Psychopharmacology (2004) 172:291–297
DOI 10.1007/s00213-003-1658-9

ORIGINAL INVESTIGATION

Ismene L. Petrakis · Stephanie O'Malley · Bruce Rounsaville · James Poling · Colette McHugh-Strong · John H. Krystal · VA Naltrexone Study Collaboration Group

Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia

Received: 22 April 2003 / Accepted: 19 September 2003 / Published online: 21 November 2003

Abstract *Objective:* Alcohol abuse in patients with schizophrenia is associated with psychiatric and social complications. While two medications have been approved by the Federal Drug Administration (FDA) for the treatment of alcoholism: disulfiram and naltrexone, no medications have been approved for individuals with alcohol dependence and comorbid schizophrenia. The purpose of this study was to evaluate the efficacy of naltrexone in alcohol-abusing schizophrenic patients. *Method:* Thirty-one patients with schizophrenia and comorbid alcohol abuse or dependence were treated for 12 weeks in an outpatient study using naltrexone or placebo in a randomized, double-blind fashion in addition to their neuroleptic medication. Patients also participated in a weekly therapy using cognitive-behavioral drug relapse prevention strategies combined with skills training. Outcomes included drinking measured by the time line follow-back method, craving using the Tiffany Craving Questionnaire, psychotic symptoms using the Positive and Negative Symptoms Scale (PANSS), side effects and a measures of abnormal involuntary movements. *Results:* There were no significant differences in treatment exposure or medication compliance between groups. Naltrexone treated patients had significantly fewer drinking days, heavy drinking days (>5 drinks) and reported less craving compared to the placebo treated patients. Naltrexone did not affect symptoms of schizophrenia, such as psychosis. The medication was well tolerated and there were no group differences in side effects. *Conclusions:* These data suggest that naltrexone may be an effective medication for individuals with comorbid alcohol dependence and schizophrenia. Given the widespread problems associated with alcohol misuse in this population, and the lack of effective pharmacotherapies, these findings represent an exciting clinical development.

Keywords Naltrexone · Alcohol · Schizophrenia · Comorbidity · Dual diagnosis

Introduction

Schizophrenia is a devastating clinical disorder that affects approximately 1% of the general population. The prevalence of alcohol abuse among schizophrenic patients is greater than the rate observed in the general population (Regier et al. 1990). Alcohol abuse in this population is associated with increased psychotic symptoms (Dixon 1999), an increased rate of medication noncompliance (Gerding et al. 1999), more frequent and longer hospitalizations (Gerding et al. 1999) and a higher rate of crisis oriented service utilization and consequently a higher cost of care (Gerding et al. 1999). Social problems associated with alcohol abuse in this population include legal problems, housing instability, lower rates of employment and poor money management (Dixon 1999). Currently two medications have been approved by the Federal Drug Administration (FDA) for the treatment of alcoholism: disulfiram and naltrexone. Disulfiram has been reported to worsen psychosis in schizophrenic patients (Hansen and Larsen 1982), while other reports suggest it may be used safely in this group (Mueser et al. 2003) and there

Preliminary results from this study were presented at the Society of Biological Psychiatry 57th Annual Scientific Convention, Philadelphia, Pa., USA in May 2002. The VA Naltrexone Study Collaboration Group: West Haven: Diana Congdon, Ned Cooney, Roberto Gil, Kathy Keegan, Debra Miles, Alison Oville, Barbara Peluse, Louis Trevisan; Northampton: Lynn Gordon, John Reino, Wayne Costello, Christopher Cryan; Bedford: Nitigna Desai, Marylee Losardo, Doreen Farrell, Barbara E. Rofman. W. Costello is deceased.

I. L. Petrakis · S. O'Malley · B. Rounsaville · J. Poling · C. McHugh-Strong · J. H. Krystal
Department of Psychiatry, Yale University, New Haven, Conn., USA

I. L. Petrakis (✉)
West Haven Veterans Administration Medical Center #116-A, 950 Campbell Avenue, West Haven, CT 06516, USA
e-mail: ismene.petrakis@yale.edu
Tel.: +1-203-9325711 ext 2244
Fax: +1-203-9374791

are no controlled trials evaluating the efficacy of naltrexone in this population.

