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NALTREXONE VERSUS ACAMPROSATE: ONE YEAR FOLLOW-UP OF ALCOHOL DEPENDENCE TREATMENT

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Abstract — Naltrexone and acamprosate reduce relapse in alcohol dependence. They have not yet been compared in a published trial. The aim of this study was to compare the efficacy of these compounds in conditions similar to those in routine clinical practice. Random allocation to a year of treatment with naltrexone (50 mg/day) or acamprosate (1665–1998 mg/day) was made in 157 recently detoxified alcohol-dependent men with moderate dependence (evaluated using the Addictions Severity Index and Severity of Alcohol Dependence Scale). All were patients whom a member of the family would accompany regularly to appointments. Alcohol consumption, craving and adverse events were recorded weekly for the first 3 months, and then bi-weekly, by the treating psychiatrist who was not blinded. At 3-monthly intervals, investigators who were blinded to the treatment documented patients' alcohol consumption based on patients' accounts, information given by the psychiatrists when necessary, and reports from patients' families. Serum gamma-glutamyltransferase (GGT) was also measured. Efforts were made to sustain the blindness of the investigators. The same investigator did not assess the same patient twice. The integrity of the blindness was not checked. There was no difference between treatments in mean time to first drink (naltrexone 44 days, acamprosate 39 days) but the time to first relapse (five or more drinks in a day) was 63 days (naltrexone) versus 42 days (acamprosate) ($P = 0.02$). At the end of 1 year, 41% receiving naltrexone and 17% receiving acamprosate had not relapsed ($P = 0.0009$). The cumulative number of days of abstinence was significantly greater, and the number of drinks consumed at one time and severity of craving were significantly less, in the naltrexone group compared to the acamprosate group, as was the percentage of heavy drinking days ($P = 0.038$). More patients in the acamprosate than the naltrexone group were commenced on disulfiram during the study. Naltrexone patients attended significantly more group therapy sessions, though this could not explain their better outcome. There were non-significant trends for the naltrexone group to comply better with medication, to stay in the study longer, and to show greater improvement over baseline in serum GGT.

INTRODUCTION

Alcoholism is an important and difficult problem from several public health perspectives. For a long time, pharmacological treatments have been limited mainly to the detoxification period exclusively, and to the use of aversive drugs over the rehabilitation period (incorporating the time and process during which 'normal' levels of intake are attained and maintained). In the last decade, naltrexone and acamprosate have been proposed for use in the treatment of alcohol dependence.

Naltrexone is an opioid receptor antagonist, with a verified efficacy for the reduction of euphoria, alcohol intake and relapse risk by alcohol-dependent or -misusing individuals (Volpicelli *et al.*, 1992, 1995*a*,*b*, 1997; O'Malley *et al.*, 1992; Anton *et al.*, 1999; Chick *et al.*, 2000*b*). These actions seem to be mediated by the property to block opiate receptors (Ulm *et al.*, 1995), not least in forebrain areas. This antagonism appears to inhibit the actions of endogenous opioids, released because of alcohol intake, upon the mesolimbic pathway, which would otherwise produce a rise in dopamine (DA) in the accumbens nuclei (Benjamin *et al.*, 1993; Valenzuela and Harris, 1997; Catafau *et al.*, 1999). Naltrexone efficacy has been demonstrated in short-term double-blind studies (6–12 weeks) (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992, 1995*a*, 1997; Anton *et al.*, 1999; Chick *et al.*, 2000*b*). However, from the available evidence, naltrexone efficacy has not yet been verified in long-term studies.

Long-term efficacy studies (6–12 months) have been carried out, however, on acamprosate, calcium acetyl homotaurinate, a drug marketed in Europe. This has been shown to increase the time to relapse, to reduce the number of days of consumption and to augment the abstinence period (Pelc *et al.*, 1992; Ladewig *et al.*, 1993; Paille *et al.*, 1995; Sass *et al.*, 1996; Geerlings *et al.*, 1997; Poldrugo, 1997; Besson *et al.*, 1998; Tempesta *et al.*, 2000). However, not all the studies confirm its efficacy compared to placebo (Chick *et al.*, 2000*a*). This compound modulates the GABA-ergic transmission and decreases postsynaptic potentials in the neocortex, possibly via its action on NMDA (*N*-methyl-D-aspartate) receptors. Hypotheses have been drawn up concerning its actions on calcium channels as well as on the NMDA receptors reducing conditioned alcohol-withdrawal craving (Littleton, 1995).

The aim of this study was to demonstrate the efficacy and treatment compliance of naltrexone compared to acamprosate in typical treatment conditions for these patients. An open randomized trial has been chosen for two reasons: (1) this is the experimental situation most similar to daily clinical practice; (2) if a double-blind trial had been carried out, both drugs would have to be administered in three doses per day (because of the pharmacokinetics of acamprosate and manufacturer's recommendations). However, taking into account the resistance to treatment compliance in these patients, especially in the medium and long-term, a double-blind trial in which the medication was administered three times a day would place naltrexone at a disadvantage since this drug is usually given in a single daily dose.

PATIENTS AND METHODS

Design

This was a randomized 12-month single-blind trial of naltrexone versus acamprosate. The treatment conditions were as similar as possible to daily clinical practice.

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The participants were alcohol-dependent males who had requested detoxification in the Addictive Behaviour Unit of 'Doce de Octubre Hospital'. Inclusion criteria were as follows: (1) male gender aged between 18 and 65 years; (2) meeting DSM-III-R criteria for alcohol-dependence (American Psychiatric Association, 1987); (3) having a stable family environment so that the family can help with treatment compliance and provide information during follow-up visits. Exclusion criteria were: (1) presence of another substance use disorder (with the exception of nicotine); (2) presence of another psychiatric disorder diagnosed by SCID for DSM-III-R (SCID); (3) a medical condition which could hinder treatment compliance; (4) impaired liver function [an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value more than three times normal values]; (5) previous treatment with naltrexone or acamprosate.

After completing detoxification, in the hospital or as an outpatient, the subjects were informed about the study objectives. They were informed about the two pharmacological treatments, naltrexone or acamprosate, elective treatments at the time of the study for the treatment of alcohol-dependence, but were told that the drug they would receive would be chosen at random. They would know which drug they would receive. They were told that relapse, or not taking the prescribed treatment punctually, would not lead to their being asked to leave the trial. However, they would be taken out of the trial if they did not keep in touch with the investigators for more than 15 days (i.e. two consecutive visits). They were also told that they could choose to leave the study at any time.

