

NALTREXONE, A RELAPSE PREVENTION MAINTENANCE TREATMENT OF ALCOHOL DEPENDENCE: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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(Received 20 October 2000; in revised form 19 April 2001; accepted 19 May 2001)

Abstract — The objective of this study was to review the evidence for the efficacy and toxicity of naltrexone, a treatment of alcohol dependence. A systematic review and meta-analysis of randomized controlled trials of naltrexone used in the treatment of alcohol dependence was conducted. We searched MEDLINE, EMBASE, PsychLIT and the Cochrane Controlled Trials Registry for articles published between 1976 to January 2001. The manufacturer of naltrexone was asked to submit additional complete trial reports not in the literature. We analysed data from seven studies that compared naltrexone to placebo. The meta-analysis of benefit indicates that naltrexone is superior to placebo. Subjects treated with naltrexone experience significantly fewer episodes of relapse, and significantly more remain abstinent when compared to placebo-treated subjects {risk difference of relapse rates = -14% [95% confidence interval (CI): -23%, -5%]; and risk difference of abstinence rates = 10% (95% CI: 4%, 16%)} after 12 weeks of treatment. The naltrexone-treated subjects also consume significantly less alcohol over the study period than do placebo-treated subjects. There is no significant difference between naltrexone and placebo in terms of the number of subjects with at least one adverse event or the number of subjects who discontinued the trial due to an adverse event.

INTRODUCTION

Following successful alcohol withdrawal, most alcohol-dependent patients enter a psychosocial rehabilitation programme that aims to reduce or eliminate the desire to drink (i.e. relapse prevention). Although psychosocial treatments are effective in reducing alcohol consumption and in maintaining abstinence in many patients, a substantial proportion of patients resume drinking within a year after treatment (Swift, 1999). Therefore psychosocial therapy is often combined with pharmacological therapy to improve success rates.

Naltrexone is an opioid receptor antagonist (a substance that blocks opioid receptors in the brain without itself producing positive effects), and a new pharmacological relapse-prevention agent employed as an adjunct to psychosocial therapies in the treatment of alcohol dependence. Its exact mode of action is not clearly defined. However, some studies have shown that the craving or reinforcing properties of drinking alcohol is related in part to increases in endogenous opioid activity following alcohol use. This has been a postulated mechanism of action for the opioid antagonist therapies reported by Schaffer and Naranjo (1998). Reductions in craving are associated with longer abstinence (Swift, 1999). Genetic differences have also been detected with respect to endogenous opioid responses to alcohol intake and the risk of alcoholism (Gianoulakis and de Waele, 1994).

The efficacy of naltrexone, as an effective adjunct in the treatment of alcohol dependence, has been demonstrated in a number of published trials (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992, 1995a). These trials suggested that, when the drug is taken daily, it appears to reduce the number of occasions during which a person is likely to drink, and to reduce the amount of alcohol consumed during any one occasion when they do drink. Naltrexone is now available in Australia as a 'relapse-preventing' agent for patients who are receiving

rehabilitative treatment for alcohol dependence. The purpose of this meta-analytical review is to evaluate the aggregate efficacy and potential toxicity of naltrexone, compared to placebo, as an adjunct treatment of alcohol dependence. Both published and unpublished randomized controlled trials (RCTs) of naltrexone were used.

METHODS

Data sources

We performed a comprehensive literature search of MEDLINE and EMBASE for English-language articles published from 1976 up to the most recent database available for on-line searching as at January 2001 on the use of naltrexone in the treatment of alcohol dependence. The search terms used included 'naltrexone' (exploded); 'randomized controlled trial' or 'random allocation' or 'all random'; 'human', 'alcohol' and 'English language'. A similar search was also carried out using the PsychLIT database and the Cochrane Controlled Trials Registry. The retrieved abstracts were printed off, and duplicate articles were removed. Bibliographies of relevant articles were manually examined for additional RCTs. The manufacturer of naltrexone was asked to contribute any additional complete reports of RCTs not already identified in the medical literature. Discussions were also held with key investigators in the field.