After preclinical studies suggested that the opioid antagonist naltrexone may be an effective pharmacological agent in treatment of alcohol dependence, naltrexone was evaluated in two now well-known, clinical trials (O'Malley et al. 1992; Volpicelli et al. 1992) and subsequently approved by the Food and Drug Administration (FDA) for the treatment for use in alcoholism. Self-administration, human laboratory and retrospective patient reports from clinical trials have provided evidence for a potential mechanism of action for naltrexone. Naltrexone appears to reduce the rewarding effects of alcohol consumption and to reduce the ability of an initial alcohol consumption to prime for further drinking (Swift et al. 1994; Volpicelli et al. 1995; Davidson et al. 1996; O'Malley et al. 1996, 2002). A meta-analysis of all published placebo-controlled trials using naltrexone has shown that naltrexone has a modest effect on alcohol consumption (Kranzler and Van Kirk 2001). However, a large multi-site trial in alcohol-dependent veterans failed to confirm any effect of naltrexone on drinking outcomes (Krystal et al. 2001), and its role in alcoholism is still not well defined.

Available evidence suggests that naltrexone is safe in patients with severe mental illness. Naltrexone and another opioid antagonist, naloxone, have either shown no worsening of the symptoms associated with schizophrenia or a modest therapeutic improvement in psychotic symptoms (Pickar et al. 1982; Sernyak et al. 1998). A few pilot studies have evaluated naltrexone in dually diagnosed patients. An open label pilot study of naltrexone for medicated depressed patients with alcoholism suggests naltrexone is effective in decreasing alcohol use and may improve depressive symptoms as well (Salloum et al. 1998). A safety study of over 500 patients, which included a large percentage of dually diagnosed patients simultaneously receiving medications for other comorbid mental disorders, was conducted by Croop and colleagues (Croop et al. 1997). In that study, the rate of adverse events in naltrexone treated patients did not differ in patients with and without comorbid mental disorders or as a function of concurrent psychotropic medication. In another study, a chart review of 72 alcohol dependent outpatients with comorbid major psychiatric illnesses, including schizophrenia, bipolar disorder and schizoaffective disorder, suggested that naltrexone can have a good clinical response as measured by treatment retention and alcohol consumption (Maxwell and Shinderman 2000).

We conducted a multi-center, double-blind, placebo controlled trial of the efficacy of naltrexone in individuals with schizophrenia or schizoaffective disorder and comorbid alcohol abuse or dependence in conjunction with a standard psychosocial treatment for 12 weeks.

Materials and methods

Subjects

This study was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System and the Northampton and Bedford, Massachusetts VAs, which are all affiliated with the New England Mental Illness and Research Education Clinical Center (MIRECC). Subjects were recruited from the patients who were treated in clinics at these MIRECC facilities. Subjects met current DSM IV criteria for schizophrenia or schizoaffective disorder and current DSM-IV criteria for alcohol dependence (n=30) or alcohol abuse (n=1) but were without other lifetime axis I disorders, besides nicotine dependence. These diagnoses were determined by structured clinical interview (Spitzer et al. 1992) and confirmed by clinical interview. Subjects had been abstinent no more than 29 days. Exclusion criteria were unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of naltrexone.

After signing informed consent, subjects underwent an intake assessment, which included a physical examination, laboratory assessments and an interview with a psychiatrist. Of the 78 patients meeting initial eligibility criteria, 17 declined to participate or dropped out, 30 were excluded and 31 were randomized. Reasons for exclusion included: transportation difficulties or geographical constraints (n=8), unstable or significant medical condition (n=4), psychiatric instability (n=5), current DSM-IV dependence criteria for substances other than alcohol or nicotine (n=4), abstinent more than 30 days (n=5) and participating in another research study (n=4). Thirty-one subjects were randomized, 16 received naltrexone and 15 received placebo. All subjects were outpatients at the time of randomization and only five out of 31 (16%) had required medically assisted detoxification prior to randomization.

Treatments

Following completion of these baseline assessments, subjects were randomized in a double-blind fashion to receive either naltrexone 50 mg or placebo once per day for 12 weeks. Study medications were blue opaque capsules: active naltrexone tablets were ground up and placed in the capsules, while the placebo was an identical capsule filled with lactose. Participants in the study were not charged for treatment and also participated in a weekly therapy using an approach adapted from Roberts et al. (1999). This approach uses cognitive-behavioral drug relapse prevention strategies originally developed for non-mentally ill substance abusers and incorporates a skills training method originally developed to teach social and independent living skills to schizophrenics. The treatment was administered by an experienced master's level clinician who encouraged abstinence as a goal. Most subjects identified abstinence as their goal as well, although this was not a requirement for entry into the study. All participants continued to receive psychiatric treatment as usual. Subjects were reimbursed weekly ($10) for attending research sessions (weeks 1–11), and reimbursed $20 for the baseline assessments and $30 for the endpoint evaluations for a total of $160. The study was originally designed as an 8-week study and then amended to be 12 weeks, so the first two subjects completed only 8 weeks of treatment. The first two subjects completed the study without incident and therefore the study was amended to last for 12 weeks in order to be consistent with other published naltrexone trials.