Procedure and assessments

After signing the informed consent, participants were assessed with the following instruments: a structured clinical interview for DSM-III-R (SCID) (Spitzer *et al.*, 1992); the Addiction Severity Index (ASI) (McLellan *et al.*, 1980), Severity of Alcohol Dependence Scale (SADS) (Rubio *et al.*, 1998); three analogue scales to measure craving (frequency, duration and intensity) (Anton *et al.*, 1999); and a weekly calendar in which participants recorded all alcohol consumed, so that the 'time-line follow-back' method could be used to document the pattern of consumption during follow-up (Miller, 1996). The following baseline biological parameters were determined: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), bilirubin, and carbohydrate-deficient transferrin (CDT).

After randomizing the patients (using a random numbers table), patients received either one tablet (50 mg) per day of naltrexone, or six tablets (or five if of lower body weight) of acamprosate (i.e. 1665–1998 mg/day) divided into three doses following the manufacturer's recommendation. Patients visited their psychiatrists every 7 days (± 3 days) over the first 3 months, after which they visited every 15 days, till the end of the study. In the event of relapse, the 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 were checked, together with craving, and whether the patient continued the treatment. Consumption and compliance data were compared with information given by the family.

Both groups of patients were offered supportive group therapy, once weekly over the entire study period. The groups were 'open' groups. Therapy was less structured than in classical relapse prevention programmes. Basic relapse prevention was tackled (dealing with situations of risk, craving and negative emotional states). Abstinence was positively reinforced. Patients also received symptom-directed pharmacological treatment for complaints, such as anxiety, depression, insomnia, etc., when these symptoms presented during follow-up. If anxiety or depression emerged, sertraline could be prescribed (100–200 mg/day), and for insomnia patients were given hydroxyzine, an H_1 receptor antagonist of the piperazine family used as a hypnotic (50–100 mg/night). In cases of relapses which were difficult to control pharmacologically or psychotherapeutically, disulfiram was added to the treatment until the relapse was fully over (2–3 weeks).

The 'blind' investigators

Study data on outcome were collected by investigators (at 3, 6 and 12 months) who were blind to the drug taken by the patients. They used the following sources of data: (1) the patient himself, who was asked not to talk about the type of medication he was receiving; (2) the psychiatrist appointed to the case, who provided any data required about the clinical records, including biochemical results, and who was requested not to divulge the treatment prescribed; (3) the patient's family who provided information about drinking and any attempts by the patient to cease the pharmacological treatment. The degree of concordance between data from the family and the psychiatrists increased from 80% in the first few months to 95% in the final 3 months.

It was hoped that asking the family would help reduce the bias, which could occur if the information were obtained only from the psychiatrist who had prescribed the treatment. The investigators never interviewed the same patient at the three time points, since, at the end of an interview, they could have knowledge of the type of treatment the patient was receiving, which could affect future interviews with the same patient. Patients and relatives were asked not to tell the investigator the name of the treatment they were taking, its appearance, or how often per day they were taking it. Information from the psychiatrist was to complement that obtained from patients and their families and consisted mainly of data from clinical records and results of analyses. The main role of the psychiatrists in the study was to encourage patients to take the medication and to attend psychotherapy sessions.

Outcome measures

The primary outcome variables were: days of accumulated abstinence and days to first relapse (relapse is defined as the consumption of more than five drinks or 40 g ethanol per day). Additional outcome variables were number of drinks consumed per week, number of drinks consumed at a time, craving, abandonment of pharmacological treatment, drop-out from the study and 3-monthly serum GGT.

Statistical analysis

Pairwise χ^2- and *t*-tests were used to analyse differences between the two therapeutic groups, naltrexone versus acamprosate. All outcome analyses were conducted under an intention-to-treat analysis plan, with drop-outs regarded as relapsed for the abstinence and relapse analyses. Time to relapse and time to first drink were analysed by Kaplan–Meier

survival analysis. The difference in variables, such as number of drinks consumed per day, drinks consumed at one time or percentage of days abstinent, were analysed by analysis of covariance (ANCOVA), taking baseline levels as covariants, and for drop-outs using the last observation carried forward. The biological drinking markers, CDT and GGT levels, were evaluated by both repeated measures and end-point ANCOVA with baseline levels as covariants. A composite craving severity score was created, as the average of the three scale scores (intensity, duration and frequency). Group differences were analysed by repeated measures ANCOVA with baseline values on the respective scales used as covariants.

RESULTS

Recruitment and retention

The total number of patients from the different health centres considered for inclusion in the study was 356, of whom 197 were examined at the start of the study (Fig. 1). Of these, some were not selected: 30% refused to participate; in 30% the family could not commit themselves to accompany the patient to the Centre throughout the follow-up period; 27% had been treated previously with naltrexone or acamprosate; 25% presented comorbidity of another disorder; and in 15% naltrexone was contra-indicated because of impaired liver function. Of 160 subjects selected, three then refused to participate, so 157 were submitted to the pre-treatment analysis.

Randomization gave 77 (naltrexone) and 80 (acamprosate). Sociodemographic variables respectively were: age (mean ± SD = 43 ± 10; and mean = 44 ± 12 years), married (95 and 92%), employed full time (75 and 75%), secondary education (84 and 85%). There was no significant difference between the groups in any of these variables. There was no significant difference between the variables when related to severity of dependence; in both groups the severity of dependence measured with both the ASI and the SADS was moderate (Table 1).

The average period between the last drink and the start of treatment was 16 days (range 10–22).

A total of 26 patients dropped out during the study (eight naltrexone, 18 acamprosate). In the naltrexone group, two patients dropped out in the 1st month, four in the 3rd month and two in the 4th month. In the acamprosate group, two dropped out in the 1st month, five in the 2nd, five in the 3rd, four in the 4th, one in the 7th and one in the 8th month. The reasons for drop-out are shown Fig. 1.

Efficacy

At the end of the treatment year the number of abstinent patients in the naltrexone group was twice that in the acamprosate group and the accumulated abstinence was significantly greater in the former (Table 2). The survival until the first relapse was longer for naltrexone than acamprosate patients ($P = 0.02$) (Fig. 2). At the end of the study, 41% of the naltrexone group had not relapsed and 54% were abstinent since the last assessment (6 months), compared to 17 and 27%, respectively, in the group treated with acamprosate. Table 2 shows further alcohol consumption data, including the drinks consumed in a session, which was less for patients receiving naltrexone than those receiving acamprosate. In the group treated with naltrexone fewer patients used disulfiram. If a patient drank some alcohol, relapse occurred on average 12 days later in the naltrexone group (SD = 16) whereas it occurred in the group treated with acamprosate after 6 days (SD = 8).

A survival curve of time to first alcohol consumption revealed no significant differences between the two groups (the mean number of days to the first consumption was 44 for the naltrexone group and 39 for the acamprosate group; $P = 0.34$).