Study selection

Studies were considered for the meta-analysis if they were RCTs involving patients (adults ≥ 18 years of age) with a diagnosis of alcohol dependence or abuse alone [defined by DSM-III-R (American Psychiatric Association, 1987) for alcohol dependence or abuse] from both in-patient and out-patient settings, and compared naltrexone 50 mg daily with placebo or another active drug licensed in Australia. The trials were included if they measured the following relevant clinical endpoints (i.e. at least: relapse rates, abstinence rates and

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percentage of patients discontinuing due to adverse events or percentage of patients with at least one adverse event), and the active treatment period was a minimum length of 3 months. In addition, the trial reports were of studies with complete databases. Studies for which only conference proceedings were available for detail were excluded.

Data extraction

To obtain data for our evidence tables, we developed a data extraction form, a follow-up results form, and a trial methodology quality-rating form. The data extractor, although not blinded to any aspect of the publication or report, was experienced at abstracting data from clinical trial reports. Data were extracted regarding the participants, the setting, details of the intervention, the outcomes (including adverse events) and the methodological quality of the studies.

Description of outcomes

The parameters for the evaluation of efficacy used in this analysis include: relapse rates, abstinence rates, and, as measures of alcohol consumption during the trial, the mean percentage of reported drinking days per subject, and the mean number of drinks per drinking day per subject.

With respect to safety and tolerability data, we summarized both the numbers and incidence of subjects who discontinued the trial due to an adverse event, and the number of subjects reporting at least one adverse event. The numbers of subjects to report at least one adverse event were measured only during the treatment phase of the trials.

In this evaluation, the term 'full analysis set' (FAS) is used to describe the study populations included in the efficacy and safety analyses. The 'full analysis set' includes all patients randomized to treatment who received at least one dose of the assigned treatment. This term is as close as possible to the intention-to-treat (ITT) ideal of including all randomized subjects (Food and Drug Administration, 1998).

Transformation of survival analysis data to rates of abstinence or non-heavy drinking

Studies 004, 005 and 007 did not directly report relapse and abstinence rates, but instead reported the time to first heavy drinking episode or time to first alcoholic drink episode respectively. The survival analysis data provide us with the percentage of subjects who at 12 weeks had remained abstinent (i.e. time to first drink) or who had not yet relapsed (i.e. time to first relapse drinking). The relapse rate was determined by subtracting from 100 the percentage of subjects at 12 weeks who had not yet relapsed. From these percentages we could calculate the actual number of subjects who fulfilled the outcome, using the total number of subjects in each treatment arm.

Methodological quality of the studies

The individual studies are rated for quality with the use of a quality rating score (summarized in Table 1). The quality rating score is comprised of seven factors: (1) level of security of the randomization method (scale: 0, not stated; 0.5, under investigator control, e.g. sealed enveloped; 1, by pharmacy, central registry or using blinded drug supply); (2) whether comparable groups were achieved at baseline through randomization (scale: 0, not stated or potentially important between-group differences; 1, comparable groups); (3) the degree of blinding

(scale: 0, open; 0.5, single-blind with respect to patient; 1, blinded observer; 2, double-blind); (4) adequacy of follow-up [scale: 0, significant number of drop-outs (no trial assessment), rates different between groups; 1, some drop-outs (no trial assessment), equivalent rates between groups; 2, assessment in all patients who were not lost to follow-up]; (5) adequacy in describing the inclusion/exclusion criteria and concomitant therapy (scale: 0, no; 0.5, partially; 1, fully); (6) the reliability of outcomes assessment (scale: 0, method not stated; 1, sub-optimal but acceptable; 2, highly accurate method, e.g. antibody titre); and (7) the comprehensiveness of the data analysis, specifically whether follow-up of drop-outs (withdrawals and lost to follow-up) was sufficient to allow ITT analysis as well as per protocol (scale: 0, per protocol only; 1, per protocol for key efficacy criteria, with ITT for safety; 3, ITT for efficacy and safety). The maximum score is 12 (range 0–12). In calculating the score, each quality rating is given equal weighting. The quality rating for each study is dependent on the amount of information provided by each trial report. The assessment of quality is performed independently of the study's findings on efficacy of the pharmacological intervention.

In this analysis, the quality ratings are used purely as descriptive information, since all studies have been rated similar scores and are ultimately given the same weight in the meta-analysis.

Methodology of pooling results

The key comparison of interest is between naltrexone and placebo. Data on comparisons between naltrexone and other drugs licensed in Australia are not available for analysis. Only randomized double-blind trials are included in the analysis. The meta-analysis of the endpoints is necessarily limited to those studies with outcomes presented in a comparable way. In addition, for the studies to be included in the meta-analysis, the mean results had to report their standard deviation where indicated in the paper or were obtainable from the authors.

