

Targeted Use of Naltrexone Without Prior Detoxification in the Treatment of Alcohol Dependence: A Factorial Double-Blind, Placebo-Controlled Trial

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Several studies have shown the opioid antagonist naltrexone to be effective when combined with psychosocial therapies for the treatment of patients who are dependent on alcohol with fixed medication and time (12 weeks). In this study, 121 nonabstinent outpatients with alcohol dependence (DSM-IV) were treated with sessions of cognitive coping skills (N = 67) or supportive therapy (N = 54) and either naltrexone 50 mg/day (N = 63) or placebo (N = 58) daily for the first 12 weeks and thereafter for 20 weeks only when craving alcohol (i.e., targeted medication) in a prospective one-center, dual, double-blind, randomized clinical trial. The dropout rate for all subjects was 16.5% during the first 12-week period and approximately twice that level by the end of the study. There were no significant group differences in study completion and therapy participation rates. After the continuous medication (12 weeks), the coping/naltrexone group had the best outcome, and coping/placebo had the worst. This difference remained during the targeted medication period (the following 20 weeks). Naltrexone was not better than placebo in the supportive groups, but it had a significant effect in the coping groups: 27% of the coping/naltrexone patients had no relapses to heavy drinking throughout the 32 weeks, compared with only 3% of the coping/placebo patients. The authors' data confirm the original finding of the efficacy of naltrexone in conjunction with coping skills therapy. In addition, their data show that detoxification is not required and that targeted medication taken only when craving occurs is effective in maintaining the reduction in heavy

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THE USE OF naltrexone in the treatment of alcoholism is well supported by several controlled clinical trials.^{1–4} A double-blind, placebo-controlled trial by Volpicelli and colleagues¹ first showed clinically that naltrexone reduced alcohol drinking and especially relapsing to heavy drinking. Naltrexone-treated patients had a lower overall number of drinking days and less craving than the placebo-treated individuals.

The study was replicated by O'Malley and associates,² who showed that naltrexone in general decreased relapse rates, the percentage of drinking days, and the total number of drinks during the study in comparison with placebo. An interaction between the medication and the psychotherapy was found in that naltrexone had a significant effect on craving and relapse to heavy drinking in the coping groups but not the supportive ones.

One important limitation to any pharmacologic treatment is subject compliance. This is well demonstrated with the use of naltrexone for alcoholism treatment, as shown by Volpicelli and associates,³ who found that compliance with medication played an important role in the increased efficacy of naltrexone over placebo. In this study, detoxified patients received either daily 50 mg of naltrexone or placebo and relapse prevention therapy. The treatment outcome was dependent on compliance: among the highly compliant subjects, there was a significant negative correlation between medication compliance with naltrexone and percentage of days of drinking during the study. In contrast, among less compliant subjects, naltrexone produced significant benefits only on liver enzyme markers of drinking. However, there was no significant difference in craving between the naltrexone-treated and the placebo-treated subjects between the treatment groups.

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Preclinical findings and the results from these and other earlier clinical trials suggested that the efficacy of naltrexone may be dependent on the protocol with which it is used.⁴⁻⁸ Clinical trials with support of abstinence and preclinical studies in which opioid antagonists were given only during abstinence had not found significant benefits from naltrexone, but trials with instructions that did not preclude all drinking and preclinical studies in which animals were given antagonists while drinking had found positive effects.⁹ This suggested that a protocol might be used in which prior detoxification was omitted and that naltrexone could be given in a "targeted" manner, i.e., only when patients are drinking. Furthermore, the previous results had suggested that naltrexone continues to be effective as long as it is administered, but the benefits begin fading gradually once the medication is terminated.¹⁰ This suggested that treatment should be continued beyond the 3- or 6-month periods previously tested.

The aim of our study was to replicate the reported data^{1-4, 11} and test these new strategies for increasing the efficacy of naltrexone in the treatment of alcohol dependence. This report presents the findings from a prospective, one-center, randomized, double-blind, 32-week trial of the efficacy of naltrexone or placebo started without detoxification, added to manual-guided¹² cognitive-behavioral group therapy allowing some drinking or group therapy supporting total abstinence for outpatients dependent on alcohol. The first 12 weeks are seen as an induction period, and the final 20 weeks with targeted medication (taken only when craving was high), as the test period.