Regarding the composite score, severity of craving, patients receiving naltrexone had significantly lower scores over the entire study period.

Treatment compliance

In the naltrexone group there was a trend towards fewer drop-outs, fewer attempts to abandon pharmacological treatment, more weeks of completed treatment, and greater attendance at psychotherapy support sessions. The latter reached statistical significance. We considered the hypothesis that the number of days of abstinence could be related to attendance at therapy sessions, rather than to the use of naltrexone or acamprosate. To test this, we compared the mean number of days of abstinence at 3, 6 and 12 months follow-up, taking the number of psychotherapy sessions as the covariant (ANCOVA). The results showed that, in the naltrexone group the mean number of days of abstinence remained constant after the 3rd month, whereas in the acamprosate group the mean number of days of abstinence decreased over the follow-up period ($F = 8.23$, df = 2, 248, $P > 0.05$).

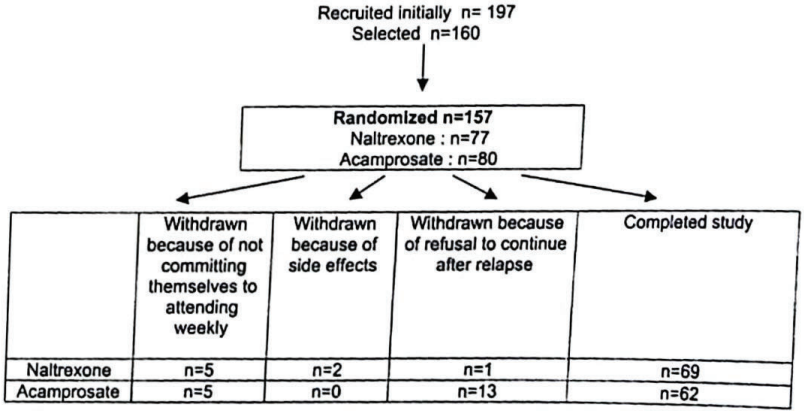


Fig. 1. Retention in the study.

Table 1. Severity of alcoholism, recent consumption pattern and biological markers of drinking at study entry

Parameter	Naltrexone group (n = 77) Mean	SD	Acamprosate group (n = 80) Mean	SD
Severity of Alcohol Dependence Scale	29	5	28	6
Addiction Severity Index	0.70	0.14	0.71	0.12
Composite craving severity score	52	19	51	22
Percentage of days drinking in past 6 months	87	20	87	21
No. of drinks per drinking day	12.3	5.0	12.2	5.1
Gamma-glutamyltransferase (IU/l)	110	98	125	101
Aspartate aminotransferase (IU/l)	81	21	84	19
Alanine aminotransferase (IU/l)	64	30	67	31
Carbohydrate-deficient transferrin (U/l)	25	17	26	20
Days between last drink and start of study medication	15	3	16	5

No significant group differences were detected ($P > 0.05$). All comparisons were t-tests with df = 155.

Sertraline was prescribed for two patients in whom a depressive episode emerged, and hydroxyzine was prescribed to 16 patients because of inability to fall asleep. The distribution between treatment groups was even, although this was not the case with prescriptions for disulfiram, which was prescribed to significantly more patients in the acamprosate group than the naltrexone group (Table 2).

The GGT determinations done at 3, 6 and 12 months were compared with baseline levels and ANCOVA showed significant temporal improvements in the whole sample ($F = 52.3$, df = 2, $P < 0.0001$). Table 3 shows the number of days of heavy drinking and the mean values of GGT. There was a non-significant trend for greater improvement in GGT in the naltrexone patients but a significant reduction in percentage of days of heavy drinking.

Side-effects were more common in the group receiving naltrexone, the most important of which were: nausea (25 vs 4%, $\chi^2 = 14.1$, $P = 0.0001$), abdominal pain (23% vs 4%, $\chi^2 = 12.9$, $P = 0.0003$), drowsiness (35 vs 2%, $\chi^2 = 27.4$, $P = 0.0000$), nasal congestion (23 vs 1%, $\chi^2 = 12$, $P = 0.0004$), headache (13 vs 6%, $\chi^2 = 2.0$, $P = 0.15$), diarrhoea (1 vs 4%, Fisher test $P = 0.3$) and epigastric discomfort (4 vs 4%, Fisher test $P = 0.64$). These side-effects gradually disappeared after the first 2 weeks of the study.

DISCUSSION

Naltrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at any one time and reducing craving, compared to acamprosate. There was a trend for naltrexone to be associated with a greater retention in the treatment programme.

It is difficult to compare our results with those of other studies, since ours is the first published comparative study of these two

Table 2. Outcome after 1 year

Parameter	Naltrexone group (n = 77) n	%	Acamprosate group (n = 80) n	%	Analysis χ^2 (df = 1)
Subjects who completed study	69	90	62	78	4.14, $P = 0.14$
% subjects abstinent since last assessment (6 months)	41	54	22	27	14.5, $P = 0.0002$
No. of subjects prescribed disulfiram	17	22	42	52	15.3, $P = 0.0002$
No. of subjects who received sertraline to treat depression	1	1	1	1	0.0, $P = 0.9$ (Fisher test, $P = 0.74$)
No. of subjects receiving hydroxyzine to treat insomnia	7	9	9	11	0.20, $P = 0.6$
Patients who tried to abandon pharmacological treatment[a]	28	36	37	46	1.57, $P = 0.21$
Subjects who relapsed during the study	32	41	14	17	10.89, $P = 0.0009$
	Mean	SD	Mean	SD	t (df = 155)
No. of weeks of study completed	44	6	35	6	1.92, df = 1, 154, $P = 0.53$
No. of therapy sessions attended	43	5	32	8	6.8, df = 1, 154, $P = 0.01$
	Mean	SD	Mean	SD	F, df, P
Days to first alcohol consumption	44	36	39	28	2.19, df = 1 $P = 0.34$[b]
Days to first relapse (≥5 drinks per day)	63	38	42	32	6.96, df = 1, $P = 0.02$[b]
No. of drinks consumed at one time	4	6	9	7	7.01, df = 1, 141, $P = 0.01$
No. of days abstinence (accumulated abstinence)	243	115	180	129	5.76, df = 1, 140, $P = 0.03$
Composite craving severity score	11.3	10.1	15.3	12.1	6.2, df = 1, 139, $P = 0.01$

[a]This information was provided by the family member accompanying the patient.
[b]Kaplan–Meier survival (log-rank) statistic.