Risk difference and relative risk meta-analyses were performed on naltrexone-versus-placebo-treated patients to examine the treatment effect for each of the main outcomes. The pooled risk difference and pooled relative risk estimates were calculated using the RevMan 4.1 software package (Cochrane Collaboration, 2000). Mantel-Haenszel fixed-effects modelling was used and heterogeneous results were checked with a Der Simonian and Laird random-effects model (Der Simonian and Laird, 1986; Robins *et al.*, 1986). The χ^2 -test was performed to detect whether the individual trial results were homogeneous.

For the continuous variables, mean percentage of drinking days per subject and mean number of drinks per drinking day per subject, the effect sizes were calculated for each study as the weighted mean difference (WMD) along with its 95% confidence intervals (CIs) using both the fixed effects (inverse variance methodology) and random effects (Der Simonian and Laird methodology) models. These results were also tested for homogeneity using the χ^2 -test as outlined above.

RESULTS

Results of the literature search

Of the 71 references identified by the electronic search, 13 articles met the inclusion criteria for this meta-analysis,

Table 1. Summary of all studies included in the meta-analysis

Study no.	Type of report referred to in this analysis	Other references to the same study	Location of study (multi/single centre)	No. of subjects randomized	Subjects and diagnostic instrument	Level of blinding	Weeks of treatment	Principal outcomes	Quality rating
001	Journal article (Volpicelli <i>et al.</i> , 1997)		Philadelphia, USA (single centre)	97	M and F; DSM-III-R	DB	12	Relapse and abstinence rates	10.5
002	Journal article (Oslin <i>et al.</i> , 1997a)	Oslin <i>et al.</i> (1997b)	USA (single centre)	44	M, DSM-III-R	DB	12	Relapse and abstinence rates	10
003	Journal article (Anton <i>et al.</i> , 1999)		South Carolina, USA (single centre)	132	M and F; DSM-III-R	DB	12	Relapse and abstinence survival analysis	10
004	Internal co. report (DuPont Merck 393-102)	Chick <i>et al.</i> (2000)	UK (6 sites)	175	M and F; DSM-III-R	DB	12	Relapse and abstinence survival analysis	10
005	Internal co. report (Dupont Merck 393-103)		Germany (7 sites)	171	M and F; DSM-III-R	DB	12	Relapse and abstinence survival analysis	10
006	Internal co. report (DuPont Merck 393-901)	O'Malley <i>et al.</i> (1992, 1996b), Jaffe <i>et al.</i> (1996)	Connecticut, USA (single centre)	105	M and F; DSM-III-R	DB	12	Relapse and abstinence survival analysis	11
007	Internal co. report (DuPont Merck 393-902)	Volpicelli <i>et al.</i> (1990 ^a , 1992, 1995a,b), O'Brien <i>et al.</i> (1996 ^b)	Philadelphia, USA (single centre)	109	M veterans Met 5 of the 9 DSM-III-R criteria	DB	12	Relapse and abstinence rates	11

^aPaper reports data from the first 30 subjects recruited into the trial.

^bIncludes non-veteran subjects.

M, male; F, female; DB, double blind; DSM-III-R, selected patients met the DSM-III-R criteria for alcohol abuse or alcohol dependence.

Quality rating: maximum score = 12.

which reported the results of six separate trials (Table 1). Four complete, unpublished, internal company reports were available from the Orphan office, Melbourne (Table 1), which included three of the published trials. When multiple citations referred to the same trial population, the report providing the most detail was included (Table 1).

All seven studies were double-blind randomized trials of 12-week duration, conducted in out-patient specialist alcohol dependence treatment units, which allowed the analysis of the comparative efficacy and adverse event profile of naltrexone compared to placebo, as adjunct to either psychosocial therapy or a standard alcohol rehabilitation programme. The type of psychosocial therapy varied between the trials (summarized in Table 2).

The mean age of patients ranged from 39 to 59 years (Table 3). The patient selection criteria of all studies were designed to produce a study population of individuals recently detoxified from alcohol with no significant psychiatric disease or co-existing drug addiction other than to alcohol. All patients were alcohol-dependent as defined by the DSM-III-R criteria.

