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REVIEW ARTICLE

Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials

Manit Srisurapanont and Ngamwong Jarusuraisin

Department of Psychiatry, Faculty of Medicine, Chiang Mai University, Amphur Muang, Chiang Mai 50200, Thailand

Abstract

Many trials of naltrexone have been carried out in alcohol-dependent patients. This paper is aimed to systematically review its benefits, adverse effects, and discontinuation of treatment. We assessed and extracted the data of double-blind, randomized controlled trials (RCTs) comparing naltrexone with placebo or other treatment in people with alcoholism. Two primary outcomes were subjects who relapsed (including heavy drinking) and those who returned to drinking. Secondary outcomes were time to first drink, drinking days, number of standard drinks for a defined period, and craving. All outcomes were reported for the short, medium, and long term. Five common adverse effects and dropout rates in short-term treatment were also examined. A total of 2861 subjects in 24 RCTs presented in 32 papers were included. For short-term treatment, naltrexone significantly decreased relapses [relative risk (RR) 0.64, 95% confidence interval (CI) 0.51–0.82], but not return to drinking (RR 0.91, 95% CI 0.81–1.02). Short-term treatment of naltrexone significantly increased nausea, dizziness, and fatigue in comparison to placebo [RRs (95% CIs) 2.14 (1.61–2.83), 2.09 (1.28–3.39), and 1.35 (1.04–1.75)]. Naltrexone administration did not significantly diminish short-term discontinuation of treatment (RR 0.85, 95% CI 0.70–1.01). Naltrexone should be accepted as a short-term treatment for alcoholism. As yet, we do not know the appropriate duration of treatment continuation in an alcohol-dependent patient who responds to short-term naltrexone administration. To ensure that the real-world treatment is as effective as the research findings, a form of psychosocial therapy should be concomitantly given to all alcohol-dependent patients receiving naltrexone administration.

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Introduction

Alcoholism (alcohol dependence and abuse) is a common health problem. Its health, social, and economic consequences are usually devastating. Although many individuals do achieve long-term sobriety with therapy, others continue to relapse and deteriorate despite multiple courses of treatment.

Due to the limited success of psychosocial treatment programmes (Berglund et al., 2003), several pharmacological agents have been studied in people with alcoholism. Disulfiram has only limited clinical utility for those with high motivation, good health, and good cooperation. Even in highly motivated individuals, disulfiram may partially improve alcohol-dependent patients in some respects, e.g. drinking frequency and amount of alcohol consumption (Garbutt et al., 1999). While the results of some studies showed that lithium reduced drinking in alcohol-dependent patients with mood disorders (Fawcett et al., 1984; Merry et al., 1976), a randomized controlled trial (RCT) failed to demonstrate any benefit of this drug in either depressed or non-depressed patients (Dorus et al., 1989). The efficacy of selective serotonin reuptake inhibitors (SSRIs) remains to be tested in placebo-controlled, randomized trials with large sample sizes. Acamprosate is a promising medication, but it has not been widely approved (Overman et al., 2003).

The interaction of alcohol and the opioid system has not been fully understood because the interaction between ethanol and the mechanistic processes associated with opioid production, secretion, and binding is relatively complex (Herz, 1997). However, most animal studies suggest that the competitive binding of opioid antagonists to opioid receptors may have the propensity to diminish the rewarding effects by decreasing the dopamine released in the mesolimbic

Address for correspondence: M. Srisurapanont, M.D., Professor of Psychiatry, Department of Psychiatry, Faculty of Medicine, Chiang Mai University, Amphur Muang, Chiang Mai 50200, Thailand.
Tel.: (66-53) 945422 *Fax*: (66-53) 945426 or (66-53) 217144
E-mail: msrisura@mail.med.cmu.ac.th

pathway (Spanagel and Zieglgansberger, 1997). Due to these findings, many clinical trials have investigated both the harm and benefit of opioid antagonists in people with alcoholism. Among them, naloxone has a very short half-life and, therefore, very limited clinical utility. Nalmefene has been examined in at least two RCTs, but is not yet approved (Mason et al., 1994, 1999). Naltrexone is the agent studied most, and it has been approved for the treatment of alcoholism in several countries. We, therefore, proposed to systematically review its benefits, adverse effects, and discontinuation of treatment for alcoholism.