Methods

The study subjects were people seeking outpatient treatment for alcoholism who responded to advertisements for the research study. A total of 326 individuals were screened over the telephone, and 302 were invited for in-person screening. Of these, 137 were screened in person, and 121 gave written informed consent and were randomly assigned for the study after a 1-week run-in trial with a riboflavin-marked placebo. The inclusion criteria were age of 21 to 65 years; satisfaction of DSM-IV criteria for alcohol dependence; consumption, on average, of five or more drinks per day in the last 30 days; and a stable living situation and availability of a collateral reporter. The exclusion criteria were other current drug abuse or dependence (including marijuana), ever having abused opiates, a current major psychiatric disorder as determined by the Structured Clinical Interview for DSM-IV, a serious or unstable medical condition, current use of psychotropic or antiseizure medications or disulfiram, and liver function test results

(alanine aminotransferase and aspartate aminotransferase) greater than 250 IU.

Each patient signed a written informed consent form, and the study was conducted according to the International Conference of Harmonization's Good Clinical Practice guidelines and the Helsinki 1964 declaration. Ethical permission for the study was granted by the A-Clinic Foundation Ethical Committee (permission 101096).

Reasons for nonparticipation among the 302 individuals invited to be screened in person included the following: 55% chose not to participate, 1% had other psychiatric diagnoses, 2% had exclusionary medical conditions, and 2% lacked social stability. A total of 121 patients were included: 86 men (71.1%) and 35 women (28.9%). The mean age (\pm SD) was 45.5 (\pm 7.8) years.

The patients were treated with group sessions of cognitive coping skills ($N = 67$) or supportive ($N = 54$) behavioral therapy and either naltrexone 50 mg/day ($N = 63$) or placebo ($N = 58$) started without prior detoxification. In a dual, double-blind, randomized clinical trial, medication was provided daily for the first 12 weeks and thereafter for 20 weeks only when alcohol drinking was likely (i.e., targeted medication). In the latter targeted part of the study (weeks 13 to 32), subjects in both the coping and supportive groups were instructed to take the medication only in situations for which they considered there to be risk of sampling alcohol or when they believed that their craving would probably overwhelm their ability to resist drinking.

The study medication was purchased (ReVia, MEDA Ltd., Finland) and specially prepared for this study by the University Pharmacy, Helsinki University. Identical opaque capsules containing either 50 mg of naltrexone hydrochloride or inactive placebo were both made with 100 mg of riboflavin added to monitor compliance. A study pharmacist delivered the study medication at each visit to the subject.

The primary outcome measure for evaluation of the efficacy of naltrexone was chosen before the study and filed with the A-Clinic Foundation Ethical Committee. This chosen measure was the relapse to heavy drinking, in accordance with previous naltrexone clinical trials.^{1, 2, 4} Other measures taken included alcohol consumption (measured with drinking diaries), craving (measured with a Finnish translation of the Obsessive Compulsive Drinking Scale), adverse events, liver enzymes, and urinary riboflavin levels, which were assessed every 2 weeks or monthly.

Patients were seen in a visit 1 week before the start of treatment, at the start of treatment, and thereafter in weeks 1, 2, 3, 5, 8, 12, 16, 24, and 32. They were contacted by telephone on weeks 20 and 28. Drinking diaries (in which the patients had recorded their daily intakes of alcohol as the number of standard 12-g drinks)

were collected at each visit, including the telephone contacts. Patients received either coping or supportive therapy at four visits—in weeks 1, 2, 5, and 12. The coping (or “coping with drinking”) groups received cognitive-behavioral therapy in a group setting according to the manual used at Järvenpää Addiction Hospital.¹² The emphasis in the therapy was coping with a slip when the patient samples alcohol so as to prevent it from proceeding on to a binge of drinking. The supportive (or “support of abstinence”) groups met in a similar group setting, but here the emphasis was on support of complete abstinence from all drinking. The outlines of study flow are presented in Figure 1.