Some differences existed between the study populations. Study 001 population recruited on average younger subjects, who had been drinking on average for fewer years. Studies 001 and 003 contained a higher percentage of employed subjects, and a large proportion of subjects in study 003 were also in a stable relationship. In contrast, subjects recruited into study 002 were considerably older, and were the least likely to be in a stable relationship. Other factors, apart from age, gender, employment status, family history, social relationships and years of drinking, may influence the success of naltrexone treatment, which have not been identified here. All studies excluded patients with a major psychiatric illness, or co-existing drug addiction.

Study-specific outcomes

Four of the seven studies reported both relapse and abstinence rates, whereas the remaining three studies reported

Table 2. Types of psychotherapy employed by the different study protocols

Study no.	Psychotherapy: type and intensity
001	Individual counselling. During the first month of treatment, subjects met with their counsellor twice per week and once per week for the remainder of the study
002	Weekly group therapy: peer support and education
003	Weekly sessions of individual manual-guided cognitive behavioural therapy
004	Less intensive psychosocial therapy: the treatment type and amount of treatment were not constrained by the study protocol
005	Psychosocial therapy: the treatment type and amount of treatment were not constrained by the study protocol, although many subjects received in-patient treatment for up to a month
006	Subjects were randomized to receive either (1) supportive therapy: individual family or group format weekly; or (2) coping skills/relapse prevention therapy: interventional programme on a weekly basis
007	Alcohol rehabilitation programme. Partial 'day treatment' for the first month, followed by twice weekly group therapy sessions

survival analysis data (i.e. the time to first heavy drinking episode or time to first alcoholic drink episode respectively). The survival analysis results were transformed to rates of non-heavy drinking or abstinence results, which were then used to calculate the proportion of subjects that relapsed or that remained abstinent in each treatment group as described above.

The definition of relapse does vary from study to study, although the common underlying element is the consumption of five or more drinks on 1 day for males, or four or more drinks on 1 day for females. Other elements of the relapse rate, such as blood-alcohol concentration and early withdrawals due to relapse, are included inconsistently between the studies. These variations in outcome definitions, although not ideal, we believe are not substantial enough to prohibit the pooling of the relapse rate estimates. In the study reports, subjects were considered abstinent if they continued the study and had no intake of alcohol throughout the duration of the 12-week time period. This is the common definition used by all seven studies.

The results of the individual trials are summarized in Table 4. Two of the seven studies individually supported the hypothesis that naltrexone significantly reduces the rate of relapse to heavy drinking, compared to placebo ($P < 0.05$), while in only one study was the abstinence rate significantly higher in the naltrexone treatment group than in the placebo treatment group (Table 4).

Pooled analysis results

The results of the pooled analysis (see Table 5) indicate that the overall treatment of alcoholism by naltrexone is more efficacious than placebo. In achieving this superiority, we have analysed the mean difference in the proportion of subjects who relapsed or who remained abstinent, and the mean difference in the percentage of reported drinking days per subject, and the number of drinks per drinking day per subject.

Risk difference for relapse rates. Both the pooled fixed and random effects estimates of the risk difference in relapse rate are negative values and their 95% confidence intervals do not include zero, indicating that the pooled relapse rate for the naltrexone is significantly less than that of placebo (at the 5% level) (Table 5, Fig. 1). On average, 14% fewer subjects taking naltrexone relapsed into heavy drinking, compared to subjects taking placebo. The χ^2 -test indicated the presence of heterogeneity, in which case the random effects model results are the most appropriate with respect to the relapse rate (Fig. 1).

Risk difference for abstinence rates. Both the pooled fixed and random effects estimates of the risk difference in abstinence rate are more than zero, and the 95% CI does not include zero, indicating that the higher abstinence rate for the naltrexone group does reach statistical significance (at the 5% level) (Table 5). On average, 10% more subjects taking naltrexone remained abstinent from alcohol consumption, compared to subjects taking placebo. There was no indication of heterogeneity, so the fixed effects model results are the most appropriate to report with respect to the abstinence rate.