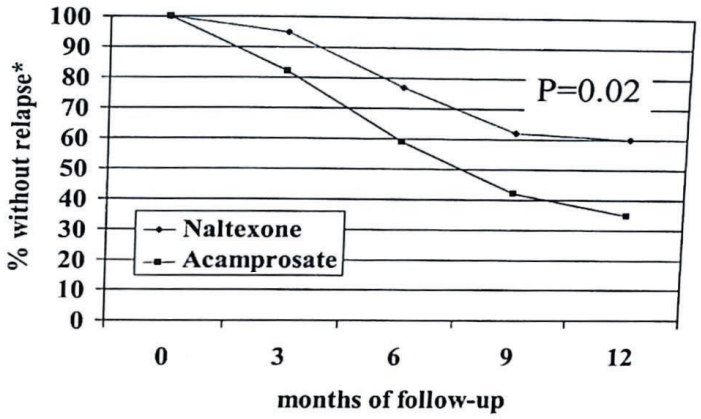


Fig. 2. Survival analysis to first relapse.
◇, naltrexone; ■, acamprosate. *Five or more drinks per day.

drugs. With regards to other research on naltrexone, in previous studies abstinence rates after 6 weeks were 23–62% (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992, 1997; Anton *et al.*, 1999; Chick *et al.*, 2000*b*). The results of our study, which was four times longer than the aforementioned ones, are within this range. The levels of abstinence with acamprosate in placebo-controlled trials with a 1-year follow-up are between 18 and 35% (Paille *et al.*, 1995; Sass *et al.*, 1996; Whitworth *et al.*, 1996; Besson *et al.*, 1998). In our study, we recorded a rate of 17%. If we extrapolate these results, it seems that long-term treatment of patients with naltrexone is more beneficial than with acamprosate.

Two hypotheses could explain the benefits of naltrexone seen in our study. First, it may be that naltrexone increases the period elapsed before the subject takes the first drink. Prolonging the abstinence period enables the learning of strategies taught in the support therapy and increases feelings of self-efficacy. Second, it may be that naltrexone has an effect on control of alcohol consumption once this has already begun, resulting in a delay in relapse. This could also increase the patients' faith in the treatment.

The first of these hypotheses was not confirmed, because the survival time to the first drink did not differentiate between treatments. In contrast, the action of naltrexone on control of alcohol consumption is shown in the survival curve to first relapse and in the number of drinks consumed at any one time. This effect has been described in other studies and has been explained by a reduction in the reinforcing effects of ethanol after drinking (O'Malley *et al.*, 1996*a,b*), or by an improvement in the ability to resist thoughts or cravings to continue drinking (Anton *et al.*, 1999). Whichever explanation, the higher degree of control over their drinking achieved by patients treated with naltrexone could explain their lesser use of disulfiram and their achieving more days of abstinence and a greater use of therapy. In our opinion, this effect could be explained as follows: the craving triggered by consumption is slightly less with naltrexone than with acamprosate, which enables those treated with naltrexone to stop drinking earlier. Since relapses are very common in these patients, those treated with naltrexone would be more capable of interrupting the relapse or diminishing its intensity. This would help to prevent progression in alcohol consumption and increase the probability that the patient seeks help from a therapist and, therefore, ultimately, curtail relapse. This is supported by the fewer absences from therapy in the naltrexone-treated group. Since naltrexone reduces the intensity of relapse, patients attend more therapy sessions. Although this latter effect has not been found by other authors (Anton *et al.*, 1999), this could be due to the shorter duration of their studies. Finally, the increased number of attempts to abandon treatment with acamprosate may relate to the number of doses required daily, and this could contribute to the smaller percentage of days of abstinence achieved by these patients.

Anticraving effects of naltrexone were more important than those of acamprosate, although this difference could be due to their different mechanisms of action and the fact that most patients drank alcohol during the study period. Given that acamprosate probably exerts its anticraving action by reducing the intensity of the symptoms of the conditioned withdrawal syndrome and naltrexone probably reduces the reinforcing effects of the alcohol, this difference would favour the use of naltrexone in patients who are likely to consume some alcohol. This would explain why the patients treated with naltrexone reported less craving than the acamprosate group over the study period (Rubio *et al.*, 1999). It is also possible that naltrexone would be more effective at reducing craving in patients with moderate dependence, in whom craving mechanisms related to positive reinforcement could be over-represented. Since our sample was of patients with moderate dependence, this could explain the results obtained.

With regards to the tolerability of both drugs, although the group treated with naltrexone experienced more side-effects, these only lasted for the first 2 weeks of the study and there was no significant difference in the rate of drop-out due to this.

Limitations of this study

This was an open study, and there is the possibility that the investigators did not remain blinded. We tried to prevent the investigators from gaining direct information about the type of

Table 3. Percentage of days of heavy drinking and serum gamma-glutamyltransferase (GGT) from baseline to 1 year

	Baseline period (90 days)		1–3 months follow-up (90 days)		4–6 months follow-up (90 days)		6–12 months follow-up (180 days)	
Group	% of days heavy drinking	GGT $n = 157$	% of days heavy drinking	GGT $n = 139$	% of days heavy drinking	GGT $n = 133$	% of days heavy drinking	GGT $n = 131$
Naltrexone	96	110 ± 98	23	76 ± 42	44	85 ± 46	33	87 ± 62
Acamprosate	96	125 ± 101	48	90 ± 75	52	99 ± 72	53	107 ± 90

% of days heavy drinking differed between the groups ($F = 5.04$; df = 1, 140; $P = 0.038$).
GGT (mean ± SD): not significant.

pharmacological treatment taken by the patients, although it is possible that they could have guessed the treatment from the patients' side-effects. However, this can also occur in double-blind trials, except in studies with total integrity of the double-blindedness (Moncrieff and Drummond, 1997). Objective outcome criteria are not subject to bias: in our study, GGT (which is a helpful, but not perfect, marker of drinking) appeared to corroborate a better reported outcome in the naltrexone group, but the advantage failed to reach statistical significance.

Some of the advantages of naltrexone seen in this study could be explained by the fact that the participants were patients with moderate alcohol dependence. Impaired liver function as an exclusion criterion will have ruled out some of the most severe cases. Possibly, the latter would have responded better to acamprosate than to naltrexone.

At the start of the study, the psychiatrists did not know which pharmacological treatment would be most effective and, therefore, had a similar attitude towards encouraging compliance with both treatments. However, as the study progressed and subjects treated with naltrexone appeared to have a better outcome, the psychiatrist may have made more effort to encourage compliance with naltrexone treatment, which could, at least hypothetically, have then introduced a bias.

Our assessment of the degree of compliance to the pharmacological treatment was conducted by questionnaires corroborated by information from the family. It would have been more accurate to use a urinary marker such as riboflavin.