Results

The demographic variables for the 121 randomly assigned subjects are presented in Table 1. There were no significant differences among the four groups on any variable. In general, the individuals in this study were well educated, employed, married, and socially stable. All subjects met the diagnostic criteria for alcohol dependence (DSM-IV). There was no significant difference in any measure of severity of alcoholism between the treatment groups. Overall, 83.5% (N = 101) of the randomized subjects completed the first 12 weeks of the study, and 69.4% (N = 84) completed the whole program: i.e., the dropout rate for all subjects was 16.5% during the first 12-week period and 30.6% by the end of the study. The study completion and therapy participation rates in the trial were high, with no differences between treatment groups.

The main outcomes are presented in Figures 2 and 3.

The primary outcome measure, chosen before the study, was the rate of relapse to heavy drinking, defined as having five or more drinks (12 g of ethanol each) on one occasion, having five or more drinking occasions in 1 week, or arriving at a visit intoxicated. Overall, there was a significant effect of treatment on this measure: the Kaplan-Meier survival analysis for the entire 32 weeks was significant ($p = 0.0397$) (Fig. 2). An interaction was found between the medication and the type of therapy, with the coping/naltrexone group having the best outcome.

The result is seen more clearly in the percentage of patients never relapsing to heavy drinking during the entire 32 weeks (Fig. 3). Naltrexone was highly significantly better than placebo in the coping groups (Fisher exact test, $p = 0.008$). In contrast, naltrexone tended to be slightly worse than placebo in the supportive groups, although the difference was not significant. The coping/naltrexone group did significantly better than the supportive/naltrexone group ($p = 0.041$). These results are from analyses of all patients (i.e., intent-to-treat patients) and not just those completing the study or those with high compliance.

The same relation is found among the patients ever relapsing to heavy drinking: 19.1% of the coping/naltrexone patients did so only once in the 32 weeks, but only 3.2% of the coping/placebo patients had only one relapse. The rates were similar in both supportive groups: 12.5% with naltrexone and 10.0% with placebo. In the coping/naltrexone group, 38.2% had at most one relapse in 32 weeks, compared with only 6.1% in the placebo/coping group, 17.2% in the supportive/naltrexone group, and 20.0% in the supportive/placebo group (interaction, χ^2 [with Yates correction, 1 *df*] = 12.02, $p < 0.001$).