Methods

Inclusion criteria

This review included all double-blind RCTs that compared naltrexone with placebo and/or other treatment in people with alcohol dependence or abuse. Subjects with alcohol dependence or abuse had to be diagnosed by the use of clearly defined diagnostic systems, e.g. DSM-III, DSM-III-R, DSM-IV, and ICD-10. All data of the patients were included regardless of age, gender, nationality, comorbidity, and hospitalization status. No language or publication restriction was applied.

Outcomes

Two primary outcomes were subjects who relapsed (including heavy drinking) and those who returned to drinking. We assigned these outcomes as being primarily beneficial because they are of concern for most researchers, clinicians, and patients. In addition, as dichotomous data, they can be interpreted and understood easily. Secondary outcomes were time to first drink, drinking days (in % or number), number of standard drinks for a defined period (e.g. week, study duration, and drinking day), and craving. As alcoholism is a chronic disease with a high relapse rate, all outcomes were reported for the short- (up to and including 12 wk), medium- (more than 12 wk and up to and including 12 months) and long-term (more than 12 months). For any outcome assessed more than once in a particular term, we extracted results of the longest duration only.

The analysis also included short-term adverse effects and discontinuation of treatment because of their importance in this treatment period. The five new-onset adverse clinical events most frequently found in the largest comparison, but not in a randomized trial of naltrexone, were examined (Croop et al., 1997). They comprised nausea, headache, dizziness, fatigue, and nervousness.

Locating trials

To look into the comparative trials, we used four electronic databases (MEDLINE, EMBASE, CINHAL, and the Cochrane Central Register of Controlled Trails) in September 2003. The terms used to identify articles were [naltrexone *or* narcotic antagonist *or* opioid antagonist] *and* [alcohol *or* ethanol]. To identify further reports, we checked the references of this preliminary list of selected studies along with references of other relevant review papers. Du Pont Pharmaceutical, the only producer of naltrexone, was contacted for information about unpublished trials. Of all papers found, only RCTs comparing naltrexone with placebo and/or other treatment in people with alcohol dependence or abuse were included.

Quality assessment of included trials and data extraction

We assessed the methodological quality of each trial included by examining its randomization (Schulz et al., 1995). Trial characteristics and the data relevant to the reviewed outcomes were extracted and recorded in a data record form. If the data in each study were relevant to two primary, four secondary, five adverse, or dropout outcomes presented in figures, they would be extracted. Because treatment or the controlled group of some studies was divided into a number of subgroups (mostly due to the difference of concomitant treatment), a continuous outcome of these subgroups could not be combined as an outcome of the whole group. In this case, the outcome of the subgroup receiving the most rigorous treatment, e.g. highest dose of drug treatment and most intensive psychotherapy, was used to represent the group.

Statistical analysis

A relative risk (RR) with 95% confidence interval (CI) was an effect measure used for dichotomous outcomes. A number-needed-to-treatment (NNT) and number-needed-to-harm (NNH) were also computed for outcomes, with a significantly different benefit and more adverse effects respectively.

A weighted mean difference (WMD) with 95% CI was used to synthesize the outcomes of time to first drink and drinking days. The outcomes relevant to standard drinks and craving were likely to be measured by various units (e.g. standard drinks per week, per month, or per drinking day) or scales (e.g. a

visual analogue scale or specially designed rating scales for craving) and, therefore, combined by using standardized mean differences (SMDs) with 95% CIs.

The data synthesis was done on an intention-to-treat basis. Because the results obtained from a random effect model of data synthesis might be more generalized, this model was used throughout the review for calculating RRs, WMDs, and SMDs (DerSimonian and Laird, 1986). The inconsistency of data was examined by looking at the graphical display of the results and also by using an *I*-square (I^2) (Higgins et al., 2003). As recommended, an I^2 of 75% or more indicates high inconsistency of data. To test the robustness of the results, relative to features of the primary studies (those carried out only in individuals with alcoholism), a sensitivity analysis was performed to examine the results including and excluding the studies conducted in alcohol-dependent patients with comorbidity. The statistical analysis was performed by the use of Review Manager 4.2 (Cochrane Collaboration, Oxford, England).