A difficulty in extrapolating the results of this study to other treatment settings could be that, in our study, there was a high level of family support available to patients. If this had not been available, the retention levels, and compliance with medication, might have been lower for both treatments, and there would possibly have been no measurable difference between them. In our opinion, further studies comparing the efficacy of these two drugs are required in varying therapeutic contexts in patients with different severity profiles.

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RAPID COMMUNICATION

Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study

Henry R. Kranzler, Vania Modesto-Lowe, and Elie S. Nuwayser

This 12-week study examined the bioavailability, tolerability, and potential efficacy of an injectable sustained-release preparation (SRP) of naltrexone (NTX). Twenty alcohol-dependent subjects took NTX 50 mg po daily for 2 weeks, followed by a 2-week, no-medication Washout Period, a 4-week Injection Period, and a 4-week Follow-up Period. Fifteen subjects (75%) received a single subcutaneous injection of 206 mg of sustained-release NTX, and five subjects (25%) received a placebo injection. All subjects also received eight weekly coping skills sessions during the Oral NTX, and the Washout and Injection Periods. *Results:* After injection, NTX plasma concentrations exceeded a mean of 1 ng/ml for 21 days. Adverse effects produced by the SRP of NTX were comparable with those resulting from oral NTX therapy. Compared with placebo, the SRP of NTX significantly reduced the frequency of heavy drinking days during the Injection and Follow-up Periods. *Conclusions:* The results of this preliminary study support the potential clinical utility of the SRP of NTX for treatment of alcohol dependence.

Key Words: Naltrexone, Sustained-Release Preparation, Alcoholism, Alcohol Dependence, Pharmacotherapy.

NALTREXONE (NTX), an opioid antagonist, reduces alcohol consumption in alcohol-dependent patients.[1,2] Despite these early results, more recent findings indicate that, as in opioid addicts,[3] the effectiveness of NTX in alcoholics is limited by problems with compliance. Recent studies by Chick[4] and Volpicelli et al.[5] failed to show an overall advantage for NTX. In these studies, the active medication was superior to placebo (PLA) in reducing alcohol consumption only among highly compliant subjects. Although compliance with a variety of medications is often problematic,[6] the importance of these findings is underscored by the fact that alcoholics show particularly low rates of medication compliance.[7,8]

One approach to ensuring medication compliance is the use of a sustained-release preparation (SRP), which may also increase the likelihood of a therapeutic response by yielding a more predictable and constant plasma concentration than oral drug administration.[9] A parenterally administered SRP may also result in a higher brain concentration of the parent compound by bypassing hepatic metabolism.[9]

Chiang et al.[10] administered a 63-mg, sustained-release NTX bead preparation to three healthy male volunteers. Concentrations of NTX were highest on the first day after subcutaneous administration and then fell to 0.2 to 0.4 ng/ml from day 2 until the end of the experiment (23 to 32 days after implantation). Local irritation occurred in two of the subjects. In a subsequent study, Chiang et al.[11] found relatively constant plasma concentrations of NTX (0.30 to 0.46 ng/ml) and 6-β-naltrexol (0.64 to 1.07 ng/ml) for 2 to 4 weeks after implantation, concentrations that partially or completely blocked the effects of intravenous challenges with 15 mg of morphine.

More recently, an SRP of NTX that uses biodegradable, injectable microcapsules was administered to four healthy volunteers with no reported adverse effects.[12] Alim et al.[13] administered the same microcapsule preparation subcutaneously to 8 cocaine-dependent subjects: 2 received a PLA injection, 3 received 103 mg of NTX, and 3 received 206 mg of NTX. Patients in the NTX and PLA groups reported mild pain during the first few days after injection, with erythema and induration occurring commonly. The present study examined the bioavailability, tolerability, and potential efficacy of this microcapsule SRP of NTX (produced by BIOTEK, Inc., Woburn, MA) in alcohol-dependent subjects.

METHODS

Procedures

Twenty alcohol-dependent subjects participated in this 12-week study. After a minimum of 3 days of abstinence from alcohol, all subjects underwent 2 weeks of treatment with 50 mg/day of oral NTX (Oral NTX Period) to identify those individuals who could not tolerate the medication. Subjects then entered a 2-week, medication-free Washout Period, followed by random assignment to receive one injection of either depot NTX (15 subjects, 75%) or placebo (5 subjects, 25%), which was expected

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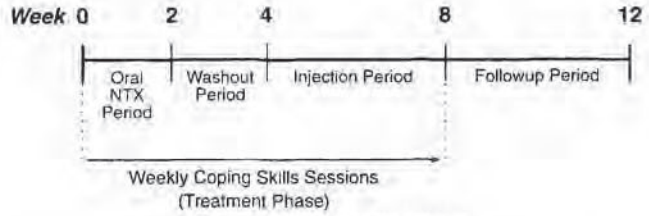


Fig. 1. Timeline of study periods.

to deliver medication for 4 weeks (Injection Period). The first 8 weeks of the study (which included the 2-week Oral NTX Period, the 2-week Washout Period, and the 4-week Injection Period) were designated as the Treatment Phase, because during this time all subjects also received weekly, individual coping skills psychotherapy.[14,15] After the 8-week Treatment Phase, all subjects underwent two research assessments over a 4-week Follow-up Period. Figure 1 shows a timeline of each subject's participation.

Assessments

The Michigan Alcoholism Screening Test,[16] Addiction Severity Index,[17] and Alcohol Dependence Scale[18] were administered at study entry to evaluate alcoholism severity and alcohol treatment history. The Time-Line Follow-Back Assessment method[19] was used to quantify drinking days, heavy drinking days (≥4 drinks in a day for females and ≥5 drinks in a day for males), and total alcohol consumption during the 4-week Pretreatment Period and for each period of the 12-week study. γ-Glutamyltranspeptidase (GGTP) levels were obtained at the same intervals to validate reported alcohol consumption.

Three assessments were repeated weekly during the 8-week Treatment Phase: breath alcohol testing, the Systematic Assessment for Treatment Emergent Events[20] to monitor adverse events, and the Beck Depression Inventory[21] to measure recent depressive symptoms.

Subjects

Subjects were recruited through advertisements. All subjects gave written, informed consent to participate. After screening, subjects were evaluated using the Structured Clinical Interview for DSM-IV,[22] clinical laboratory tests (CBC, urinalysis, blood chemistries, and, for women, a serum pregnancy test), and a physical examination. Inclusion criteria were age 18 to 60 years, ability to read English, and a current DSM-IV diagnosis of Alcohol Dependence.[23] Exclusion criteria were a current DSM-IV diagnosis of drug dependence (other than nicotine), a lifetime diagnosis of opioid dependence, psychoactive drug use in the preceding month, no stable residence, evidence of a major psychiatric or medical illness, pregnancy, or lack of birth control. As shown in Table 1, there were no significant between-group differences on any demographic or clinical variables. All subjects were Caucasian.