Assessments

Primary outcomes were the frequency and quantity of alcohol use. Self-reports of alcohol and other substance use were obtained at baseline for the preceding 30 days and weekly during treatment using the Timeline Follow-Back Interview (Sobell and Sobell 1992) administered by a research assistant at each weekly visit. Reports of alcohol use were verified through breathalyzer readings

conducted at every visit and self-reports of drug use were verified through urine toxicology screens collected weekly. Craving was assessed weekly using an adaptation of the Tiffany Craving Questionnaire (Tiffany et al. 1993). The Tiffany questionnaire was developed for assessing craving for tobacco smoking and defined five components of drug craving which could be independently assessed in alcohol craving as well: 1) desire to drink alcohol, 2) intention to drink alcohol, 3) sense that alcohol consumption would result in feeling better, 4) sense that alcohol consumption would result in reduced discomfort and 5) sense of control over alcohol consumption. The self-report scale was modified for assessing alcohol craving in the laboratory by this group, adapting each question for alcohol and using the same number of items (Petrakis et al. 1999, 2001, 2002).

Psychiatric symptoms were assessed using the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987) administered by the research staff at baseline and biweekly. The severity of movement disorder was assessed using the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976) obtained at weeks 6 and 12. Side effects and common adverse symptoms were screened for using Hopkins Symptom Checklist (Derogatis et al. 1974), (HSCL) a self-report symptom inventory. The symptoms that are known to be associated with naltrexone treatment and neuroleptic use were specifically screened for and included: dry mouth, drowsiness, poor memory, headache, trouble concentrating, sweating, difficulty sitting still, frequent urination, constipation, nausea, faintness, diarrhea, decreased appetite, muscles stiffness, blurred vision, nightmares, irregular heartbeat, tremor, ringing in ears, skin rash. Medication compliance was assessed using pill counts at each visit.

Data analysis

The primary outcomes were drinking variables, specifically the number of drinking days and the number of heavy drinking days (defined as 5 or more standard drinks) per week calculated from the timeline data. The principal analyses used for the repeated measures assessments, including drinking outcomes using the TLFB, the Tiffany Craving Scores, the PANSS and AIMS, were random intercepts hierarchical linear modeling (HLM) analyses conducted through the SPSS Mixed procedure. The use of the HLM approach to the analysis of our longitudinal data has several specific advantages. Unlike traditional repeated measures analyses, HLM can be used in datasets with missing data and allows for intra-subject serial correlation and unequal variance and covariance structures over time. HLM accomplishes this by incorporating available trend data for each individual with information on the behavior of the group from which the subject is drawn (Hedeker et al. 1991).

Analysis of variance and chi-square variables were used to evaluate differences between groups in baseline characteristics and functioning, as well as differences in treatment retention, medication compliance and frequency of the occurrence of side effect symptoms for subjects across the treatment period.

Results

The subjects for this study were 31 males recruited at the three New England MIRECC sites: West Haven, Conn. (n=23), Northampton, Mass. (n=7) and Bedford, Mass., USA (n=1). As shown in Table 1, 100% of the subjects were male, 19% of the subjects were African American (n=6) and they had an average age of 46 (SD=5.7). Only five (5) subjects were employed, and the majority (18/31 or 58%) carried the diagnosis of schizophrenia, while the rest had the diagnosis of schizoaffective disorder. Half of the subjects were on atypical neuroleptics (16/31 or 52%), and 12 subjects were taking thymoleptics (or mood stabilizers) during the study (39%), and six subjects (19%) were taking benzodiazepines. Only one subject was prescribed clozapine. Baseline mean PANSS general psychopathology score was 27.5 (±6.6), and the positive symptoms subscale was 12.7 (SD=3.8) and the negative symptoms subscale was 16.6 (SD=6.3). This is suggestive of mild/moderate psychosis, and is consistent with the clinical impression that subjects were stable on neurolep-

Table 1 Baseline characteristics of participants in the naltrexone treatment study