Results

Study inclusion and characteristics

Our searches found 28 RCTs of naltrexone in people with alcohol dependence or abuse. We excluded four studies not using the double-blindness design (Lee et al., 2001; Rubio et al., 2001, 2002) and a clearly defined diagnostic system (Huang et al., 2002). Twenty-four papers were identified as original articles presenting main findings of 24 RCTs (see Table 1). Eight papers were classified as duplicated reports presenting only additional data or representing the data (Anton et al., 2001; Jaffe et al., 1996; Modesto-Lowe et al., 1997; O'Malley et al., 1996a,b; Oslin et al., 1997a; Rohsenow et al., 2000; Volpicelli et al., 1995) of six original papers (Anton et al., 1999; Hersh et al., 1998; Monti et al., 2001; O'Malley et al., 1992; Oslin et al., 1997b; Volpicelli et al., 1992). Although some data presented in duplicated papers were also included in this review, the following parts referenced only the original articles to cause less confusion. It was noted that a nested sequence of three trials presented in a paper was considered as a trial, since the subjects in all three trials were the same (O'Malley et al., 2003). In this study, the investigators started by conducting a 10-wk RCT comparison of naltrexone + primary care management (PCM) and naltrexone + cognitive–behavioural therapy (CBT) and placebo, followed by two 24-wk RCTs in those responding to first trial treatment.

The total number of subjects included in this review was 2861. Of those, 1709 were assigned to receive naltrexone treatment. All trials diagnosed the subjects by using DSM-III-R or DSM-IV. Apart from 82 patients with dual alcohol and cocaine dependence or abuse in two trials (Carroll et al., 1993; Hersh et al., 1998) and six individuals with alcohol abuse in a study (Chick et al., 2000), all other subjects were alcohol-dependent patients. All were aged 18 yr or more. The sample sizes of most trials were between 10–99 in each arm. While one study had only nine subjects in each arm (Carroll et al., 1993), two trials had 100–200 subjects in each arm (Guardia et al., 2002; Krystal et al., 2001).

Only a few studies stated clearly the locations or countries in which the studies were carried out. According to the investigators' affiliations, it was understood that 14 studies were conducted in North American (including Puerto Rico), seven in Europe, one in Asia, and two in Australia.

Of 24 RCTs, only five provided the details of techniques used for randomization (Balldin et al., 2003; Kiefer et al., 2003; Latt et al., 2002; O'Malley et al., 2003; Volpicelli et al., 1997). With regard to study duration, only eight trials were carried out for longer than 12 wk (Anton et al., 1999; Balldin et al., 2003; Heinala et al., 2001; Knox and Donovan, 1999; Landabaso et al., 1999; Monti et al., 2001; O'Malley et al., 1992, 2003).

Of the 24 RCTs included in this review, only two did not have a placebo arm (Carroll et al., 1993; Landabaso et al., 1999). Apart from three trials (Galarza et al., 1997; Landabaso et al., 1999; Oslin et al., 1997b), naltrexone in all studies was administered daily at a dose of 50 mg/d. It was noted that one trial gave naltrexone continuously in the first 3 months and as targeted medication (only when alcohol consumption was likely) in the last 3 months (Heinala et al., 2001). All trials clearly defined the psychosocial treatment concomitantly given with naltrexone. While a trial gave a simple psychosocial treatment called medical advice (Latt et al., 2002), each of the remainder gave at least one form of intensive psychosocial treatment, e.g. coping skills and CBT.