Alcohol consumption outcomes. The pooled effect size of the mean difference in percentage of reported drinking days, and the number of drinks per drinking day per subject are statistically significant for both the pooled and random effects models (Table 5). Naltrexone-treated subjects consumed

Table 3. Baseline patient demographics

	Study no.													
	001		002		003		004		005		006		007	
	nalt	plac	nalt	plac	nalt	plac	nalt	plac	nalt	plac	nalt	plac	nalt	plac
No. of patients randomized (ITT)	48	49	21	23	68	64	90	85	84	87	105	87	55	54
No. of patients (FAS)	48	49	21	23	68	63	90	85	84	87	52	87	41	41
No. of patients discontinued	13	13	7	10	9	14	53	49	28	33	15	21	20	17
Mean (SD)	39	38	56.5	59	41	44	43	44	43	42	42.2	42	43	43
age (years)	(9.0)	(8.5)	(6.8)	(6.7)	(10)	(10)	(8.3)	(9.7)	(9.9)	(9.6)			(9.0)	(9.4)
% male	73.5	82.0	100	100	69	73	72.2	77.6	77.4	67.8	76.9	69.2	100	100
% employed	71.4	64.0	nr	nr	81	81	37.8	25.9	52.4	51.7	80.8	69.2	41.5	33.3
Years of drinking	15	16	nr	nr	nr	nr	23	26	22	21	nr	nr	22	22
(SD)	(8.6)	(9.7)					(8.7)	(11)	(11)	(8.4)			(1.3)	(1.5)
FHx of drinking (%)														
Primary	nr	nr	nr	nr	nr	nr	54.4	43.5	31.0	32.2	82.7	80.8	59	51
Secondary	nr	nr	nr	nr	nr	nr	14.4	22.4	19.0	24.1	42.3	46.2	32	22
Any relative	nr	nr	nr	nr	nr	nr	60.0	56.5	38.1	46.0	84.6	92.3	76	59
% married/relationship	42.9	46.0	14.3	17.4	66	70	41.1	38.8	46.5	46	50.0	30.8	26.8	32.5

nalt, naltrexone; plac, placebo; FAS ('full analysis set'), all patients who received at least one dose of randomized treatment; ITT, intention to treat; FHx, family history; nr, not reported.

Table 4. Summary of study outcomes (naltrexone versus placebo)

Study no.	No. of subjects ('full analysis set')	Relapse rates	Abstinence rates	Mean % of drinking days per subject	Mean no. of drinks per drinking day per subject
001	97	35 vs 53	44 vs 35	6.2 vs 10.8 ^a	nr
002	44	14 vs 35	71 vs 65	nr	nr
003	131	38 vs 60 ^a	47 vs 33	10 vs 18 ^a	2.5 vs 4.2 ^a
004	175	70 vs 69	18 vs 19	23.9 vs 22.8	10.2 vs 10.1
005	171	38 vs 38	54 vs 51	10.8 vs 8.6	8.4 vs 8.2
006	104	31 vs 60 ^a	52 vs 23 ^a	4.3 vs 10 ^a	nr
007	82	21 vs 41	56 vs 37	2.4 vs 6.2	nr

^aNaltrexone showed superior efficacy compared with placebo ($P < 0.05$); for the remainder, naltrexone did not show superior efficacy compared with placebo, although in absolute terms the rate was better or similar to placebo.

Table 5. Summary of pooled fixed and random effects estimates by outcome

Outcome	Pooled risk difference or effect size (95% CI)		Test of homogeneity			Pooled relative risk (95% CI)
	Fixed effects	Random effects ^c	χ^2	df	P -value	
Relapse rate (%)	-12 (-19, -6) ^{b*}	-14 (-23, -5) ^{c*}	11.9	6	0.06	0.72 (0.55, 0.94) ^{c*}
Abstinence rate (%)	10 (3.5, 16.3) ^{b*}	10 (2, 19) [*]	9.7	6	0.14	1.28 (1.08, 1.52) [*]
Difference in mean percentage of drinking days per subject (WMD) (%)	-3.0 (-5.4, -0.5) ^{d*}	-2.8 (-5.8, -0.2) [*]	5.75	4	0.22	
Difference in mean no. of drinks per drinking days per subject (WMD) (%)	-1.04 (-2.0, -0.1) ^{d*}	-1.04 (-2.0, -0.1) [*]	2.97	3	0.40	
Adverse events (AE) (%)	1 (-6, 8) ^b	2 (-6, 10) ^c	3.63	3	0.30	1.04 (0.95, 1.15)
Discontinuation due to an AE (%)	2 (-1, 5) ^b	1 (-1, 4) ^b	4.2	6	0.65	1.43 (0.82, 2.48)

^aSignificant heterogeneity between trials, therefore random effects model is most appropriate.