Demographic characteristics	Total (n=31)	Naltrexone (n=16)	Placebo (n=15)	Statistic	P
Age (years)	46.0±5.7	46.5±5.2	45.5±6.4	F=0.22	0.65
Gender (male)	31 (100%)	16 (100%)	15 (100%)	N/A	N/A
Ethnicity					
Caucasian	25 (80.6%)	12 (75%)	13 (86.7%)	χ^2=0.68	0.41
African-American	6 (19.4%)	4 (25%)	2 (13.3%)		
Diagnosis					
Schizophrenia	18 (58.1%)	9 (56.2%)	9 (60%)	χ^2=0.14	0.71
Schizoaffective	13 (41.9%)	7 (43.8%)	6 (40%)		
Medications[a]					
Atypical	16 (51.6%)	8 (50%)	8 (53.3%)	χ^2=0.00	1.00
Thymoleptics	12 (38.7%)	6 (37.5%)	6 (40%)	χ^2=0.00	1.00
Benzodiazepines	6 (19.4%)	4 (25.0%)	2 (13.3%)	χ^2=0.675	0.65
Baseline drinking characteristics[b]					
Drinking days	11.6±8.3	8.6±8.5	14.9±7.0	F=5.00	0.03
Heavy drinking days	9.0±7.9	7.3±8.8	10.8±6.7	F=1.50	0.23
Total drinks	127.8±126.7	133.2±163.8	122.1±74.4	F=0.06	0.81
PANSS at baseline					
General psychopathology	27.5±6.6	24.8±4.5	29.8±7.4	F=3.45	0.08
Positive symptoms	12.7±3.8	11.5±2.6	13.75±4.4	F=2.00	0.17
Negative symptoms	16.6±6.3	17.5±6.9	15.9±6.0	F=0.33	0.57

[a] Total not equal to 31 (100%) since patients may fit in one category, two categories or neither category
[b] Average across 4 weeks of baseline

tic medications at the time of randomization. Subjects drank on average 11.7 (SD=8.3) days out of 30 days prior to treatment entry, and heavily (>5 drinks per occasion) on 9.0 (SD=7.9) days out of 30 days and consumed a total of 127.8 (SD=126.6) standard drinks in total. There was a significant difference in the number of drinking days (out of 30) at baseline (8.6±8.5 for the naltrexone treated group compared to 14.9±7.0 for the placebo treated group) but no other significant differences in variables between the group that received placebo and the group that received naltrexone. The average number of heavy drinking days per week for the 30 day baseline period were 2.3 (SD=2.0) days out of a week for the entire sample, 1.8 (SD=2.2) for the naltrexone treated group and 2.7 (SD=1.7) days per week for the placebo-treated group (see Table 1).

Treatment exposure

Of the 31 subjects who were randomized and began treatment, 25 subjects reached follow-up and there was not a significant difference between the placebo treated group and the naltrexone treated group on retention (13/15 subjects or 86.7% versus 12/16 subjects or 75.0%, respectively). Of the naltrexone-treated individuals one participant discontinued because of side effects (sedation), two were lost to follow-up and one was discontinued for medical reasons (naltrexone was discontinued because of reported chest pain until a medical work-up could be completed, several weeks later the patient had a cerebrovascular accident, was hospitalized and discontinued from the study). Of the placebo treated subjects, one was lost to follow-up and one complained of side effects (nausea). The percent of study visits attended by the subjects did not differ significantly by group: the naltrexone treated group attended 75.3%of study visits, while the placebo-treated group attended 82.8% of study visits. A measure of medication adherence (n=30) was computed by dividing the number of pills taken by the number of potential medication days (84 days for all subjects, except the two subjects who participated in 56 days of treatment). There were no significant differences in medication compliance between the naltrexone-treated subjects (n=15, data was were not recorded for one subject) and the placebo-treated (n=15) subjects (68.4 versus 77.5, respectively).

Alcohol use outcomes

As a group, subjects decreased their alcohol use from baseline to post-treatment as measured by self-report. During treatment, naltrexone-treated patients reported drinking for an average of 6.2 (SD=8.0) days compared to 13.5 (SD=15.6) days for the placebo treated patients. They also reported drinking a total of 56.7 (SD=84.3) drinks compared to 83.1 (SD=98.1) for the placebo treated patients, and on average 0.37 (SD=1.1) heavy drinking days compared to 0.81 (SD=1.4) for the placebo-treated patients. Given that there were baseline differences in the number of drinking days, this was entered as a covariate in the random regression analysis of drinking days during treatment and revealed a significant overall drug effect for drinking days [F(1,248)=13.4, P<0.0001], with those assigned to naltrexone reporting less alcohol use compared with the placebo group. Random regression analysis also indicated a significant overall drug effect for heavy drinking days [F(1,248)=9.32, P=0.003] (see Fig. 1). There was no significant time [F(41,11)=0.31, P=0.98: F(41,11)=0.37, P=0.98, respectively] or drug by time effect[F(41,11)=0.29, P=0.98; F(41,11)=0.76, P=0.68, respectively] for drinking days or number of heavy drinking days.

