td>
<td>0.79</td>
</tr>
</tbody>
</table>

### Table 2. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone $(n = 168)$</th>
<th>Non-naltrexone $(n = 168)$</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence in the final 28 days of follow-up$^a$</td>
<td>119 (70.83%)</td>
<td>99 (58.93%)</td>
<td>4.715</td>
<td>1</td>
<td>0.030*$</td>
</tr>
<tr>
<td>Drop-outs</td>
<td>47 (27.98%)</td>
<td>58 (34.52%)</td>
<td>1.671</td>
<td>1</td>
<td>0.196</td>
</tr>
<tr>
<td>Subjects with absolute abstinence</td>
<td>111 (66.07%)</td>
<td>95 (56.54%)</td>
<td>2.823</td>
<td>1</td>
<td>0.093</td>
</tr>
<tr>
<td>Days of consumption$^b$</td>
<td>1.29 (8.49)</td>
<td>4.59 (16.66)</td>
<td>3.982</td>
<td>1</td>
<td>0.046</td>
</tr>
<tr>
<td>Heavy drinking days</td>
<td>0.17 (1.82)</td>
<td>3.55 (13.55)</td>
<td>7.392</td>
<td>1</td>
<td>0.007*$</td>
</tr>
<tr>
<td>Days of continued abstinence until first consumption</td>
<td>86.256 (13.972)</td>
<td>81.364 (24.249)</td>
<td>3.690</td>
<td>1</td>
<td>0.059</td>
</tr>
<tr>
<td>Patients who consume</td>
<td>10 (8.26%)</td>
<td>15 (13.63%)</td>
<td>1.211</td>
<td>1</td>
<td>0.271</td>
</tr>
<tr>
<td>Days of consumption$^c$</td>
<td>15.60 (26.69)</td>
<td>33.67 (33.34)</td>
<td>2.050</td>
<td>1</td>
<td>0.166</td>
</tr>
<tr>
<td>Heavy drinking days$^c$</td>
<td>2.0 (6.32)</td>
<td>26.00 (28.34)</td>
<td>6.851</td>
<td>1</td>
<td>0.015*$</td>
</tr>
<tr>
<td>Days of continued abstinence until first consumption</td>
<td>34.20 (22.36)</td>
<td>26.67 (29.44)</td>
<td>0.686</td>
<td>2</td>
<td>0.499</td>
</tr>
</tbody>
</table>

$^a$ For qualitative outcome variables, data are presented as $n$ (%).

$^b$ For quantitative outcome variables, data are presented as mean (SD).

$^c$ Data for patients that report any alcohol intake.
consumed, the number of days of consumption and the number of dropouts did not significantly differ in the two groups, and nor did the number of days of abstinence until first consumption. Considering the number of patients that maintained total abstinence throughout the 28 days, the result was more favorable in the naltrexone group, but the differences did not reach statistical significance ($\chi^2 = 2.823; P = 0.093$).

We found statistically significant differences in the number of days of heavy drinking ($t = 2.719; P = 0.007$), and also in the percentage of patients that were abstinent continuously in the final 28 days of the study (‘final abstinence’) ($\chi^2 = 4.715; P = 0.030$). These results suggest that the best measure of outcome when comparing the results in different subgroups would be the final abstinence variable.

**Predictor variables for continuous abstinence in the final 28 days of follow-up**

The following variables were entered into the analysis: treatment with naltrexone, craving, in- or out-patient detoxification, medical pathology associated with alcohol consumption, age at onset of drinking problems, age at onset of alcohol dependence syndrome, physical dependence, present age, family history of alcoholism, family psychiatric history, personal psychiatric history, other drug abuse/dependence, and severity of dependence. Four out of thirteen of these traits were associated with continuous abstinence in the final 28 days of follow-up: treatment with naltrexone, age at beginning of alcohol abuse (before age 25), family history of alcoholism and antecedents of abuse/dependence with other substances. We subsequently performed an analyses using the present age as a covariate, since age was associated independently with age at onset of abuse and presence of other substance use. Our analysis showed an association between naltrexone treatment and final abstinence in patients with one or more of the following traits: alcohol abuse before age 25 ($\chi^2 = 4.836; P = 0.028$), comorbid abuse of/dependence on other substances ($\chi^2 = 12.835; P < 0.001$), or presence of FHA+ ($\chi^2 = 5.714; P = 0.017$) (Table 3).