^bCalculated using the Mantel-Haenszel formulae for fixed effects model.

^cCalculated using the DerSimonian-Laird technique for random effects model.

^dCalculated using direct weights defined as the inverse of the variance of pooled mean effect size estimate for each study.

* $P < 0.05$.

WMD, weighted mean difference.

Comparison: 01 Efficacy

Outcome: 01 Difference in relapse rates between treatment groups (Naltrexone minus placebo)

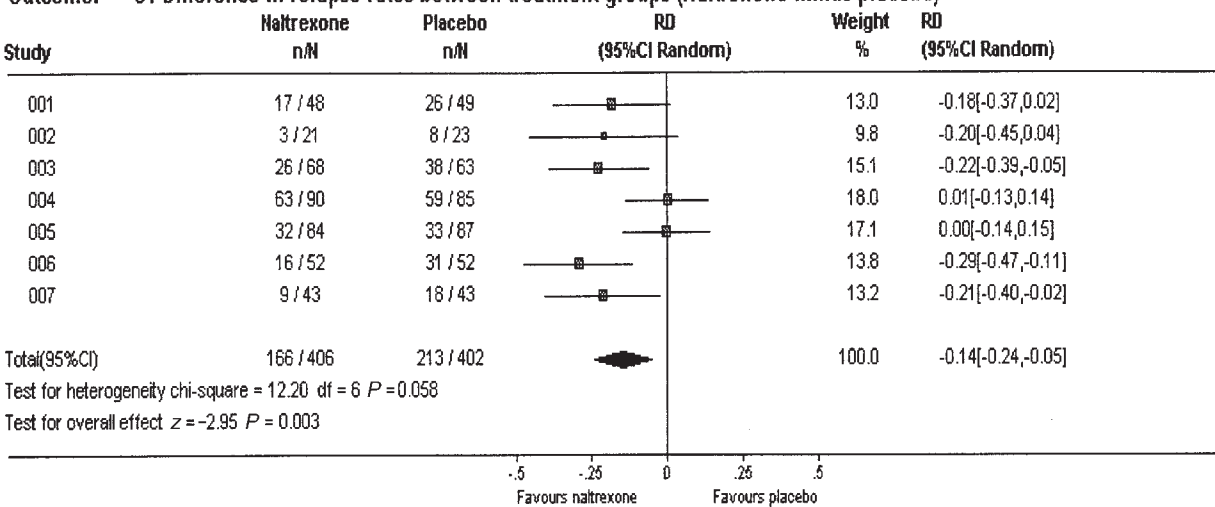


Fig. 1. Results of the meta-analysis: the difference in proportion of patients who relapsed to heavy drinking (i.e. relapse rate), naltrexone minus placebo, random effects model (95% CI).

alcohol on average 3% fewer days than placebo patients ($P < 0.05$), and drank 1.0 standard alcoholic drink less per drinking day than placebo-treated subjects ($P < 0.05$).

Testing for heterogeneity. A χ^2 -test was performed to detect whether the patients were homogeneous. The result from the χ^2 -test carried out for relapse rates indicated that there was

heterogeneity ($P \leq 0.05$), in which case the more appropriate summary estimates to report are those from the random effects model. We have, however, included the fixed effects model results for completeness. For the outcomes abstinence rates, the mean percentage of reported drinking days, and the mean number of drinks per drinking day, there was no evidence of heterogeneity. In this situation, the fixed effects model results are the most appropriate summary estimates.

Safety results (naltrexone: placebo)

The incidence of subjects reporting at least one adverse event and the incidence of subjects who discontinued the study due to an adverse event were comparable between the two treatment groups (see Table 5). Neither were the study-specific estimates and the pooled fixed and random effects risk difference estimates significantly different from 0, at the 95% level when naltrexone was compared to placebo. With respect to specific adverse events, nausea, somnolence, abdominal pain, pain, anorexia and vomiting were all reported significantly more frequently in the treatment group than in the control group, when these results were pooled. In summary, naltrexone treatment appears to be no more toxic than placebo and is not associated with a significantly greater number of study discontinuations due to adverse events.

