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A Double Blind, Placebo-Controlled Study of Naltrexone in the Treatment of Alcohol Dependence

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Abstract

The goal of this study was to assess the efficacy of a 50-mg-per-day dose of naltrexone in the maintenance treatment of alcohol-dependent patients over a 12-week treatment period. Patients were randomized to two groups. Subjects consisted of 116 male alcohol dependents who met the DSM-IV criteria for alcohol dependence and were seeking treatment. Patients received naltrexone at a dose of 50 mg per day or placebo in a double-blind placebo-controlled trial, and were treated in an outpatient clinic, offering a weekly 0.5-hour individual counseling session. Days retained in treatment were measured. Overall, 71 patients (61.2%) completed the 12-week study. Completion rates by group were 79.3% for the 50 mg naltrexone group and 43.1% for the placebo group (χ^2 = 16.01; p<0.0001). The results support the efficacy and safety of naltrexone for outpatient treatment of alcohol-dependent patients (German J Psychiatry 2002; 5(4): 85-89).

Keywords: naltrexone; alcohol dependence; relapse rates; double-blind

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Introduction

Until now very little has been known about substance dependence in Iran, and to our knowledge no scientific papers have been published about alcohol use disorders in Iran.

Substance dependence is considered a crime but the authorities are ready to consider substance dependence and abuse as a psychiatric disorder. Substance-dependent patients and substance abusers who are undergoing treatment are not meant to be prosecuted, and neither are specialists who give treatment. The costs of treatment, medication and rehabilitation are to be paid by the substance-dependent patients according to the approved tariffs, but the government will pay the costs for those unable to pay (DCHQ, 1997). Alcohol is both religiously and legally prohibited. Illicit substances are heroin, opium, alcohol, cannabis, stimulants, LSD, and other hallucinogens.

The State Welfare Organization, which is affiliated to the Ministry of Health, Treatment, and Medical education, is in charge of treatment and rehabilitation of substance-dependent patients. At the present time, there are 12 treatment and rehabilitation centers, with one center for women, in the country. Up to 1998/1999 approximately 25,000 to 30,000 individuals were admitted to these centers (90% of these referrals were ordered by courts). The average duration of stay is 2 to 6 months. The centers used to be described as having the infrastructure of an overcrowded prison. Now these centers are closed and the new approach is the introduction of outpatient treatment centers. Treatment is generally modeled on detoxification with clonidine and tranquillizers, and recently with buprenorphine or methadone. The duration of treatment ranges from 3 to 6 months, including individual therapy, family therapy, and group therapy. Sometimes, the duration of therapy may be extended to 2 years. Self-referral centers and Narcotic Anonymous centers have been developed, with approximately 5,000 members throughout the country. Relapse rates are estimated to vary between 60% and 80% according to the duration and location of therapy (Razzaghi, Rahimi, Hosseini & Chatterjee, 1999).

At present, the number of substance users is estimated to be between 1.8 million and 3.3 million, the number of I.V.drug users between 200,000 to 300,000 and the number of HIV infections in I.V.drug users is estimated to be 1,841, or 74.8% of all HIV infections (Razzaghi, Rahimi, Hosseini & Chatterjee, 1999; DCHQ 2001; Moor 2001).

Opioid antagonists such as naltrexone reduce alcohol consumption. Naltrexone as a competitive opioid antagonist has a significant inhibiting effect on central opioid receptors. Animal studies have shown that opioid antagonists such as naltrexone decrease alcohol preference (Volpicelli et al. 1986; Froehlich et al. 1987, 1990; Hubbell et al. 1991; Hyytia and Sinclair 1993). Clinical trials have shown that naltrexone 50 mg a day reduces alcohol consumption and relapse rates in alcohol dependents (Volpicelli et al. 1992; O'Malley et al. 1992; Morris et al. 2001).