Regarding the outcome measures, those related to drinking behaviour were reported in figures in most trials. Seven (Ahmadi and Ahmadi, 2002; Chick et al., 2000; Kiefer et al., 2003; Kranzler et al., 2000; Monti et al., 2001; Morris et al., 2001; O'Malley et al., 1992) and three trials (Hersh et al., 1998; Kiefer et al., 2003; Morris et al., 2001) presented the outcomes of subjects with relapses and return to drinking in graphs and *p* values respectively. Therefore, these data could not be included in the analysis. Functional outcomes were presented in only one trial (Knox and Donovan, 1999). No trial reported the outcome of patient satisfaction,

Table 1. Characteristics of RCTs comparing naltrexone with placebo or other treatment in people with alcoholism

Authors	Methods	Subjects	Interventions
O'Malley et al. (1992)	Double-blind, placebo-controlled, 12-wk study with 6-month follow-up after the completion of 12-wk treatment in the USA	Outpatients with alcohol dependence (DSM-III-R), 18–68 yr old	50 mg/d naltrexone + coping skills ($n = 29$) vs. 50 mg/d naltrexone + supportive therapy ($n = 23$) vs. placebo + coping skills ($n = 25$) vs. placebo + supportive therapy ($n = 27$); no intervention given during follow-up period
Volpicelli et al. (1992)	Double-blind, placebo-controlled, 12-wk study in the USA	Outpatients with alcohol dependence (DSM-III-R); 21–65 yr old	50 mg/d naltrexone ($n = 35$) vs. placebo ($n = 35$); all received rehabilitation treatment
Carroll et al. (1993)	Double-blind, 12-wk study in the USA	Outpatients with dual alcohol and cocaine dependence or abuse (DSM-III-R), no age specified	50 mg/d naltrexone ($n = 9$) vs. disulfiram ($n = 9$); all received weekly individual psychotherapy
Galarza et al. (1997)	Double-blind, placebo-controlled, 4-wk study in Puerto Rico	Outpatients with alcohol dependence (DSM-IV); 21–75 yr old; male only	Naltrexone (undefined dose) ($n = 10$) vs. placebo ($n = 10$); all received regular psychosocial treatment
Oslin et al. (1997b)	Double-blind, placebo-controlled, 12-wk study in the USA	Patients with alcohol dependence (DSM-III-R); 50–70 yr old	100 mg/d naltrexone on Monday/Wednesday and 150 mg naltrexone on Friday ($n = 21$) vs. placebo ($n = 23$); all received weekly group therapy and bi-weekly case management
Volpicelli et al. (1997)	Double-blind, placebo-controlled, 12-wk study in the USA	Outpatients with alcohol dependence (DSM-III-R); 21–65 yr old	50 mg/d naltrexone ($n = 48$) vs. placebo ($n = 49$); all received individual psychotherapy and counselling
Hersh et al. (1998)	Double-blind, placebo-controlled, 8-wk study in the USA	Patients with dual alcohol and cocaine dependence or abuse (DSM-III-R); 18–45 yr old	50 mg/d naltrexone ($n = 31$) vs. placebo ($n = 33$); all received individual relapse prevention psychotherapy
Anton et al. (1999)	Double-blind, placebo-controlled, 12-wk study with a 14-wk follow-up after the completion of 12 wk treatment in the USA	Outpatients with alcohol dependence (DSM-III-R); 21–65 yr old	50 mg/d naltrexone ($n = 68$) vs. placebo ($n = 63$); all received weekly CBT; no intervention given during follow-up period
Knox and Donovan (1999)	Double-blind, placebo-controlled, 6-month study in the USA	Patients with alcohol dependence (DSM-IV); 18–65 yr old	50 mg/d naltrexone ($n = 31$) vs. placebo ($n = 32$); all received 21 d in-patient chemical dependency treatment followed by a 6-month outpatient programme
Landabaso et al. (1999)	Double-blind, 24-month study in Spain	Patients with alcohol dependence (DSM-IV); mean age = 30.6 yr old	25 mg/d naltrexone + an aversive agent ($n = 15$) vs. an aversive agent alone ($n = 15$); 6-month naltrexone treatment; 12-month aversive therapy
Chick et al. (2000)	Double-blind, placebo-controlled, multicentre, 12-wk study in the UK	Outpatients with alcohol dependence or abuse (DSM-III-R); 18–65 yr old	50 mg/d naltrexone ($n = 90$) vs. placebo ($n = 85$); all received the usual psychosocial treatment programme