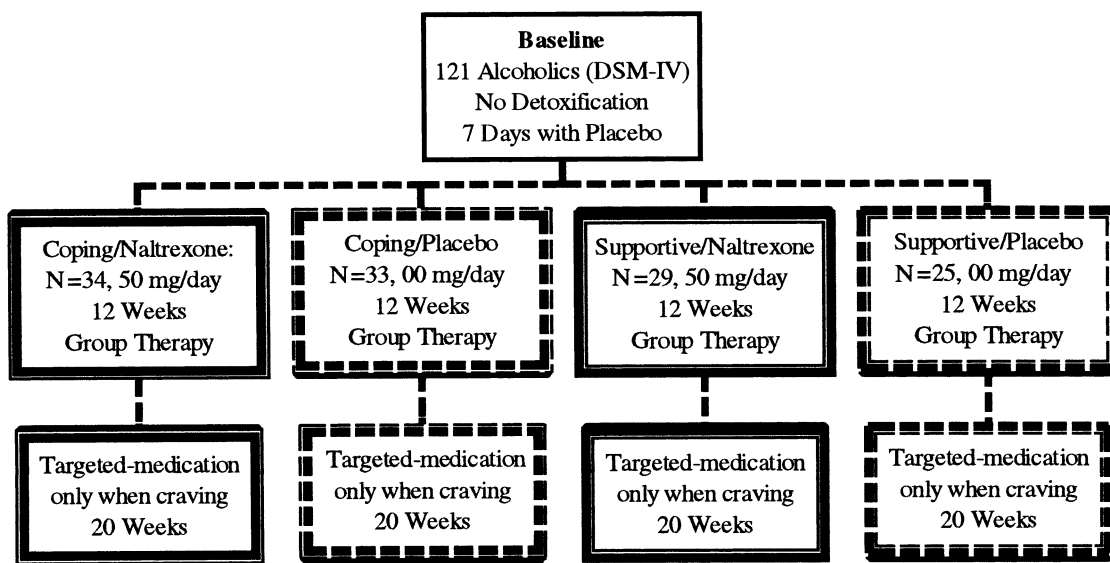


FIG. 1. Study flowchart indicating the different groups, number of patients (N), and time intervals for medication (continuous/targeted).

TABLE 1. Sociodemographic characteristics of the whole material (no significant differences between the treatment groups)

Variable	Value
Age (yrs), mean ± SD	45.5 ± 7.8
Gender, N (%)	
Male	86 (71.1)
Female	35 (28.9)
Marital status, N (%)	
Single	14 (11.6)
Married	88 (72.7)
Divorced or widowed	19 (15.7)
Living conditions, N (%)	
Alone	25 (20.7)
Together with family	90 (74.4)
Together with children	6 (5.0)
Employment, N (%)	
Unemployed	16 (13.2)
Employed	91 (75.2)
Retired or student	14 (11.6)
Previous alcohol treatments, N (%)	
None	78 (64.5)
Detoxification (but currently drinking)	14 (11.6)
Therapy at A-Clinic	16 (13.2)
Institutional therapies	13 (10.7)

During the targeted-medication phase (last 20 weeks), the only significant difference in the number of pills taken weekly was that the supportive/naltrexone group consumed significantly more (mean ± SD) (3.4 ± 0.3) than the coping/naltrexone group (2.1 ± 0.2) (Table 2).

The group differences in reported alcohol drinking

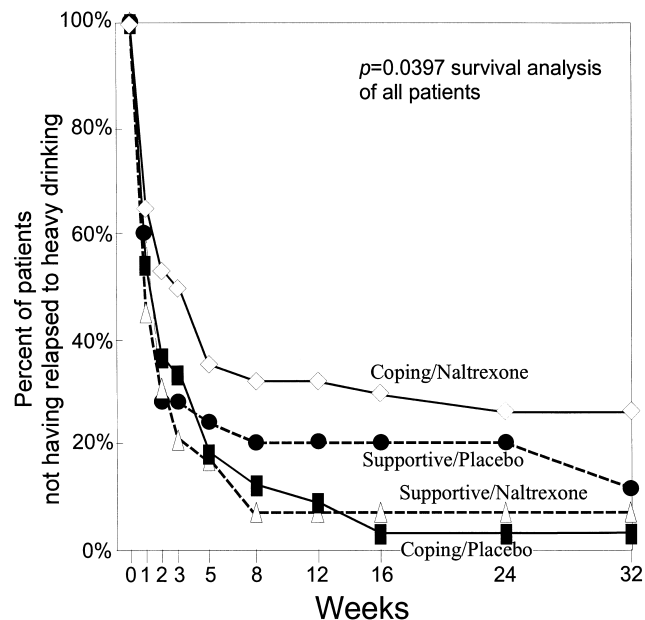


FIG. 2. Percentage of patients not relapsing to heavy drinking, i.e., five or more drinks on one occasion, five or more drinking occasions in a week, or intoxication at site visit. Kaplan-Meier survival analysis of all patients.

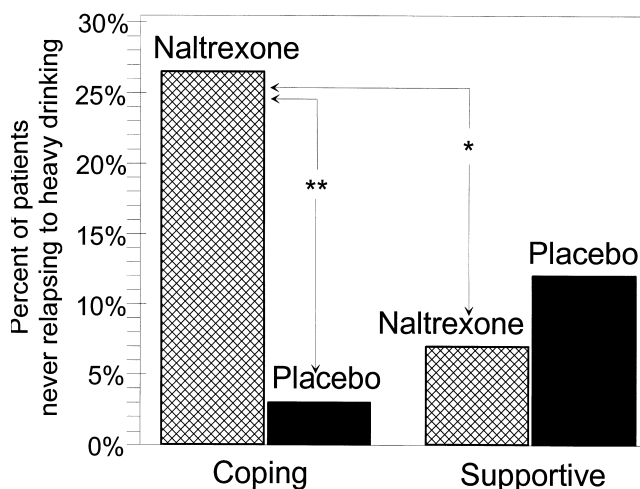


FIG. 3. Percentage of patients who had no relapses in 32 weeks. Fisher exact test, ** $p = 0.008$, * $p = 0.041$.

