

Regular article

## Naltrexone improves outcome of a controlled drinking program

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### Abstract

Naltrexone is widely used in therapeutic programs with abstinence as a goal. However, it has been used in only a few studies aimed at reducing alcohol consumption. The purpose of this study was to evaluate the efficacy of naltrexone as an adjunct in controlled drinking programs. This was an open randomized study of 12 weeks duration that compared two therapeutic strategies: use of naltrexone in a controlled drinking program (NTX+CD) and the controlled drinking program alone (CD), without NTX. Each group comprised 30 male patients with mild alcohol dependence. During treatment, there were no differences between groups in drinking behavior, though the NTX+CD group showed significantly less craving. In the 12-month follow-up period, the NTX+CD group showed significantly fewer drinking days and heavy drinking days and less craving than the CD group. The results of this study suggest a role for naltrexone in controlled drinking programs. © 2002 Elsevier Science Inc. All rights reserved.

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### 1. Introduction

Controlled drinking programs are among the most controversial forms of treatment for alcohol dependence (Sobell et al., 1995). Some authors have defended their use in certain groups of subjects (Miller, Leckman, Delaney, & Tinkcom, 1992; Orford and Keddie, 1986; Sobell and Sobell, 1994), whereas others have questioned their validity and even the ethics of this type of therapy (Pendery, Maltzman, & West, 1982). In an extensive review on the efficacy of these kinds of programs it was suggested that they could be useful in young patients with mild to moderate dependence and a short dependence course (Miller and Caddy, 1977). This kind of patient is usually seen by the general practitioner and treated with brief interventions, although some are referred to a psychiatrist for longer-term therapies, such as controlled drinking programs (Rubio, Bardón, & Lertxundi, 2000). In recent years, naltrexone has been introduced in the treatment of alcohol dependence, and has proved more effective than

placebo in both short and long term studies (Chick et al., 2000; O'Malley et al., 1996; Rubio, Jiménez-Arriero, Ponce, & Palomo, 2001; Volpicelli et al., 1997). It has also been found to improve outcome of cognitive behavioral therapy (Anton et al., 1999). Naltrexone reduces the craving before drinking and also that elicited by alcohol consumption. It also reduces the number of drinking days and the number of drinks taken each time (O'Malley et al., 1996; Volpicelli et al., 1997). Considering the ability of naltrexone to reduce craving elicited by alcohol and the large number of patients with mild dependence seen in primary care, it is surprising how few studies have used this drug as a coadjuvant in programs aimed at reducing alcohol consumption in this population. To our knowledge, only two noncontrolled open studies have been published in which the efficacy of naltrexone has been demonstrated in reducing consumption in early problem drinkers (Bohn, Kranzler, Beazoglou, & Staehler, 1994; Kranzler, Tennen, Penta, & Bohn, 1997).

The purpose of this study was to determine the ability of naltrexone to improve the results of a controlled drinking program and to establish the duration of the effect after discontinuing the medication.

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## 2. Patients and methods

### 2.1. Design

This is a randomized control trial with a 3-month treatment period consisting of a controlled drinking program + naltrexone (NTX + CD) or controlled drinking alone (CD) and a 12-month follow-up period.

Inclusion criteria were as follows: (a) males aged between 18 and 65 years; (b) to fulfill Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria for alcohol-dependence (American Psychiatric Association, 1987); (c) a Severity of Alcohol Dependence Scale (SADS) score < 21, corresponding to a mild to moderate dependence not requiring detoxification (Rubio, Urosa, & Santo-Domingo, 1998). Exclusion criteria were: (a) to meet DSM-III-R criteria for dependence on any other substance (with the exception of nicotine); (b) presence of another psychiatric disorder diagnosed by the Structured Clinical Interview for DSM-III-R; (c) a medical condition that could hinder treatment compliance; (d) liver, neurological, or psychiatric diseases for which alcohol is contraindicated; (e) having previously been treated with naltrexone.

The study participants were alcohol-dependent males selected in various primary care centers. From a total of 214 patients referred, 140 were excluded because the use of this type of program was contraindicated (103 had moderate to severe alcohol dependence with liver disease, 31 presented comorbid psychiatric disorders and 6 had cardiologic or neurological conditions). From a total of 74 selected patients, 60 were finally included in the study. The remaining 14 patients were not available to attend the weekly sessions of the program. Five of the 14 dropped out during the evaluation period before being randomized.