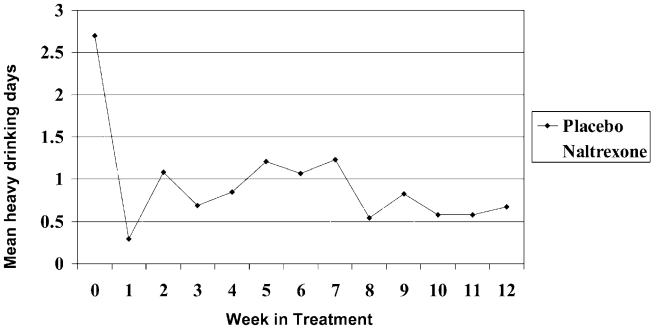

Fig. 1 Mean weekly heavy drinking days* (>5 drinks per episode) at baseline (*) and during the active phase for subjects on naltrexone versus placebo

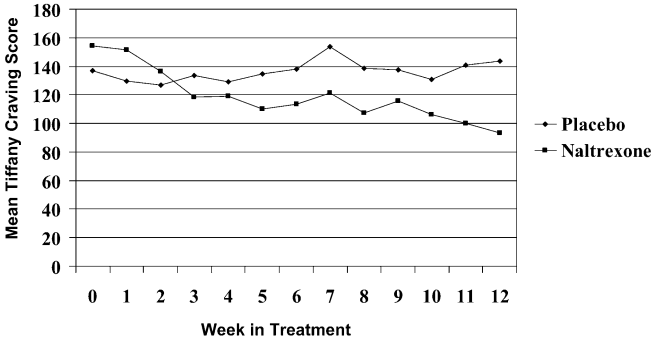

Fig. 2 Mean Tiffany Alcohol Craving Questionnaire score per week for subjects on naltrexone versus placebo

Craving

Based on the Tiffany Craving Questionnaire (TCQ) random regression analysis indicated there was a significant drug effect for self-reported craving [F(11,1)=11.5, P=0.001] and for each of the subscales Desire to drink [F(11,1)=9.6, P=0.002] and Intention to drink [F(11,1)=8.8, P=0.003] with those assigned to naltrexone reporting significantly less alcohol craving compared with the placebo group (see Fig. 2). There was no significant

Table 2 Percent of subjects in each drug condition experiencing specific symptoms across time. Analyses consisted of Fisher's exact chi-squares. Symptoms are sorted by overall symptom frequency

Symptom	Overall (n=31)	Placebo (n=15)	Naltrexone (n=16)	P-value
Dry mouth	83.9	86.7	81.3	1.00
Feeling drowsy	74.2	80.0	68.8	0.69
Poor memory	74.2	80.0	68.8	0.69
Difficulty sitting still	71.0	80.0	62.5	0.43
Frequent need to urinate	64.5	66.7	62.5	1.00
Poor concentration	64.5	80.0	50.0	0.14
Increased appetite	61.3	73.3	50.0	0.27
Headache	58.1	53.3	62.5	0.72
Sweating	58.1	60.0	56.3	1.00
Faintness/lightheadedness	58.1	66.7	50.0	0.47
Decreased appetite	58.1	53.3	62.5	0.72
Diarrhea	54.8	60.0	50.0	0.72
Blurred vision	54.8	60.0	50.0	0.72
Tremors/shakiness	54.8	53.3	56.3	1.00
Muscle stiffness	51.6	66.7	37.5	0.16
Constipation	48.4	60.0	37.5	0.29
Nightmares	48.4	46.7	50.0	1.00
Ringing in ears	48.4	60.0	37.5	0.29
Difficulty starting urination	45.2	46.7	43.8	1.00
Nausea	41.9	40.0	43.8	1.00
Trouble concentrating	38.7	40.0	37.5	1.00
Heartbeat irregular/pounding	35.5	40.0	31.3	0.72
Skin rash	29.0	20.0	37.5	0.43

time effect [$F(11,1)$=0.47, P=0.91] or drug by time effect [$F(11,1)$=1.03, P=0.44] in TCQ total scores, or in either of the subscales Desire to drink and Intention to drink.

Measures of psychosis

The mean general psychopathology PANSS scores were 26.4 (SD=5.2) in the naltrexone-treated group compared to 30.2 (SD=8.7) in the placebo treated group; positive symptoms subscale was 11.1 (SD=0 3.6) and negative scale was 15.1 (SD=5.3) in the naltrexone treated group compared to 12.8 (SD=4.8) and 17.4 (SD=6.6) in the placebo treated group. Random regression analysis indicated no significant drug effect [$F(11,1)$=3.37, P=0.06], time effect [$F(11,1)$=0.65, P=0.78] or drug by time effect [$F(11,1)$=0.16, P=0.35] in measures of psychosis, as determined by the overall PANSS scores. Similarly, there were no significant drug effect, time effect or drug by time effects in either the PANSS positive symptom subscale scores, or in the PANSS negative symptom subscale scores.