Table 1 (*cont.*)

Authors	Methods	Subjects	Interventions
Johnson et al. (2000)	Double-blind, placebo-controlled, 8-wk study in the USA	Outpatients with alcohol dependence (DSM-IV) with age of alcoholic onset <25 yr old, age 25–65 yr old	50 mg/dnaltrexone + ondansetron 4 μg/kg ($n=10$) vs. placebo ($n=10$); all participants received group CBT
Kranzler et al. (2000)	Double-blind, placebo-controlled, 11-wk study in the USA	Patients with alcohol dependence (DSM-III-R); 18–60 yr old	50 mg/d naltrexone ($n=61$) vs. 400–600 mg/d nefazodone ($n=59$) vs. placebo ($n=63$); all received coping skill training
Heinala et al. (2001)	Double-blind, placebo-controlled, 12-wk regular treatment study with 20-wk targeted medication treatment in Finland	Outpatients with alcohol dependence (DSM-IV); 21–65 yr old	First 12 wk, 50 mg/d naltrexone ($n=63$) vs. placebo ($n=58$) + either cognitive coping skill ($n=67$) or supportive psychotherapy ($n=54$); for 20 wk duration, naltrexone (undefined dose) given only when alcohol drinking was likely (targeted medication)
Krystal et al. (2001)	Double-blind, placebo-controlled, 12-wk study in the USA	Outpatients with alcohol dependence (DSM-IV), >18 yr old	50 mg/d naltrexone for 12 months ($n=209$) vs. 50 mg/d naltrexone for 3 months followed by a placebo for 9 months ($n=209$); all received 12-step facilitation counselling
Monti et al. (2001)	Double-blind, placebo-controlled, 12-month study in the USA	Outpatients with alcohol dependence (DSM-IV), mean age of 39.2 yr old	50 mg/d naltrexone ($n=64$) vs. placebo ($n=64$) for 12 wk; all received 1–2 wk of CET + CST or ERC
Morris et al. (2001)	Double-blind, placebo-controlled, 12-wk study in Australia	Outpatients alcohol dependence (DSM-III-R), 18–65 yr old	50 mg/d naltrexone ($n=55$) vs. placebo ($n=56$); all received group psychoeducation and social support
Ahmadi and Ahmadi (2002)	Double-blind, placebo-controlled, 12-wk study in Iran	Outpatients with alcohol dependence (DSM-IV), 23–56 yr old; male only	50 mg/d naltrexone ($n=58$) vs. placebo ($n=58$); all received individual counselling and relapse prevention programme
Gastpar et al. (2002)	Double-blind, placebo-controlled, multicentre, 12-wk study in Germany	Out- and in-patients with alcohol dependence (DSM-III-R); mean age (SD) = 42.7 (9.7) yr	50 mg/d naltrexone ($n=87$) vs. placebo ($n=84$); all received psychosocial alcoholic treatment programme
Guardia et al. (2002)	Double-blind, placebo-controlled, multicentre, 12-wk study in Spain	Outpatients with alcohol dependence (DSM-IV); 18–60 yr old	50 mg/d naltrexone ($n=101$) vs. placebo ($n=101$); all received rehabilitation treatment
Latt et al. (2002)	Double-blind, placebo-controlled, multicentre, 12-wk study in Australia	Patients with alcohol dependence (DSM-IV); 18–70 yr old	50 mg/d naltrexone ($n=56$) vs. placebo ($n=51$); all received medical advice
Balldin et al. (2003)	Double-blind, placebo-controlled, multicentre, 6-month study in Sweden	Outpatients with alcohol dependence (DSM-IV); 18–65 yr old	50 mg/d naltrexone + CBT ($n=25$) vs. 50 mg/d naltrexone + supportive therapy ($n=31$) vs. placebo + CBT ($n=30$) vs. placebo + supportive therapy ($n=32$)

[*continued overleaf*

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