Procedures followed were in accord with the standards of the Committee on Human Experimentation of 12 de Octubre Hospital.

### 2.2. Procedure and assessments

After signing the informed consent form, participants were assessed with the following instruments: (a) Structured Clinical Interview for DSM-III-R (Spitzer, Williams, Gibbon, & First, 1992); (b) Severity of Alcohol Dependence Scale (SADS; Rubio et al., 1998) – this is an instrument based on the Severity Alcohol Dependence questionnaire (Stockwell, Sitharthan, McGrath, & Lang, 1994); (c) Addiction Severity Index (ASI; McLellan, Luborsky, Woody, & O'Brien, 1980); (d) Three analog scales to measure craving (frequency, duration, intensity; Anton et al., 1999); and (e) A weekly calendar on which participants recorded all alcohol consumed (the Time-line Follow-back was used to obtain the sequence of consumption during the study; Miller, 1996). The following baseline biological parameters were also determined: gammaglutamyltranspeptidase (GGTP) and carbohydrate-deficient transferrin (CDT).

#### 2.2.1. Treatment period

After randomizing the patients (using a random number table), the CD+NTX group ( $n = 30$ ) received one 50-mg tablet of naltrexone per day, and both groups were included in the controlled drinking program.

The controlled drinking program consisted of individual weekly therapy sessions over a 3-month period. In the first month, subjects were requested to abstain completely from drinking and were allowed to drink again after the fourth week of treatment. During this first month we analyzed risk situations and how subjects coped with them. Those who could not remain abstinent during the first month or who subsequently drank more than the agreed maximum amount (more than 3 drinks per day or drinking more than 3 days a week) were given the opportunity to leave the program and begin therapy aimed at abstinence. Subjects could abandon the program at any time. During the first month 3 patients drank (2 from the NTX group), but none of them drank more than 3 drinks per day or drank on more than 3 days in a week, so that there were no drop-outs.

The controlled drinking program was based on those designed by Sánchez-Craig, Annis, Bornet, & MacDonald, (1984), and consisted of 12 individual therapy sessions with the following aims: (a) to try to reduce the number of drinks taken (to less than 9 drinks a week and no more than 3 drinks per day); (b) to record drinking behavior (type of drink, number of drinks, where they drank, with whom, with what consequences); (c) to change the drinking pattern and replace spirits by wine and beer, and to drink mainly at mealtimes; (d) to train participants in assertive behavior to refuse drinking opportunities; (e) to establish a reinforcement program aimed at achieving objectives; (f) to learn in which situations it is easier to control drinking; (g) to learn to cope with certain situations without drinking; (h) to learn how to avoid relapse (Rubio et al., 2000).

Assessment of therapeutic compliance was carried out weekly by counting the pills taken since the previous visit. On each visit, entries in the alcohol consumption diary were reviewed, and patients were asked whether they wanted to continue with the treatment. At the beginning and end of the treatment period CDT and GGTP levels were measured. In addition to these sessions, patients were offered the possibility of contacting the therapist in order to cope with potential risk situations. At the end of the controlled drinking program, treatment with naltrexone was terminated in the group that had been taking it. All of the psychiatrists participating in the study attended the same number of patients from each group (those taking and those not taking NTX).

#### 2.2.2. Follow-up period

At the end of the treatment period, patients were monitored on monthly visits for a period of 1 year. During these visits, they were praised for their achievements and the incidences of drinking since the previous visit were analyzed. Emphasis was placed on explaining aspects of the

program that remained unclear to the patient. Drinking days and the number of drinks taken since the last interview were recorded, and CDT and GGTP levels were measured every 3 months.

### 2.2.3. Blind researchers

Data related to patients' evaluations were collected (at the end-point of the treatment period and at 3, 6, 9 and 12 months of follow-up) by researchers who were blind to the drug taken by the patients. The following sources of data were used: (a) the patient himself, who was requested not to talk about whether he was receiving any pharmacological treatment; (b) the psychiatrist and/or psychotherapist appointed to the case, who were requested not to divulge the treatment prescribed to the patient. Any data required from the clinical records or clinical analyses were also provided by the psychiatrist.