showed a pattern similar to that for relapses to heavy drinking, with the coping/naltrexone group tending to do better than the other three groups. The pattern became more pronounced during the course of the study and became significant only in the last 8 weeks, when the reported drinking (g/wk) (mean ± SD) was 231 ± 40 for the coping/naltrexone group, 354 ± 62 for the coping/placebo group, 357 ± 81 for the supportive/naltrexone group, and 326 ± 80 for the supportive/placebo group (t -test assuming unequal variances comparing coping/naltrexone with the other three groups combined: $t [75] = 1.99, p = 0.05$).

Table 3 shows the side effects. No severe problems related to ethanol withdrawal were evident. Naltrexone was well tolerated compared with the placebo. The general rate of reporting adverse effects was high, but the number of patients reporting them was not significantly higher in the naltrexone than placebo groups ($\chi^2 [1 df] = 2.91, p > 0.05$). No individual side effect was seen significantly more often in the naltrexone than placebo groups. The prevalence of naltrexone-related side effects depended on the type of therapy. Among the supportive groups, the percentage of patients reporting side effects was significantly higher with naltrexone than with placebo ($\chi^2 [1 df] = 5.77, p < 0.05$), but naltrexone did not cause a significant increase in side effects among the coping groups.

TABLE 2. Number of pills per week during last 20 weeks (mean ± SE)

Group	Coping	Supportive
Naltrexone	2.1 ± 0.2 ^a	3.4 ± 0.3
Placebo	2.7 ± 0.3	2.4 ± 0.5

^a $p = 0.05$ versus the supportive/naltrexone group.

TABLE 3. Number (%) of patients showing various side effects for the entire 32 weeks

Side Effect	Group					
	Coping/Naltrexone (N = 34)	Coping/Placebo (N = 33)	Supportive/Naltrexone (N = 29)	Supportive/Placebo (N = 25)	Naltrexone (N = 63)	Placebo (N = 58)
Intestinal disorders	6 (17.6)	3 (9.1)	6 (20.7)	3 (12.0)	12 (19.0)	6 (10.3)
Headache	4 (11.8)	6 (18.2)	2 (6.9)	4 (16.0)	6 (9.5)	10 (17.2)
Sexual dysfunction	4 (11.8)	2 (6.1)	6 (20.7)	2 (8.0)	9 (14.3)	4 (6.9)
Daytime fatigue	3 (8.8)	2 (6.1)	6 (20.7)	2 (8.0)	9 (14.3)	4 (6.9)
Nausea	3 (8.8)	0 (0.0)	4 (13.8)	2 (8.0)	7 (11.1)	2 (3.4)
Dry mouth	1 (2.9)	1 (3.0)	3 (10.3)	2 (8.0)	4 (6.3)	3 (5.2)
Pollacisuria	3 (8.8)	2 (6.1)	1 (3.4)	0 (0.0)	4 (6.3)	2 (3.4)
Insomnia	1 (2.9)	2 (6.1)	1 (3.4)	1 (4.0)	2 (3.2)	3 (5.2)
Other	7 (20.6)	6 (18.2)	11 (37.9)	6 (24.0)	18 (28.6)	12 (20.7)
All	17 (50.0)	16 (48.5)	21 (72.4) ^a	10 (40.0)	38 (60.3)	26 (44.8)

^aSignificantly higher than the supportive/placebo group, $p < 0.05$; no significant difference in any parameters among the other groups.