In the most widely accepted hypothesis for the efficacy of naltrexone, Volpicelli (1987) said that opioid antagonists block alcohol-stimulated increase in endogenous opioid activity, resulting in reduction of euphoria or "high". A 1996 study (Gianoulakis et al.) showed an alcohol/endogenous opioid association in offspring of alcoholic patients (dose-dependent enhancement in β-endorphine-related peptides to test doses of alcohol). In addition, alcoholic individuals treated with naltrexone reported a decreased subjective high (Volpicelli et al. 1995) and reduced craving (O'Malley et al. 1996) after an alcohol "relapse". In a controlled study of naltrexone and alcohol effects in social drinkers, naltrexone reduced the subjective stimulant effects and enhanced the sedative effects of alcohol (Swift et al. 1994). In a study in which naltrexone was combined with cognitive-behavior therapy over a period of 12 weeks, a reduced relapse to heavy drinking and decrease in the total number of drinking days and the frequency of drinks per drinking day were observed (Anton et al. 1999). A number of studies assessed naltrexone in more select patient populations (Carrol et al.1993; McCaul et al. 1996; Osline et al. 1997, King et al. 1977; Weinrieb et al. 1997) and showed that naltrexone has variable efficacy for alcohol dependence. A follow-up study in the USA showed that naltrexone was only superior to placebo in the patients who completed treatment (Volpicelli et al. 1997). Studies in the UK showed similar results (Litten and Ferting 1996; Chick et al. 2000).

The objective of the current study was to examine the effect of naltrexone in the maintenance treatment of alcohol-dependent patients. We carried out a 12-week randomized double-blind placebo-controlled trial of naltrexone 50 mg per day in an urban outpatient clinic including a weekly 0.5-hour individual counseling session. We assessed the efficacy of naltrexone on maintenance of abstinence and prevention of relapse to alcohol drinking.

Materials and Methods

Patients

This research study was a two-group, randomized, double blind, placebo-controlled design, comparing a 50 mg dose of naltrexone to placebo over a 12-week treatment period on 116 alcohol-dependent males. The present study was conducted in the Iranian city of Shiraz. Patients were recruited from alcohol-dependent, self-referred individuals. Informed consent was obtained from all subjects. The inclusion criteria were: males aged 23-56 years; a current diagnosis of alcohol dependence; and maintenance of at least 3 days, and at most 30 days, sobriety before study entry. The exclusion criteria were: other current drug abuse or dependence (excluding tobacco); current use of opioids (including opioids contained in analgesics) or disulfiram; bilirubin level and alanine aminotransferase higher than five times normal and intake of neuroleptic drugs.

One hundred and sixteen patients were recruited and screened.

Procedure

Assessments included physical and psychiatric examinations, urine toxicology for prescribed and illicit drugs, urinalysis, and blood hematology and biochemistry (including bilirubin, gamma glutamyl transfrerase (GGT) and ALT). Patients had an interviewer-assisted detailed review of daily alcohol use patterns for the 30 days before the beginning of abstinence.

Subjects were allocated randomly to receive either naltrexone 50 mg per day or an identical placebo capsule for 12 week. Patients and research staff were blind to the capsule prescribed. All subjects were required to attend 12 weekly 0.5-hour individual counseling sessions, and were provided with information about alcohol use and abuse, and the consequences of alcohol dependence. The program provided training in relapse prevention through identifying situations, places and people that cue drinking behavior, and by teaching subjects techniques to either avoid or manage these situations.

Patients were seen every week to monitor the past week's alcohol consumption using the time-line follow back calendar method for daily estimation of drinking (Sobeli & Sobeli, 1992), a pill count check medication compliance, and systematic enquiries about adverse experiences and the use of concomitant prescribed and non-prescribed medications. At weeks 4, 8 and 12, subjects were re-evaluated. At these times repeat liver function test (GGT), urinalysis and urine toxicology screens were also performed. In the final stage of

the study, physical examination and liver function tests were repeated.

Study Outcomes

The primary study outcomes were: (1) the maintenance of abstinence, and (2) relapse to drinking. A return to drinking any alcohol was considered the end of abstinence and the beginning of relapse. Relapse to drinking was defined as either drinking five or more standard drinks (1 standard drink is equal to 10 g of alcohol) on one drinking occasion, or drinking on 5 or more days per week.