In this way, it was hoped to reduce bias that may occur if the information was obtained only from the psychiatrist who had prescribed the treatment. Researchers never interviewed the same patient at the four time points, because at the end of an interview they could discover the type of treatment the patient was receiving, which would affect future interviews with the same patient. Information from the psychiatrist was complementary to that obtained from the patients, and mainly consisted of data from the clinical records and results of analyses. The main role of the psychotherapists in the study was to encourage patients' compliance with the program.

### 2.3. Outcome variables

The variables recorded in the 3-month treatment period and the follow-up were: number of drinking days; number of heavy drinking days (>3 drinks/day); total number of drinks; and total number of drinks taken on heavy drinking days.

During the treatment and follow-up period two outcome groups were established in relation to heavy drinking behavior: subjects with heavy drinking days and those without heavy drinking days. The good outcome group, therefore, comprised subjects who reported no heavy drinking days, whereas the poor outcome group comprised the remaining subjects.

### 2.4. Statistical analyses

Quantitative variables were compared using two techniques: a parametric technique consisting of a means test based on Student's *t*-test, and a non-parametric technique, the Mann-Whitney test. Qualitative variables were analyzed by chi-square and Fisher's test. To establish a possible association between the number of drinks taken and the severity of dependence, an ANCOVA was applied, using the SADS score as a covariant. The time elapsed until the first heavy drinking day was analyzed using the Kaplan-Meier

survival table. Levels of the biological drinking markers, carbohydrate-deficient transferrin and gamma-glutamyl-transferase, were evaluated by both repeated-measures and end-point ANCOVA, with baseline levels as covariants.

## 3. Results

The sample was made up of 60 males with a mean age of 30 years ( $30.0 \pm 3.4$ ) and mild alcohol dependence (SADS:  $15.9 \pm 4.8$ ). They did not drink daily, but their average intake when they did drink was 12 units ( $12.2 \pm 2.8$ ). 35% had a family history of alcoholism and 77% had previously tried to stop drinking. A total of 23% met criteria of other drug abuse, apart from nicotine. The ASI alcohol composite scores were  $0.53 \pm 0.13$  and the analog craving scale scores were  $52 \pm 14$ . GGTP levels were  $51 \pm 21$  (normal values < 50 IU) and CDT levels were  $19 \pm 12$  (normal values  $\leq 17$ ). No significant differences were found for these variables across the groups. In the NTX+CD group the patient's self-report of therapeutic compliance coincided in 93.3% of cases with the weekly pill count.

Table 1  
Drinking variables during treatment and follow-up in relation to type of treatment

Variable	NTX-CD GROUP ( <i>n</i> = 30)	CD-GROUP ( <i>n</i> = 30)	
Treatment period (Last 2 months)			
Total number of drinking days during treatment	15.7 ± 5.8	18.3 ± 3.6	<i>ns</i>
Total number of drinks during treatment	25.3 ± 13.0	39.8 ± 13.5	<i>ns</i>
Number of heavy drinking patients during treatment <sup>a</sup>	4 (13%)	3 (10%)	<i>ns</i>
Months elapsed before first heavy drinking day.	2.7 ± 0.8	1.0 ± 0.7	<i>F</i> = 2,19; <i>df</i> = 1, <i>p</i> = .144*
Score in craving scale.	10 ± 8.0	16 ± 10	<i>F</i> = 2,1; <i>df</i> = 29,29, <i>p</i> = .03
Days of naltrexone treatment.	85 ± 10	–	
Follow-up period (12 months)			
Total number of heavy (+3) drinking days during follow-up	69.0 ± 20.8	103.9 ± 11.8	<i>F</i> = 3,5; <i>df</i> = 29,29; <i>p</i> = .0005
Total number of drinks during follow-up	97.5 ± 50.1	214.3 ± 71.5	<i>F</i> = 2,0; <i>df</i> = 29,29; <i>p</i> = .03
Number of patients with heavy drinking during follow-up	11 (37%)	12 (40%)	<i>ns</i>
Craving scale score	16 ± 10	22 ± 10	<i>F</i> = 3,2; <i>df</i> = 29,29, <i>p</i> = .02

<sup>a</sup>  $\geq 3$  or more drinks per day (1 drink = 1 Unit = 8 gr ethanol).

\* Kaplan-Meier survival curve.