Discussion

Naltrexone had significant benefits over placebo when used in conjunction with coping therapy on the preassigned endpoint measure: it reduced the rate of relapse into heavy drinking during the test period in the coping groups. Naltrexone did not significantly affect the ingestion of the first drink (either time to first drink or total abstinence rate).

The study design, and possibly the nature of the cognitive coping skills and supportive group therapy, led to high retention, completion, and compliance in all treatment groups. This, combined with a low level of missing data and high internal validity, led to sufficient statistical power for determining differences between groups. Thus, a significant difference was present in our total material without modification for completion or compliance.

Overall, the results of this trial support the observations made in earlier trials¹⁻⁴ and particularly those reported from the recent clinical trial in Sweden.^{13, 14} The general conclusion from the Swedish trial and from ours is that naltrexone can be beneficial in the treatment of alcoholism, but only in combination with a suitable behavioral therapy. Both trials have found significant benefits of naltrexone over placebo when used in conjunction with coping therapy, but neither has found any significant benefits from naltrexone used together with supportive therapy. This conclusion also can be made with regard to the original study of O'Malley and colleagues.²

The fundamental major difference between the two therapies was that the coping groups received cognitive-behavioral therapy that did not demand abstinence as a firm goal of treatment, whereas abstinence was strongly emphasized in the supportive groups. Animal studies have also found that naltrexone was most effective when paired with alcohol drinking.^{15, 16} This seems reasonable because naltrexone is generally believed to affect alcohol drinking by blocking the effects of endorphins released by alcohol, and this only occurs after

drinking. The finding in this study and in nearly all previous clinical trials that naltrexone did not significantly delay the time to the first drink is also consistent with the conclusion that during abstinence, naltrexone is not helping to prevent drinking from starting again.¹⁷ Two mechanisms have been suggested for why naltrexone is more effective in conjunction with drinking than with abstinence. First, drinking alcohol while the reinforcement is blocked by naltrexone should extinguish the drinking behavior.¹⁵ Second, naltrexone may allow the person with alcohol dependence to keep at least partial control over alcohol consumption after a slip drinking episode, either because it can reduce the euphoria^{3, 6} or block the stimulatory effect¹⁸ from the alcohol in the first drink that otherwise may encourage further imbibing.

The results demonstrate the safety and effectiveness of naltrexone in patients with alcohol dependence who have not first undergone detoxification and withdrawal. Naltrexone has previously been used without detoxification in open-label studies,¹⁹⁻²¹ but this is the first controlled study to use naltrexone with patients addicted to alcohol who were currently drinking. Little or no cross-dependence has previously been found between alcohol and opiate addictions. In agreement with this, no serious reactions were observed with the onset of medication in this study. Indeed, naltrexone seemed to be somewhat better tolerated than in previous clinical trials^{1, 2} in which naltrexone was used after detoxification. Here there was no overall significant difference between the naltrexone and placebo groups in the number of patients reporting side effects, primarily because it was so well tolerated in the coping/naltrexone group. The ability to use naltrexone without prior alcohol withdrawal is of particular relevance from a public health standpoint¹⁷ because it increases the total number of patients who can be treated.

During the targeted-medication phase (last 20 weeks), the only significant difference in the number of pills taken weekly was that the supportive/naltrexone group

consumed significantly more than the coping/naltrexone group. Because the instructions were to take a pill only when craving alcohol, the result suggests that the supportive/naltrexone group was craving alcohol more frequently than were the patients in the coping/naltrexone group. It also demonstrates that the superior relapse results in the coping/naltrexone group were not caused by their taking more naltrexone.

The benefits from naltrexone together with coping therapy that developed during the first 12 weeks of continual medication persisted during the subsequent 20 weeks of targeted medication when naltrexone was taken only when drinking was likely. Targeted naltrexone has previously been used in animal experiments²² and open-label studies,^{17, 20} but this is the first controlled clinical trial to demonstrate its efficacy. Comparison of the earlier clinical trials lasting 12 weeks,^{1, 2, 4} the Swedish trial lasting 24 weeks,¹³ and this 32-week treatment shows that naltrexone continues to provide benefits over placebo as long as the medication is given, but follow-up studies indicate that the benefits disappear gradually during the weeks after the medication is terminated.^{10, 13, 14} This suggests that naltrexone treatment should continue indefinitely. Taking the medication every day is, however, expensive and is more likely to produce supersensitivity of the opioid receptors and other side effects. Our finding that taking naltrexone only when craving is high is still effective provides a less expensive and perhaps safer solution for continued alcoholism treatment.