Safety and side effects

In terms of serious adverse events, four subjects required psychiatric hospitalization during the study. Two naltrexone-treated subjects and one placebo treated subject had psychotic decompensations, but were able to restart study medications and continue the study. Of those, two (one in each group) completed the study and the other (naltrexone treated individual) was discontinued for medical complications, as mentioned above. One naltrexone treated subject was admitted for detoxification, and later completed the study.

Overall, all subjects (100%) reported experiencing one or more symptoms potentially related to medication side effects, with dry mouth as the most common complaint (48.4%). There were no symptoms that distinguished the naltrexone and placebo treated subjects (see Table 2). There were no significant drug effects [$F(2,1)$=0.87, P=0.35], time effects [$F(2,1)$=0.21, P=0.81] or drug by time effects [$F(2,1)$=0.31, P=0.74] in dyskinesia based on the AIMS examination. Similarly there are no significant drug effects [$F(2,1)$=0.16, P=0.69], time effects [$F(2,1)$= 0.58, P=0.58] or drug by time effects [$F(2,1)$=1.3 P=0.29] in dystonia based on the AIMS examination.

Discussion

The results of this 12-week double blind, placebo controlled trial of naltrexone for alcohol use in alcohol dependent patients with comorbid schizophrenia suggest that, compared to placebo, subjects treated with naltrexone (1) had a significantly fewer drinking days and therefore more days of abstinence; (2) fewer heavy drinking days; and (3) significantly lower self-reported craving. There were no differences between the groups on symptoms of psychosis and in other adverse effects. Furthermore, naltrexone was well tolerated in this group of patients. Taken together, these data suggests that naltrexone may be a promising agent for treating alcohol dependence in individuals with comorbid schizophrenia.

Subjects treated with naltrexone decreased both the number of heavy drinking days and the days of drinking, and had more days of abstinence than those treated with placebo. How do these results fit in with the existing literature on the role of naltrexone in the treatment of alcoholism? These results are consistent with most

published studies that have found that naltrexone has a modest effect on alcohol consumption (Kranzler and Van Kirk 2001). A modest effect on alcohol consumption is likely to be a clinically significant finding in individuals with serious mental illness. First of all, individuals with mental illness may suffer the consequences of alcohol use at a lower rate of alcohol consumption than individuals without mental illness (Kavanagh et al. 2002), so even small changes in alcohol consumption may have a big clinical impact. Second, the patients with a severe mental illness may not be able to benefit as fully from the highly effective forms of treatments that have been developed for alcohol dependent individuals (Project Match Research Group 1997), so medication effects may be more readily apparent. For example, the large multi-site trial in alcohol-dependent veterans who did not have schizophrenia failed to find significant effects of naltrexone on drinking outcomes (Krystal et al. 2001) when tested in conjunction with manualized twelve12-step facilitation, a highly effective form of treatment.

One factor that may have influenced outcome is that all subjects in this study were on neuroleptic medication. It is conceivable that neuroleptics facilitate the effect of naltrexone, improving its efficacy in alcohol-related outcomes. There are a number of studies that have suggested that the dopamine system plays an important role in alcohol dependence (Koob 2000). Clinical studies are harder to interpret, since there have been both positive (Shaw et al. 1987) and negative studies (Wiesbeck et al. 2001; Marra et al. 2002) evaluating the use of dopamine receptor antagonist medications in alcohol dependent patients without comorbid disorders. The class of neuroleptic may also be a factor since, there is some promising evidence that atypical neuroleptics have a greater effect on alcohol and other substance use than do typical neuroleptics in individuals with comorbid disorders (Drake et al. 2000). However, all subjects met criteria for alcohol dependence criteria before enrolling in the study, and the two groups had a similar distribution of typical versus atypical neuroleptics. Further studies evaluating the differential effects on alcohol consumption by the different classes of antipsychotics, and the possible interaction with naltrexone are important areas for future research.

An important finding from this study is that naltrexone did not worsen symptoms of schizophrenia. Subjects' positive and negative symptoms were largely unchanged during the study, and there was no effect of naltrexone on these symptoms. This is consistent with existing literature that has shown opiate antagonists do not worsen psychosis in non-alcohol abusing schizophrenic patients (Pickar et al. 1989; Sernyak et al. 1998) and in alcohol abusing schizophrenic patients (Batki et al. 2002). It is interesting to note that despite reductions in alcohol use, there was no significant improvement in the PANSS. Since subjects in this study were stable psychiatric patients with baseline PANSS scores in the mild to moderate range, there is the possibility of a "floor" effect. Another possibility is that the length of this study (12 weeks) was inadequate to detect a significant improvement in psychotic symptoms. Finally, it is possible that the level of drinking found in this cohort does not substantially influence psychotic symptoms. Interesting follow-up studies could evaluate these hypotheses.