### 3.1. Results of the 2-month treatment period

Results in Table 1 show that during the last 2 months of the treatment period, when subjects were allowed to drink, NTX+CD group drank for fewer days and took a smaller number of drinks than the CD group. However, these differences were not significant, nor were there significant differences between the mean values of CDT ( $F = 1.53$ ,  $df = 29.29$ ,  $p = 0.13$ ) and GGTP ( $F = 1.02$ ,  $df = 29.29$ ,  $p = 0.34$ ) at the start and at the end of the treatment period. Four patients from the NTX+CD group and three from the CD group reported at least 1 day of heavy drinking. Survival analysis was performed on the time elapsed to the first heavy drinking day following the first month of the treatment period. This occurred at 2.7 months in the NTX+CD group and at 1.0 months in the CD group (Table 1). During the month of abstinence and the 2 months of controlled drinking the NTX+CD group had significantly lower craving scores than the other group. A total of 87% of the NTX+CD group and 90% of the CD group finished the treatment period without reporting any heavy drinking days.

### 3.2. Results of the follow-up period

During follow-up, the group treated with NTX+CD reported a mean of 69 drinking days/year and around 97 drinks/year, significantly lower values than those recorded for the CD group (Table 1). Craving scores were also significantly lower. In the NTX+CD group, 37% of subjects reported heavy drinking days, as compared to 40% of the other group. There were no significant differences

between the CDT and GGTP levels of the two groups at 3, 6, 9 and 12 months ( $F = 1.72$ ,  $df = 1.57$ ,  $p = 0.45$ ).

Subjects reporting heavy drinking days during the study were compared using the same set of variables (Table 2). Subjects in the NTX+CD group drank on significantly fewer days than subjects from the CD group. Although the number of heavy drinking days was not significantly different between the groups, the NTX subjects never had more than 6 drinks on a heavy drinking day, whereas the CD group had an average of 9 drinks/day. None of the patients received abstinence-oriented treatment in the 12-month follow-up.

## 4. Discussion

The results of the present study show that, during a 2-month controlled drinking program, naltrexone added to the program significantly reduced craving but failed to alter other drinking variables, beyond the controlled drinking program alone. However, at the one-year follow-up the number of drinking days and the number of drinks were lower in the naltrexone group than in the standard treatment group. At the one-year follow-up, 63% of the NTX+CD group and 60% of the CD group reported no heavy drinking days.

The efficacy of other controlled drinking programs at one-year follow-up has been found to range from 21% to 68% (Vogler et al., 1977); more recent studies have shown similar success rates (Miller, Benefield and Tonigan, 1993). In trials with a longer follow-up period (3.5–8 years), up to 40% of subjects on this type of program were abstinent or reported asymptomatic drinking at the end of the study (Miller et al., 1992). In our study, more frequent visits during follow-up could explain why the results are in the top of the range. Although many factors have been associated with the outcome of these programs, severity of dependence appears to be one of the most consistent in the long term (Miller et al., 1992).

In spite of some methodological problems with studies not aimed at abstinence that used NTX as a coadjuvant treatment, they have shown some success. Kranzler et al. (1997) carried out an open, noncontrolled 4-week study in which patients could use NTX as part of a brief skills training program. The reduction in number of drinking days, drinks taken each time and days of heavy drinking was maintained for 3 months post-treatment, and reduced values for these variables were correlated with patients' use of NTX. Bohn et al. (1994) used NTX for 6 weeks in patients included in a brief counseling program and found similar results. The problem with these studies is that they both lacked a control group, which makes it difficult to gauge the relevance of NTX in therapeutic success.

This lack of significant differences in consumption during the treatment period is in contrast to the results reported by other authors (Anton et al., 1999; Chick et al., 2000;

Table 2  
Differences between the drinking variables of patients with heavy drinking days in the two treatment groups

Variable	NTX-CD GROUP (n = 11)	CD-GROUP (n = 12)	
Total number of drinking days during follow-up	83.8 ± 23.8	111.5 ± 7.2	$F = 10.82$ ; $df = 10.11$ ; $p = .0002$ ; Mann-Whitney $p = .0007$
Total number of heavy drinking days during follow-up	5.0 ± 3.8	8.0 ± 5.5	$F = 2.0$ ; $df = 11.10$ ; $p = .13$ ; Mann-Whitney $p = .16$
Total number of drinks during follow-up	144.6 ± 55.9	281.1 ± 60.3	$F = 1.16$ ; $df = 11.10$ ; $p = 0.40$ ; Mann-Whitney $p = .00017$
Total number of drinks taken on heavy drinking days	24.6 ± 21.3	76.9 ± 51.0	$F = 5.75$ ; $df = 11.10$ ; $p = .0002$ ; Mann-Whitney $p = .05$