DISCUSSION

The interest generated by recent reports documenting that naltrexone is more effective than placebo in the treatment of alcohol dependence appears warranted by the strength of the evidence provided in this pooled analysis. The findings across seven (six published and one unpublished) trial reports consistently demonstrated that naltrexone was similar to, or more effective than, placebo. The results of this meta-analysis, involving a total of 804 subjects, indicate that subjects taking naltrexone have significantly improved outcomes with respect to relapse rates, abstinence rates and alcohol consumption measures, compared to subjects taking placebo over a short-term treatment period of 12 weeks. In addition, naltrexone is no more toxic than placebo.

Our results are comparable to those reported in a recently conducted Cochrane Review evaluating the use of opioid antagonists for alcohol dependence (Srisurapont and Jarusuraisin, 2000). The conclusion drawn from this review was that naltrexone has some short-term benefits in the treatment of patients with alcohol dependence, especially when psychosocial treatments are administered concurrently with naltrexone treatment. The benefit of naltrexone was demonstrated to be significant in the three efficacy outcomes of abstinence rates, amount of alcohol consumed per drinking day, and the number of drinking days per subject treated (Srisurapont and Jarusuraisin, 2000).

All seven RCTs of naltrexone included in our meta-analysis were conducted using a similar methodology, assessed to be of similar quality, using common outcome measures, and were conducted over the same duration of time (12 weeks). All seven studies clearly described their inclusion/exclusion criteria and adequately described their outcome measures. All seven studies also clearly described their randomization procedure, with respect to using either central registry or a

blinded drug supply. Studies 001, 006 and 007 reported using both a central computer-generated registry and a blinded drug supply, whereas studies 002, 003, 004 and 005 employed a blinded drug supply only. This consistency between the seven trials allows us to comfortably combine the trial results.

In addition, six of the seven studies provided a description of the numbers of, and reasons for drop-outs (studies 001, 003, 004, 005, 006 and 007), in other words, indicating exactly how they handled the attrition of subjects. Six studies employed the method of 'last observation carried forward'. It is unlikely therefore that any difference in the way the attrition of subjects was handled between the studies introduced systematic biases into our analyses.

One of the major limitations of these trials, however, is their briefness in duration, and their inability to measure the effect of naltrexone on the incidence of alcohol-related complications, the reduction of which is the ultimate goal in alcohol withdrawal therapy. It should be noted that study 006 was extended to include a 6-month follow-up period, where, at the end of the 12-week treatment trial, the study medication was discontinued, but the outcomes were re-evaluated after 6 months. The results of this study indicated that the benefit of a 12-week treatment of naltrexone appears to be lost within 6 months of discontinuing pharmacotherapy (O'Malley *et al.*, 1996a).

Outcome efficacy estimates used in this meta-analysis included: relapse rates, abstinence rates, and, as measures of alcohol consumption during the trial, the mean percentage of drinking days per subject, and the mean number of drinks per drinking day per subject. These outcomes, although they do not directly measure the long-term benefits of reducing alcohol consumption and the incidence of alcohol-related events, are indicative of potential long-term gains achieved from naltrexone therapy.

Although there is some heterogeneity for one of the outcomes analysed (relapse rates), the general trend of all the results was to favour naltrexone. Variations in treatment effect between the different studies may be explained by a number of factors, including sample size of the study (inadequate power), treatment compliance rates, the period of abstinence prior to study entry, and the measurement of outcomes and their validation. Inadequate power was the most likely reason for study 002's failure to detect any significant differences between naltrexone and placebo with respect to relapse and abstinence rates. The duration of detoxification prior to study entry was found to be longer for studies 004 and 005, which may also explain the absence of significant differences between naltrexone and placebo with respect to their study outcomes.

Several investigators in this field of research have evaluated and recommended the usefulness of gamma-glutamyl transpeptidase (GGT) as a biological marker of alcohol consumption (Rosalki and Rau, 1972; Chick *et al.*, 1981; Salaspuro, 1986). Changes in GGT levels are important since they are not subject to reporting inaccuracies, and are generally not open to bias. Although the change in GGT was reported in most studies, the majority of included studies did not report sufficient detail with respect to actual values of change in GGT concentrations to allow us to pool the results. Five of the seven studies did, however, report whether the change in serum GGT activity was or was not significantly different between treatment groups. A significantly greater reduction in serum GGT activity for the naltrexone group, compared to the

placebo group, was reported in studies 001, 004 and 005. No significant decrease in GGT between treatment groups was observed in studies 002 and 003.