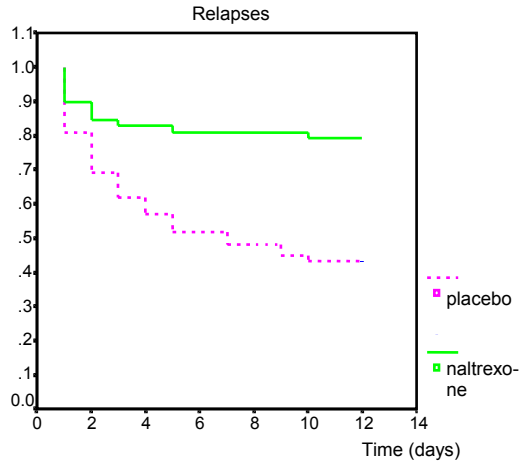
Data analysis

Analyses were done separately for the naltrexone and the placebo studies. Two group samples were compared on baseline characteristic using one-way analysis of variance for continuous variables and χ^2 analyses for categorical variables. Efficacy in the two groups was compared using χ^2 analysis. Two-sided tests were used at ≤0.05.

Table 1. Sample Characteristics

Mean Age		
Group	**N**	**Mean age**
Naltrexone	58	42.7 (SD9.6)
Placebo	58	43.19 (SD 8.8)
Total	116	42.97 (SD 9.2)
F= 0.862; df=1, 115; p=0.80 (N.S.)		
Frequency Distribution by Age Group		
Age group (years)	N	%
20-24	3	2.6
25-29	16	13.8
30-34	4	3.4
35-39	2	1.7
40-44	29	25.0
45-49	31	26.7
≥ 50	31	26.7
Total	116	100
Marital Status		
	N	**%**
Single	15	12.9
Married	101	87.0
Total	116	100
Educational Status		
	N	**%**
Primary School	18	15.5
High School	57	49.1
Higher Education	41	35.4
Total	116	100
Occupational Status		
	N	**%**
Worker	19	16.4
Employee	19	16.4
Self-employment	51	44.0
Unemployed	19	16.4
Other	8	6.9
Total	116	100

Figure 1. Kaplan-Meier Survival Analysis of Relapses



Results

Demographic variables

One hundred and sixteen male alcohol-dependent patients were allocated randomly to receive naltrexone (N=58) or placebo (N=58). Patients were stratified to dose and duration of drinking alcohol. There were no significant differences between two groups on mean age, educational status and occupational status. The sample characteristics are recorded in Table 1.

Effect of naltrexone on alcohol response

Overall 71 patients completed the 12-week study (Table 2). Completion rates were 46 (79.3%) for the naltrexone group and 25 (43.1%) for the placebo group (χ^2 = 16.01; p<=0.0001; two-sided). The Kaplan-Meier survival analysis is given in Figure 1.

Side effects

In treatment-emergent side effects, patients treated with naltrexone reported more complaints of nausea than patients treated with placebo (20 vs. 9). Other side effects were: lethargy (13 vs. 5), nightmares or hallucinations (5 vs. 0); dizziness (7 vs. 1); insomnia (10 vs. 4); headache (14 vs. 6) and anxiety (14 vs. 10).

Table 2. Frequency distribution of completers by group

Group	Completers		Noncompleters	
	N	%	N	%
Naltrexone	46	79.3	12	20.7%
Placebo	25	43.1	33	56.9%

$\chi^2 = 16.0$; $p<0.0001$

Discussion

Our findings show that naltrexone decreased the relapse rate in alcohol-dependent patients, which is consistent with other human studies (Volpicelli et al. 1996) and also with animal studies reporting that opioid antagonists decrease alcohol preference (Altschuler 1980; Volpicelli et al. 1986; Forehlich et al. 1987, 1990; Hubbell et al. 1991; Hyytia and Sinclair 1993).

The mechanisms underlying naltrexone's effect on relapse are not clear. Explanations include: 1- a reduction in craving for alcohol, 2- blocking reward signals from alcohol that are mediated through the opioid receptor system, and 3- the production of a mild unpleasant subjective experience on drinking alcohol (Litten & Allen, 1998).

The most important limitation of our research study was that all patients were males and that it did not address use of naltrexone in females. It is possible that women may respond better to naltrexone than men, although this has not been observed in studies that included both males and females. The standard dose of naltrexone (50mg) may provide a higher serum level of this drug in females. This may result in greater efficacy in females, because higher levels of β-naltrexone (an active metabolite of naltrexone) are associated with better results (Litten & Allen, 1998).

In conclusion, completion rates for naltrexone-treated patients were significantly higher than for the placebo group. Fewer naltrexone-treated patients relapsed than placebo-treated patients. Therefore we conclude that naltrexone can be useful for Iranian alcohol-dependent patients to enhance success rates.

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