O'Malley et al., 1996; Rubio et al., 2001; Volpicelli et al., 1997), though it should be noted that in these reports treatment was used to support abstinence. The results of our study may be explained by the conditions included in the controlled drinking program: first month of abstinence and two months of drinking less than 3 days a week and less than 3 drinks per day.

The duration of the effect once treatment with naltrexone is suspended has been described by others. O'Malley et al. (1996) followed up for a 6-month period a group of patients that terminated treatment with naltrexone or placebo. Naltrexone-treated subjects were significantly less likely to drink heavily than subjects who had received placebo for up to 4 months following NTX cessation.

The maintenance of reduced alcohol consumption once treatment with naltrexone is terminated may be due, at least in part, to the drug's ability to facilitate control of drinking. It may be that, with NTX, patients learn to drink with less craving and lower resistance, and that this learning is maintained for at least a year.

Two different hypotheses could be proposed to explain these findings: (a) the ability of NTX to block the reinforcing effects of alcohol; or (b) its capacity to increase resistance to craving. With regard to the first hypothesis, NTX is known to block opioid receptors and to reduce the reinforcing effects of alcohol (Davidson, Palfai, Bird, & Swift, 1999; Rohsenow et al., 2000); it also reduces the craving experienced before drinking and that elicited by alcohol consumption (O'Malley et al., 1996; Rubio et al., 2001; Sinclair, 2001). In our study, this hypothesis was supported by the significant reduction in the number of drinks taken by all patients treated with NTX, regardless of whether or not they presented heavy drinking days, and by the reduced craving scores during treatment and the follow-up period. Because patients taking NTX do not experience as much pleasure from drinking and are not so likely to lose control, their feelings of self-control may be increased and the conditioning effect of the alcohol weakened. This extinction process has been extensively investigated by Sinclair, though it may possibly apply not only to alcohol (De Wit, Svenson and York, 1999). Using a conditioned place preference paradigm in mice, Bormann and Cunningham (1997) demonstrated that opioid antagonists can facilitate the extinction of conditioned reinforcing effects of alcohol in the absence of alcohol intake. In summary, increased self-efficacy and the extinction of the alcohol's reinforcing effects would explain the more marked reduction in consumption observed in the group treated with naltrexone.

Other authors suggest that NTX improves the subject's ability to resist drinking thoughts or the desire to continue drinking (Anton et al., 1999). In our study we did not assess the capacity to resist craving, but rather the intensity of this craving. Nevertheless, when a patient refers to a highly intense craving it is difficult to know whether he is describing the intensity of the craving or his difficulty in

resisting it. In any case, even if this were the mechanism of NTX, the consequences would be similar, because it would improve expectations of self-efficacy and facilitate control of alcohol consumption.

We believe that our group of young males without psychiatric comorbidity or other drug dependence may be the group of alcohol-dependent patients most likely to benefit from a controlled drinking program with naltrexone. This kind of patient presents few years' history of alcohol dependence and does not drink every day, but when s/he does, s/he loses control. These patients have been described as early problem drinkers, presenting as a main feature the loss of control. These results strongly support the need for further controlled studies using placebo in order to determine the effectiveness of naltrexone as coadjuvant of controlled drinking programs.

Because this was an open study, it is possible that the psychiatrists who treated these patients showed more empathy towards patients taking naltrexone. In fact, some authors have associated the efficacy of these techniques with the style of the therapist (Miller et al., 1993). It is also possible that part of the beneficial effect could be explained by an expectation effect. Patients taking the medication had been told about its action mechanism and its results in previous studies on relapse prevention. This information could influence the results independently of the actual pharmacological effect of NTX. This limitation could have been removed by using a double-blind study design with placebo. It is possible that this type of combined treatment (NTX + CD) does not work for patients with stronger dependence or for those that do not lose control. Moreover, further research is needed to demonstrate the efficacy of this type of treatment in women.

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