Treatment

Prior to injection, the microcapsule preparation was reconstituted in a suspending medium, to a total volume of 2.4 ml. The preparation was administered subcutaneously as a single injection in the gluteal region. The active SRP contained 206 mg of NTX, the maximal dose previously administered to humans.[13] The PLA preparation contained vehicle and microcapsules, but no NTX. A research pharmacist randomly assigned subjects to a medication group, with double-blind conditions maintained throughout the study.

Laboratory Analysis

Blood was collected nine times over the course of the 8 weeks after injection (i.e., during the Injection and Follow-up Periods). Solid-phase extraction and derivitization, followed by gas chromatography-negative ion chemical ionization-mass spectrometry, were used to measure plasma concentrations of NTX and 6-β-naltrexol.[24] The precision and accuracy of this procedure have previously been demonstrated.[24]

Table 1. Pretreatment Demographic and Clinical Features by Medication Group

	NTX (n = 15)	PLA (n = 5)	Test	p
Demographics				
Gender (% male)	73.3	80.0	FET	1.00
Employment (% full time)	66.7	80.0	FET	1.00
Marital status (% married)	80.0	40.0	FET	0.13
Age (years)	47.0 (9.0)	48.2 (4.3)	F = 0.08	0.77
Education (years)	14.9 (2.8)	15.0 (4.1)	F = 0.00	0.96
Clinical Features				
BDI* score	1.7 (2.5)	1.0 (1.7)	F = 0.24	0.63
DSM-IV† criteria	4.9 (1.0)	5.2 (1.3)	F = 0.24	0.63
MAST‡ score	21.9 (8.4)	24.0 (14.0)	F = 0.17	0.69
ADS§ score	13.1 (3.1)	15.2 (8.2)	F = 0.49	0.49
Years of heavy drinking#	19.8 (10.6)	23.2 (7.2)	F = 0.44	0.51
Prior treatments for alcoholism#	0.47 (0.64)	0.80 (0.45)	F = 1.15	0.30

* BDI, Beck Depression Inventory (Beck et al., 1961).
† Alcohol Dependence Criteria (American Psychiatric Association, 1994).
‡ MAST, Michigan Alcohol Screening Test (Selzer, 1971).
§ ADS, Alcohol Dependence Scale (Skinner and Allen, 1982).
From the Addiction Severity Index (McLellan et al., 1988).

Data Analysis

A two-tailed criterion of $p < 0.05$ was used to define statistical significance. One-way analysis of variance (ANOVA) was used to compare groups on continuous measures and Fisher's Exact Test (FET) was used for categorical measures. Paired t tests were used to compare mean weekly adverse effects during the Oral NTX Period with those occurring during the Injection and Follow-up Periods. The Pearson correlation coefficient was used to examine the degree of association between changes in GGTP level and changes in total alcohol consumption during the Oral/Washout, Injection, and Follow-up Periods and to examine the association between adverse effects and changes in alcohol consumption.

Hierarchical multiple regression was used to examine the effect of the SRP (i.e., NTX versus PLA) on adverse effects and drinking outcomes, after controlling for the respective measures during the Oral NTX and Washout Periods. Measures from these periods were entered into the analyses prior to medication group to examine change from the time of random assignment through the end of the study (i.e., the only time over which the injection could have exerted its effects). Because drinking measures from the Pretreatment Period did not contribute significantly to the variance in drinking outcomes during the study, they were not included in the regression equations. Regression analyses were conducted separately for the Injection and Follow-up Periods. Based on prior reports,[1,2] we hypothesized that the SRP of NTX would exert its greatest effects on the percentage of heavy drinking days.

RESULTS

Plasma Concentrations

Plasma concentrations of NTX and 6-β-naltrexol were obtained after the Washout Period (i.e., immediately prior to the depot injection), and then a mean of 1, 3, 8, 13, 20, 27, 34, 42, and 64 days after the injection. As can be seen in Fig. 2, the mean plasma NTX concentration exceeded 1 ng/ml, the concentration thought to produce opioid antag-

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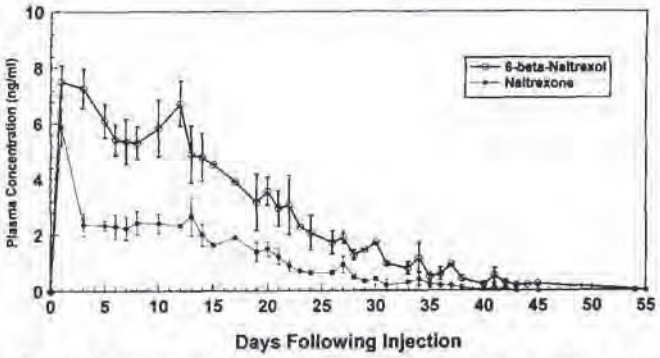


Fig. 2. Naltrexone and 6-β-naltrexol plasma concentrations after a single depot injection in 15 alcoholics. Values are mean (SEM) for days on which multiple measurements were taken.

Table 2. Means for Drinking Measures by Study Period and Medication Group Prior to Depot Injection

	NTX (n = 15)	PLA (n = 5)	p Value*
Pretreatment Period (4 weeks)			
% drinking days	68.1 (19.1)	71.3 (16.1)	0.73
% heavy drinking days	50.2 (30.0)	64.7 (29.0)	0.36
Average drinks/day	4.9 (3.6)	6.1 (4.0)	0.61
Oral NTX Period (2 weeks)			
% drinking days	11.4 (14.9)	5.8 (7.4)	0.44
% heavy drinking days	2.9 (9.3)	0	0.51
Average drinks/day	0.3 (0.5)	0.1 (0.2)	0.37
Washout Period (2 weeks)			
% drinking days	21.0 (24.3)	19.1 (19.4)	0.88
% heavy drinking days	7.3 (13.6)	0	0.26
Average drinks/day	0.8 (1.1)	0.5 (0.6)	0.57

* Using ANOVA.

onist effects,[10,25] for 21 days after the active SRP was administered.

Medication Tolerance

Seven subjects [5 NTX (33.3%) and 2 PLA (40%)] complained of a burning sensation at the time of the injection (FET = 0.59). In three of these cases (2 NTX and 1 PLA), soreness at the injection site persisted over the week after injection. An area of induration was evident at the injection site among 13 subjects [11 NTX (73%) and 2 PLA (40%) (FET = 0.29)], with the size of the induration ranging from 0.5 cm (NTX subject) to 4.0 cm (PLA subject) in diameter. The induration resolved completely to palpation over a period of 2.8 (SD = 1.3) weeks (range = 1 to 5 weeks).