Further confirming naltrexone's safety in this population is the finding that the naltrexone treated patients did not experience more side effects than the placebo-treated patients. The most common side effect was dry mouth, a common side effect of neuroleptics. Of note is that nausea was reported equally between groups. This may be due to the anti-emetic properties of antipsychotic medications. These data, in conjunction with data from a large safety study which included a large percentage of dually diagnosed individuals (Croop et al. 1997) and a retrospective chart review of outpatients with comorbid major psychiatric illness (Maxwell and Shinderman 2000), suggest that naltrexone can be used with relative safety in this population.

The design features of this investigation were intended to maximize the pharmacologic effect of treatment. Strengths of the study include the use of a psychotherapy tailored to this group of patients in both medication conditions, the low attrition rate and the comprehensive assessments of symptoms of psychosis as well as alcohol use outcomes. The limitations to this study include the relatively small sample size and the possible lack of generalizability to other clinical settings, since this study was based on a male VA sample. Further, there were confounding factors that could have contributed to outcome, such as neuroleptic class and the use of adjunctive medications.

Overall, the results from this study have some important implications for treatment of alcohol abuse in patients with comorbid schizophrenia. This study represents the first placebo controlled, randomized clinical trial to demonstrate efficacy for a medication as treatment for alcohol dependence in schizophrenic patients. Given the widespread problems associated with alcohol misuse in this population, and the lack of effective pharmacotherapies to treat this disorder, these findings represent an exciting development. Further evaluations of the effectiveness of naltrexone in patients with major psychiatric disorders are ongoing in our clinics and elsewhere. Replication of this study's efficacy findings would warrant further evaluations of its mechanisms of action, durability and range of effects, clinical safety, and the extent to which outcomes can be enhanced with various levels of concurrent psychosocial treatment.

Acknowledgments Support for this study was provided by NARSAD (PI=Petrakis), the Veterans Affairs MERIT grant (PI=Petrakis), the VA-Yale Alcoholism Research Center (PI=Krystal), and the VISN I Mental Illness Research and Clinical Center (MIRECC) (PI=Rounsaville) and the National Institute on Alcohol Abuse and Alcoholism (K02 AA00171=O'Malley and K02 AA00261=Krystal). The authors would like to thank Rachel Alpert, Diana Limoncelli, Adam Linkov and Ran Wu for their assistance in preparing the manuscript.

References

Batki S, Dimmock J, Cornell M, Wade M, Carey K, Maisto, S (2002) Directly observed naltrexone treatment of alcohol dependence in schizophrenia: preliminary analysis. Alcohol Clin Exp Res 26:83A

Croop RS, Faulkner EB, Labriola DF (1997) The safety profile of naltrexone in the treatment of alcoholism. Results from a multicenter usage study. The Naltrexone Usage Study Group. Arch Gen Psychiatry 54:1130–1135

Davidson D, Swift R, Fitz E (1996) Naltrexone increases the latency to drink alcohol in social drinkers. Alcohol Clin Exp Res 20:732–739

Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L (1974) The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 19:1–15

Dixon L (1999) Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res 35:S93–100

Drake RE, Xie H, McHugo GJ, Green AI (2000) The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull 26:441–449

Gerding LB, Labbate LA, Measom MO, Santos AB, Arana GW (1999) Alcohol dependence and hospitalization in schizophrenia. Schizophr Res 38:71–75

Guy W (1976) ECDEU assessment manual for psychopharmacology. Publication 76-338, Washington D.C.

Hansen L, Larsen N (1982) Metabolic interaction between perphenazine and disulfiram. Lancet 2:1472

Hedeker D, Gibbons R, Davis J (1991) Random regression models for multicenter clinical trials data. Psychopharmacol Bull 27:73–77

Kavanagh D, McGrath J, Saunders J, Dore G, Clark D (2002) Substance misuse in patients with schizophrenia: epidemiology and management. Drugs 62:743–755

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative symptom scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276

Koob GF (2000) Neurobiology of addiction. Toward the development of new therapies. Ann N Y Acad Sci 909:170–185

Kranzler H, Van Kirk J (2001) Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 25:1335–1341

Krystal J, Cramer J, Krol W, Kirk G, Rosenheck R (2001) Naltrexone in the treatment of alcohol dependence. N Engl J Med 345:1734–1739