Table 4 presents the results of a logistic regression analysis to determine the effect of the naltrexone treatment in each group. This analysis confirmed the association between naltrexone and final abstinence among those with alcohol abuse onset before age 25 ($OR = 2.004; P = 0.014$), comorbidity substance use ($OR = 6.348; P < 0.001$) or presence of FHA+ ($OR = 2.084; P = 0.010$). Figure 1 shows the percentage of patients who presented with heavy drinking over the course of the study for each treatment group, by age of onset, family history and comorbid substance use, each analysis adjusted for the remaining two factors and current age.

**Association between naltrexone and outcome according to number of predictors**

The differences observed in the effects of predictors of outcome according to whether or not a patient receives NTX are shown in Table 5. Among the subjects not treated with NTX, the greater the number of predictor variables, the lower the abstinence rates (chi-square for linear trend: 17.169; $P = 0.0003$). This statistically significant association was not observed in the group treated with NTX (chi-square for linear trend: 0.039; $P = 0.844$); the number of patients maintaining abstinence in the final 28 days was similar in all the groups.
treated with NTX. Thus, the more the predictors of poor outcome in a subject, the greater the relative benefit attributable to the use of NTX. The difference between these two tendencies was statistically significant (chi-square for linear trend: 9.528; \( P = 0.002 \)).

**DISCUSSION**

Our data indicate that naltrexone is beneficial in the treatment of alcoholic patients, particularly those who meet the following characteristics: onset of alcohol abuse before age 25, family history of alcoholism and history of abuse of other substances. In other words, patients with these features show poorer outcome, which can be attenuated by NTX treatment.

The limitations of our study derive mainly from the fact that its method is not double-blind. The need to include a sample of patients similar to the subjects normally treated in our clinical settings (who tend to be more severe cases than those usually included in double-blind studies) made it advisable to maintain continuous control of the treatment by the therapists, which in turn made it difficult to carry out a double-blind study. The professionals treating these patients tend to have a greater experience with respect to the effectiveness of NTX, and this may have influenced the expectations of the patients they treated. In order to avoid the bias of these psychiatrists in the evaluation of effectiveness, “blind” interviewers were included, and attempts were made to control their “blindness” by various methods.

Our results coincide with studies finding that family antecedents of alcoholism are a marker of better response to treatment with NTX (King et al., 1997; Monterosso et al., 2001). The predictor variables for response to naltrexone found in this study are usually included among the traits of type 2 (Cloninger et al., 1988) and type B alcoholics (Babor et al., 1992; Volpicelli et al., 1995b). It has been hypothesized that such patients present dysfunctions of the dopaminergic and opioid systems (Gianoulakis et al., 1989, 1992; Blum et al., 1990; Noble, 2000). The consumption of alcohol may produce a greater release of endogenous opioids in the offsprings of alcoholics (Gianoulakis et al., 1989). It has been pointed out that some patients with phobic features may be particularly sensitive to experiencing craving in situations of anxiety, and that such craving could be related to opioid hyperstimulation induced by stress (Volpicelli et al., 1986, 1995b). In these patients, naltrexone may also help to prevent relapse. The blocking of opioid hyperactivation as a result of alcohol consumption would also block the dopaminergic hyperactivation responsible for the phenomena of reinforcement and priming (Di Chiara and Imperato, 1988; Koob and Bloom, 1988; Benjamin et al., 1993; Di Chiara et al., 1996). These data led us to hypothesize that the better response to NTX achieved in these individuals may be explained by their capacity for blocking the effects of alcohol on a dysfunctional opioid and/or dopaminergic system. A functional polymorphism of the mu-opioid receptor gene has recently been associated with NTX response in alcoholic patients (Oslin et al., 2003).

Our result may be helpful for understanding some inconsistencies found in published articles on the effectiveness of naltrexone (Gastpar et al., 2002). The under- or over-representation of patients with the characteristics found in our study may explain the global effectiveness results (Rubio et al., 2002). That is, in samples with low prevalence of comorbidity with other substance-use disorders (Gastpar et al., 2002) and low proportions of FHA+, the effectiveness of naltrexone will probably be quite similar to that of placebo. The negative result of Krystal et al. (2001) goes against our hypothesis in that the prevalence of FHA+ in our study was lower than in their study. However, other suggestions have been offered (Rubio et al., 2002) to explain the lack of naltrexone effectiveness in the study of Krystal et al.
CONCLUSIONS

Our findings indicate the need to distinguish between different types of alcoholism before choosing the pharmacological strategy in a given patient. It would be of great interest to complete these studies with the inclusion of biological (genetic, biochemical, physiological) markers, which might aid the correct identification of patients.

REFERENCES