The results of the meta-analyses also indicate that the benefit of naltrexone pharmacotherapy is not limited to a specific treatment approach or to a specific patient population. Instead, these findings suggest that naltrexone may be broadly applicable to a variety of psychological treatment programmes for alcohol recovery. The studies included in this analysis differed in the type and intensity of the psychotherapy programme used and in the characteristics of the patients, including demographic and years of heavy drinking. Generally, studies providing more naturalistic settings appeared to detect more significant improvements with respect to naltrexone. In all studies, however, the patients were selected for having alcoholism without substantial co-morbidity for other drug addiction and/or psychiatric disorders, and for their willingness to participate in a study of a new medication.

Despite including only the most conservative results from each study (i.e. FAS results), our pooled analyses still demonstrated that naltrexone is more effective than placebo at reducing relapse drinking and improving abstinence from alcohol. Publication bias can be a major concern for meta-analysis when the methods rely solely on published information to derive summary estimates of treatment effect. We are fortunate that our analyses include both published and unpublished studies, and, in doing so, any concerns regarding the effect of publication bias were reduced. However, the inclusion of the unpublished study has perhaps modified the summary estimate in a conservative direction, as the results of the published studies overall seem to suggest a clear publication bias. In addition, the inclusion of the 'full analysis set' results, rather than per protocol results, only further weakens the observed effect of naltrexone and does not make an intervention appear effective when it is not. Notwithstanding their inclusion, neither of these factors appears to have significantly altered the overall conclusion drawn.

There were two published RCTs that compared the therapeutic effect of naltrexone to placebo, which did not meet our study selection criteria. Both of the studies produced negative results. One was conducted in patients with combined alcohol and cocaine dependence (Hersh *et al.*, 1998). The other study compared the therapeutic effect of nefazodone, a serotonin (5-HT) antagonist and weak 5-HT reuptake inhibitor, to that of naltrexone and placebo in alcohol-dependent subjects (Kranzler *et al.*, 2000). This study was excluded from our meta-analysis for two reasons: (1) nefazodone is currently not licensed in Australia; (2) the active treatment period lasted 11 weeks, less than that specified by our selection criteria. The results of this study indicated, however, that neither medication reduced drinking. Although this study may have not been adequately powered, no trend emerged.

With respect to long-term treatment studies with naltrexone, we are only aware of one open-label 2-year follow-up study that aimed to evaluate the effectiveness of low-dose naltrexone (i.e. 25 mg daily) for a 6-month treatment in combination with a daily aversion treatment for 12 months, compared to daily aversion treatment alone for 12 months in 30 alcoholics (Landabaso *et al.*, 1999). Abstinence and relapse rates were analysed in this study by means of a risk estimate calculated at 6, 12, 18 and 24 months; at all time points, it was found that

the probability of remaining abstinent was significantly higher than that seen in the control group. Abstinence rates for the naltrexone treatment group were 73, 73, 67 and 40% respectively. However, limitations of this trial included the small sample size, and the per protocol analysis of results in a setting where there were differential rates of drop-outs between treatment groups. The trial also only evaluated naltrexone in combination therapy prescribed concurrently with an aversion therapy (i.e. disulfiram).

This systematic review of naltrexone RCTs has also allowed us to evaluate where further research is required in the study of naltrexone treatment for alcohol-dependent patients. The conclusions drawn to date are that naltrexone is more effective than placebo at reducing relapses to heavy drinking, and at improving alcohol abstinence in the short term. However, these conclusions are drawn only from data collected over a 12-week period of treatment. Optimal duration of treatment with naltrexone therefore cannot be determined, especially since we are evaluating a treatment for a condition that is a chronic relapsing disorder. Neither are we able to evaluate properly the effect of the treatment programme post cessation of naltrexone therapy. Additional follow-up studies with suitable comparison groups and longer-term outcome results will be necessary to further examine the long-term efficacy and tolerability of naltrexone treatment, particularly with respect to any influence on the incidence of alcohol-related complications, before any recommendation can be made.

Acknowledgements — The authors thank Jeffrey Joseph, Associate Director, Biometrics, DuPont Pharmaceuticals Company, for his helpful comments on the manuscript. The concept of performing this meta-analytical evaluation arose from a technical report commissioned by Orphan, Australia.

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