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References

- Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 1992;49:876-80.
- O'Malley SS, Jaffe AJ, Chang G, et al. Naltrexone and coping skills therapy for alcohol dependence. *Arch Gen Psychiatry* 1992;49:881-7.
- Volpicelli JR, Rhines KC, Rhines JS, et al. Naltrexone and alcohol dependence: role of subject compliance. *Arch Gen Psychiatry* 1997;54:737-42.
- Anton RF, Moak DH, Waid LR, et al. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. *Am J Psychiatry* 1999;156:1758-64.
- Volpicelli JR, Watson NT, King AC, et al. Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995;152:613-5.
- O'Malley SS, Jaffe AJ, Rode S, et al. Experience of a "slip" among alcoholics treated with naltrexone or placebo. *Am J Psychiatry* 1996;153:281-3.
- Hyttiä P, Sinclair JD. Responding for oral ethanol after naloxone treatment by alcohol-preferring AA rats. *Alcohol Clin Exp Res* 1993;17:631-6.
- Weiss F, Mitchiner M, Bloom FE, et al. Free-choice responding for ethanol versus water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine, and methysergide. *Psychopharmacology (Berl)* 1990;101:178-86.
- Sinclair JD. Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol Alcohol* 2001;36:2-10.
- O'Malley SS, Jaffe AJ, Chang G, et al. Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Arch Gen Psychiatry* 1996;53:217-24.
- O'Malley SS, Croop RS, Wroblewski JM, et al. Naltrexone in the treatment of alcohol dependence: a combined analysis of two trials. *Psychiatry Ann* 1995;25:681-8.
- Koski-Jännes A. Alcohol addiction and self-regulation. A controlled trial of a relapse prevention program for Finnish inpatient alcoholics [academic dissertation], vol 41. Helsinki, Finland: The Finnish Foundation for Alcohol Studies, 1992.
- Balldin J, Berglund M, Borg S. A randomized 6 month double-blind placebo-controlled study of naltrexone and coping skills education programme [abstract]. *Alcohol Alcohol* 1997;32:325.
- Månsson M, Balldin J, Berglund M, et al. Six-month follow-up of interaction effect between naltrexone and coping skills therapy in outpatient alcoholism treatment [abstract]. *Alcohol Alcohol* 1999;34:454.
- Sinclair JD. Drugs to decrease alcohol drinking. *Ann Med* 1990;22:357-362.
- Sinclair JD. Laboratory animal research in the discovery and development of the new alcoholism treatment using opioid antagonists. *Scand J Lab Anim Sci* 1996;23[suppl 1]:379-90.
- Sinclair JD. New treatment options for substance abuse from a public health viewpoint. *Ann Med* 1998;30:406-11.
- Kiianmaa K, Hoffman PL, Tabakoff B. Antagonism of the behavioral effects of ethanol by naltrexone in BALB/c, C57BL/6, and DBA/2 mice. *Psychopharmacology (Berl)* 1983;79:291-4.
- Bohn MJ, Kranzler HR, Beazoglou D, et al. Naltrexone and brief counseling to reduce heavy drinking. *Am J Addict* 1994;3:91-9.
- Kranzler HR, Tennen H, Penta C, et al. Targeted naltrexone treatment of early problem drinkers. *Addict Behav* 1997;22:431-6.
- Maxwell S, Shinderman MS. Use of naltrexone in the treatment of alcohol use disorders in patients with concomitant mental illness. *J Addict Dis* 2000;19:61-9.
- Sinclair JD, Vilamo L, Jakobson B. Selective extinction of alcohol drinking in rats with decreasing doses of opioid antagonists. *Alcohol Clin Exp Res* 1994;18:489-93.