Nine subjects [2 PLA (40%) and 7 NTX (46.7%)] reported other adverse effects during the Injection Period (FET = 0.60). The mean number of weekly complaints during this period was 0.40 (SD = 0.54) for the PLA group and 1.33 (SD = 1.95) for the NTX group. Adverse effects reported after depot NTX were comparable in frequency to those reported during the Oral NTX Period (mean = 1.80, SD = 1.82, paired $t_{14} = 1.07$, $p = 0.30$). Although the number of adverse effects during the Oral NTX Period predicted the number of adverse effects during the Injection Period [$\beta = 0.457$, $F(1,18) = 4.74$, $p = 0.043$], the depot NTX and PLA groups did not differ significantly on this measure [$\beta = 0.257$, $F(1,16) = 1.59$, $p = 0.23$].

Of the adverse effects reported during the Injection Period, fatigue was most common (n = 3: no PLA subjects and 20% of NTX subjects), followed by complaints of mood changes (n = 2: no PLA subjects and 13.3% of NTX subjects). Rash, palpitations, headache, nausea, vertigo, and insomnia were each reported by one NTX subject. No complaints of a severe nature were reported during the Injection Period. All adverse effects resolved spontaneously.

During the Follow-up Period, eight NTX subjects (40%) and no PLA subjects reported adverse effects (FET = 0.051). The mean number of weekly complaints by NTX subjects during this period was 1.27 (SD = 1.67), which does not differ statistically from the comparable measure during the Oral NTX Period (paired $t_{14} = 0.81$, $p = 0.43$). There was a trend for the number of complaints reported during the Follow-up Period to be correlated with both the number of complaints during the Oral NTX Period [$\beta = 0.455$, $F(1,18) = 4.22$, $p = 0.055$] and with the medication group [$\beta = 0.402$, $F(1,16) = 4.16$, $p = 0.059$]. During the Follow-up Period, 1 NTX subject reported severe vomiting, which resolved spontaneously.

Validation of Self-Reported Drinking

NTX subjects' GGTP levels (n = 15) declined from 40.9 units/liter (SD = 28.9) at baseline to 29.4 units/liter (SD = 21.3) for the Injection Period and 30.1 units/liter (SD = 21.4) for the Follow-up Period. PLA subjects' levels (n = 4; one subject failed to provide one specimen) declined from 43.0 units/liter (SD = 19.9) at baseline to 33.5 units/liter (SD = 16.4) for the Injection Period and 38.5 units/liter (SD = 7.1) for the Follow-up Period. Between-group comparisons of GGTP levels were nonsignificant (p's all > 0.10). However, change in GGTP level was significantly correlated with change in total alcohol consumption during the Oral and Washout Periods combined [$r = 0.48$, $p = 0.017$] and during the Injection Period [$r = 0.47$, $p = 0.021$]. There was also a trend for an association between the change in these measures during the Follow-up Period [$r = 0.33$, $p = 0.084$].

Drinking Measures

Table 2 shows drinking measures for the three study periods preceding the depot injection. ANOVA revealed no between-group differences on these measures (p's all >0.10).

Table 3 shows drinking measures for the Injection and Follow-up Periods. These comparisons control for the corresponding measures during the Oral NTX and Washout Periods.

Injection Period. During the Injection Period, the percentage of drinking days was predicted by the comparable

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Table 3. Means for Drinking Measures by Study Period and Medication Group after Depot Injection

	NTX (n = 15)	PLA (n = 5)	p Value*
Injection Period (4 weeks)			
% drinking days	21.0 (25.5)	28.4 (34.5)	0.42
% heavy drinking days	3.7 (10.7)	5.3 (8.4)	0.03
Average drinks/day	0.7 (0.6)	0.9 (1.2)	0.08
Follow-up Period (4 weeks)			
% drinking days	28.2 (35.8)	44.6 (31.4)	0.58
% heavy drinking days	7.8 (18.2)	23.0 (32.8)	0.04
Average drinks/day	1.1 (1.7)	1.9 (1.7)	0.04

* Using linear regression, controlling for the corresponding measures during the Oral NTX and Washout Periods.

measure during the Oral NTX [$\beta = 0.72$, $F(1,18) = 19.25$, $p < 0.001$] and Washout [$\beta = 1.31$, $F(1,17) = 27.80$, $p < 0.001$] Periods. The medication group did not affect this measure [$\beta = -0.09$, $F(1,16) = 0.70$, $p = 0.42$].

The percentage of heavy drinking days during the Injection Period was predicted by the comparable measure during the Oral NTX Period [$\beta = 0.84$, $F(1,18) = 40.54$, $p < 0.001$], but not by heavy drinking days during the Washout Period [$\beta = 0.47$, $F(1,17) = 3.85$, $p = 0.067$]. However, as hypothesized, the SRP of NTX produced a significantly lower percentage of heavy drinking days during the Injection Period [$\beta = -0.26$, $F(1,16) = 5.46$, $p = 0.034$], an effect (f^2) = 0.269.[26]

Mean drinks/day during the Injection Period was predicted by the comparable measure during both the Oral NTX Period [$\beta = 0.70$, $F(1,18) = 17.63$, $p = 0.001$] and the Washout Period [$\beta = 0.74$, $F(1,17) = 13.45$, $p = 0.002$]. There was a trend [$\beta = -0.23$, $F(1,16) = 3.4$, $p < 0.083$] for the SRP of NTX to reduce the mean number of drinks/day during the Injection Period.

Follow-up Period. During the Follow-up Period, there was a trend for the percentage of drinking days to be predicted by the comparable measure during the Oral NTX Period [$\beta = 0.45$, $F(1,18) = 4.45$, $p = 0.05$]. The comparable measure during the Washout Period was a significant predictor [$\beta = 1.65$, $F(1,17) = 24.72$, $p < 0.001$]. However, there was no effect of the SRP of NTX on the percentage of drinking days during the Follow-up Period [$\beta = -0.09$, $F(1,16) = 0.32$, $p = 0.58$].