Marra D, Warot D, Berlin I, Hispard E, Notides C, Tilikete S, Payan C, Lepine J, Dally S, Aubin H (2002) Amisulpride does not prevent relapse in primary alcohol dependence: results of a pilot randomized, placebo-controlled trial. Alcohol Clin Exp Res 26:1545–1552

Maxwell S, Shinderman MS (2000) Use of naltrexone in the treatment of alcohol use disorders in patients with concomitant major mental illness. J Addict Dis 19:61–69

Mueser K, Noordsy DL, Fox L, Wolfe R (2003) Disulfiram treatment for alcoholism in severe mental illness. Am J Addict 12:242–252

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992) Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry 49:881–887

O'Malley SS, JA, Rode S, Rounsaville BJ (1996) Experience of a "slip" among alcoholics treated with naltexone or placebo. Am J Psychiatry 153:281–283

O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek J (2002) Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacologia 160:19–29

Petrakis I, Trevisan L, D'Souza DC, Gil R, Krasnicki S, Boutros N, Cooney N, Krystal JH (1999) CSF monoamine metabolite and beta-endorphin levels in recently detoxified alcoholics and healthy controls: prediction of alcohol cue-induced craving. Alcohol Clin Exp Res 23:1336–1341

Petrakis IL, Trevisan L, Boutros NN, Limoncelli D, Cooney NL, Krystal JH (2001) Effect of tryptophan depletion on alcohol cue-induced craving in abstinent alcoholic patients. Alcohol Clin Exp Res 25:1151–1155

Petrakis IL, Buonopane A, O'Malley SS, Cermik O, Trevisan L, Boutros NN, Limoncelli D, Krystal JH (2002) The effect of tryptophan depletion on alcohol self-administration in non-treatment seeking alcoholic individuals. Alcohol Clin Exp Res 26:969–975

Pickar D, Vartanian F, Bunney WE, Maier HP, Gastpar MT, Prakash R, Sethi BB, Lideman R, Belyaev BS, Tsutsulkovskaja MVA, Jungkunz G, Medopil N, Verhowven W, Praag H (1982) Short-term nalaxone administration in schizophrenic and manic patients. Arch Gen Psychiatry 39:313–319

Pickar D, Bunney W, Douillet P, Sethi B, Sharma M, Vartanian M, Lideman R, Naber D, Leibl K, Yamashita I, Koyama T, Verhoven W, Vartanian F, Morozov P, Khac T (1989) Repeated naloxone administration in schizophrenia: a phase II World Health Organization study. Biol Psychiatry 25:440–448

Project Match Research Group (1997) Matching alcoholism treatments to client heterogeneity: project MATCH posttreatment drinking outcomes. J Stud Alcohol 58:7–29

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study [see comments]. JAMA 264: 2511–2518

Roberts L, Shaner A, Eckman T (1999) Overcoming addictions: skills training people for people with schizophrenia. W.W. Morton & Company, New York

Salloum IM, Cornelius JR, Thase ME, Daley DC, Kirisci L, Spotts C (1998) Naltrexone utility in depressed alcoholics. Psychopharmacol Bull 34:111–115

Sernyak MJ, Glazer WM, Heninger GR, Charney DS, Woods SW, Petrakis IL, Krystal JH, Price LH (1998) Naltrexone augmentation of neuroleptics in schizophrenia. J Clin Psychopharmacol 18:248–251

Shaw G, Majumdar S, Waller S, MacGarvie J, Dunn G (1987) Tiapride in the long-term management of alcoholics of anxious or depressive temperament. Br J Psychiatry 150:164–168

Sobell LC, Sobell MB (1992) Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten R, Allen J (eds) Measuring alcohol consumption. Humana Press, Clifton, N.J.

Spitzer RL, Williams JB, Gibbon M, First MB (1992) The structured clinical interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 49:624–629

Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H (1994) Naltrexone-induced alterations in human ethanol intoxication. Am J Psychiatry 151:1463–1467

Tiffany ST, Singleton E, Haertzen CA, Henningfield JE (1993) The development of cocaine craving questionnaire. Drug Alcohol Depend 34:19–28

Volpicelli JR, Alterman A, Hayashida M, O'Brien CP (1992) Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 49:876–880

Volpicelli JR, Watson NT, King AC, Sherman CE, O'Brien CP (1995) Effect of naltrexone on alcohol "high" in alcoholics. Am J Psychiatry 152:613–615

Wiesbeck G, Weijers H, Lesch O, Glasser T, Toennes P, Boening J (2001) Flupenthixol decanoate and relapse prevention in alcoholics: results from a placebo-controlled study. Alcohol 36:329–334