The percentage of heavy drinking days during the Follow-up Period was predicted by the comparable measure during the Oral NTX Period [$\beta = 0.56$, $F(1,18) = 8.25$, $p = 0.010$], but not by heavy drinking days during the Washout Period [$\beta = 0.05$, $F(1,17) = 0.02$, $p = 0.88$]. Again, as hypothesized, individuals receiving the SRP of NTX had significantly fewer heavy drinking days during the Follow-up Period [$\beta = -0.43$, $F(1,16) = 5.18$, $p = 0.037$], an effect (f^2) = 0.245.[26]

The mean number of drinks/day during the Follow-up Period was predicted by the comparable measure during both the Oral NTX Period [$\beta = 0.55$, $F(1,18) = 7.71$, $p = 0.012$] and the Washout Period [$\beta = 0.71$, $F(1,17) = 7.12$, $p = 0.016$]. A significant advantage for the SRP of NTX on this outcome measure emerged during the Follow-up Period [$\beta = -0.35$, $F(1,16) = 5.01$, $p = 0.040$], an effect (f^2) = 0.239.[26]

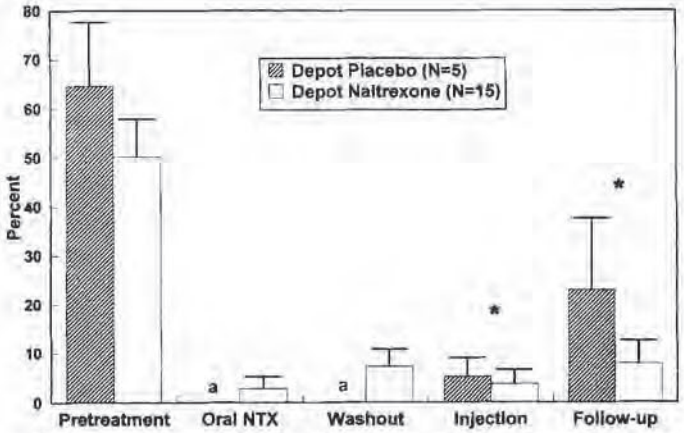


Fig. 3. Percent (mean + SEM) heavy drinking days by medication group and study period. *$p < 0.05$, after controlling for heavy drinking days during the Oral NTX and Washout Periods. [a]No heavy drinking by placebo subjects during the Oral NTX and Washout Periods.

Relations Between Adverse Events and Changes in Alcohol Consumption

When correlations between the number of adverse events reported and the change in each of the three drinking measures were examined separately for the Injection and Follow-up Periods, all were found to be nonsignificant (r's all <0.34, p's all >0.10).

Integrity of the Double Blind

When subjects were asked to judge which medication they received, the majority (12, or 60%) guessed incorrectly. One PLA subject (20%) and 7 NTX subjects (46.7%) correctly identified their medication assignment (FET = 0.60).

DISCUSSION

This study provides preliminary evidence for the bioavailability, tolerability, and efficacy of an SRP of NTX for the treatment of alcohol dependence. A clinically significant effect of NTX on the frequency of heavy drinking was evident during the 4-week Injection Period. This effect persisted during the 4-week Follow-up Period (Fig. 3). An effect of similar magnitude was observed on the mean number of drinks per day, but only during the Follow-up Period. GGTP level did not differ by treatment group, which may be due to the fact that GGTP levels are a relatively insensitive measure of alcohol consumption,[27] and they were only modestly elevated in this subject sample at baseline. However, correlations with GGTP level observed herein support the validity of self-reported alcohol consumption. Because participants were no better able to

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identify the medication they received and there was no correlation between adverse events and changes in self-reported drinking, it appears that there was a direct pharmacological effect of the SRP of NTX on alcohol consumption.

Olsen and Kincl[28] listed the following criteria for an ideal NTX sustained-delivery system: ease of administration, absence of an adverse tissue reaction, a relatively constant release of the drug for at least 30 days, and biodegradation within a short time after that. Using these criteria, the microcapsule formulation described herein, although promising, is not ideal. The volume of fluid that was injected produced discomfort. Although the induration lasted beyond the immediate Injection Period, in all cases it resolved spontaneously within 5 weeks of injection. Because an NTX concentration in excess of 1 ng/ml was maintained for 21 days, this preparation can be expected to block opioid agonist effects for at least that long.[10,25] Furthermore, NTX was detectable in plasma, and clinical effects were present for >30 days after injection.

Although during the Follow-up Period, there was a trend toward a greater number of adverse effects among subjects receiving the active injection, the frequency of adverse effects of the SRP of NTX was comparable with that of oral NTX. Furthermore, the lack of association between adverse and therapeutic effects suggests that it may feasible to increase tolerability without reducing the efficacy of the preparation. For example, by reducing the total dose of NTX in each injection, the volume injected and the peak plasma concentration would be reduced, which could reduce adverse effects. However, more frequent injections would be required to sustain the therapeutic effects.

Given the small number of subjects included and the fact that each subject received only one dose of the SRP, this study provides only preliminary data on this formulation of NTX. Nonetheless, a number of clinically significant therapeutic effects were observed. These were demonstrable despite the low level of drinking that was evident during the Oral NTX and Washout Periods, which served as the baseline against which the effects of the injection were evaluated. A larger study of this SRP should include patients with a wide range of alcohol dependence severity. Furthermore, because the medication effects were obtained in the context of weekly, individual psychotherapy, it may also be useful to evaluate the SRP in conjunction with a less intensive psychosocial intervention.

Based on the findings reported herein, an SRP of NTX may have an important place in the treatment of alcohol dependence, particularly in light of variable compliance with the oral medication in this patient population.[4,5] Additional study of this formulation appears warranted. Ultimately, comparison with oral NTX therapy should help to determine which individuals might be most likely to benefit from the SRP of NTX.

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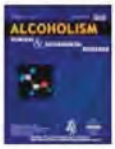
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Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study

Henry R. Kranzler, Vania Modesto-Lowe, Elie S. Nuwayser

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Abstract

This 12-week study examined the bioavailability, tolerability, and potential efficacy of an injectable sustained-release preparation (SRP) of naltrexone (NTX). Twenty alcohol-dependent subjects took NTX 50 mg po daily for 2 weeks, followed by a 2-week, no-medication Washout Period, a 4-week Injection Period, and a 4-week Follow-up Period. Fifteen subjects (75%) received a single subcutaneous injection of 206 mg of sustained-release NTX, and five subjects (25%) received a placebo injection. All subjects also received eight weekly coping skills sessions during the Oral NTX, and the Washout and Injection Periods. Results: After injection, NTX plasma concentrations exceeded a mean of 1 ng/ml for 21 days. Adverse effects produced by the SRP of NTX were comparable with those resulting from oral NTX therapy. Compared with placebo, the SRP of NTX significantly reduced the frequency of heavy drinking days during the Injection and Follow-up Periods. Conclusions: The results of this preliminary study support the potential clinical utility of the SRP of NTX for treatment of alcohol dependence.

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