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Treatment of Late-Life Depression Complicated by Alcohol Dependence

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Abstract

Objectives—Among elderly patients, mental and physical illness are often present along with alcohol dependence. The interaction between alcohol use and concurrent physical or mental disabilities is complex and complicates treatment planning. The aim of this study was to test the efficacy of naltrexone combined with sertraline for the treatment of older adults with major depression and alcohol dependence.

Methods—The sample was 74 subjects, age 55 and older, who met criteria for a depressive disorder along with alcohol dependence. All subjects were randomly assigned to 12 weeks of naltrexone 50 mg/day or placebo. Also, all subjects received sertraline 100 mg/day and individual weekly psychosocial support. Treatment response for alcohol consumption and depression was measured during the 12 weeks of treatment.

Results—At baseline, the average age of subjects was 63.4, and subjects were drinking an average of 10.7 drinks per drinking day. The overall results are encouraging; 42% of the subjects had a remission of their depression and had no drinking relapses during the trial. There was no evidence for an added benefit of naltrexone in combination with sertraline, but there was significant correlation between any alcohol relapse during the trial and poor response to depression treatment.

Conclusion—Patients with concurrent mental disorders, such as major depression and alcohol dependence, are increasingly prevalent in clinical practice and have been demonstrated to show poorer treatment response and higher treatment costs. The results of this trial underscore the importance of addressing alcohol use in the context of treating late-life depression.

Major depression is one of the most common and harmful serious mental illnesses in the United States. However, major depression is often associated with other behavioral health problems. In the National Comorbidity Study, the most common concurrent psychiatric conditions for major depression included alcohol dependence and anxiety disorders.[1] Alcohol use disorders, in particular, have been found to be associated with major depression and have led to speculation regarding treatment choices and treatment outcome.[2] In addition to the Epidemiologic Catchment Area (ECA) study that found alcoholism present 1.6 times more often in depressed than nondepressed subjects, other community epidemiologic studies have also demonstrated a higher-than-expected rate of alcoholism in depressed subjects.[1,3,4] Comorbidity is also common in late life and is often more the rule than the exception.[5–7] For example, among older subjects discharged from a psychiatric hospital, Blixen found that

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37% of the elderly subjects with major depression had a concurrent diagnosis of alcoholism. Moreover, in a study by Blow and colleagues,[8] concurrent depression and alcohol dependence showed an age-related increase in comorbidity across the entire life cycle, thus making this issue particularly relevant in late life.

There are some inconsistencies in the literature regarding the consequences of concurrent depression and alcohol dependence among middle-aged and younger adults. Many studies have found that depressed younger adults with alcohol dependence have a more complicated clinical course of depression, with an increased risk of suicide, more social dysfunction than nondepressed alcohol-dependent adults, and a worse long-term prognosis.[3,9–14] Patients with concurrent disorders also seek more treatment and utilize more health services.[15] However, other studies have not shown that comorbidity is a significant factor in treatment response. Three recent studies have failed to demonstrate an association between drinking and depression over time.[3,16,17]

Few studies have specifically explored the effects of comorbid substance abuse on late-life depression. Cook and colleagues[9] found that a previous history of alcohol abuse predicted a more severe and chronic course for late-life depression. Similarly, several studies have shown that alcohol problems earlier in life increase the risk for developing depression or dementia in subsequent years, even after prolonged periods of abstinence from alcohol.[18–20] Oslin and colleagues[21] conducted a longitudinal descriptive study of middle-aged and older adults who have recently received a “driving under the influence” (DUI) charge.[21] The results demonstrated greater self-rated disability among older subjects who were suffering from concurrent alcoholism and major depression than subjects with either alcohol abuse or depression alone.

There are also a limited number of studies that address the treatment of patients who present with comorbid alcoholism and depression. Rigorous treatment recommendations are scarce because many patients with comorbid substance use are excluded from clinical trials. For example, concurrent alcohol or drug misuse was found to be the greatest factor (17%) for exclusion of subjects from antidepressant clinical trials.[22] Among younger adults, there have been a few treatment studies focusing on the use of antidepressants in the treatment of patients with concurrent depression and alcohol dependence and no randomized trials combining treatments for depression and alcohol dependence, such as the combination of an antidepressant and naltrexone. In several small, placebo-controlled trials of an antidepressant (desipramine, imipramine, sertraline, and nefazadone), medication was shown to reduce depressive symptoms, compared with placebo, but it had only limited improvement in drinking outcomes.[23–26] One promising study, using fluoxetine treatment, conducted in patients with primary major depression and comorbid alcoholism did show a positive effect on both depression and alcohol use.[27] Finally, in what appears to be a contradictory finding, Pettinati and colleagues found that sertraline was more effective at reducing alcohol use in nondepressed alcohol-dependent subjects than those with a lifetime history of depression.[28]

Pharmacotherapy for the treatment of alcohol dependence has developed at a slower pace than that for depression. Naltrexone, an opioid-receptor antagonist, is one of two FDA-approved treatments for alcohol dependence. The use of naltrexone is based on an endorphin-compensation model developed from animal and preclinical studies that suggested a dysregulation of the reward pathways regulating alcohol use; these include dopamine and opioid neurotransmission.[29–31] Based on the preclinical research, clinical-trials research has demonstrated that, when used in conjunction with a psychosocial treatment program, naltrexone can improve treatment outcomes, particularly, relapse to clinically significant drinking, for alcohol-dependent individuals.[32–39]

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The purpose of this study was to examine the added benefit of treating alcohol dependence in older adults who are receiving treatment for major depression. Thus, the trial hypothesized that patients treated with the combination of naltrexone and sertraline would have overall better improvement in depression and drinking response than patients treated with placebo and sertraline. A secondary objective was to test the association between alcohol use during treatment and improvement in depressive symptoms. We designed this as an augmentation trial for both practical reasons (ensuring sufficient recruitment) and because there appeared to be sufficient evidence that antidepressants have efficacy for depression in this context. Moreover, monotherapy with an antidepressant appeared insufficient to address both the depressive symptoms and the drinking problems.

Methods

Subjects

Seventy-four outpatients were enrolled in a 12-week, placebo-controlled, randomized trial of naltrexone 50 mg/day for alcohol dependence as an adjunct to sertraline 100 mg/day. Study participants were recruited through advertisements in the local media and from clinical referrals. Eligible subjects had to be at least 55 years old, meet DSM-IV criteria for alcohol dependence, and criteria for a depressive disorder (substance-induced or primary major depression), and successfully complete detoxification from alcohol, as defined by a minimum of 3 consecutive days of abstinence before the start of the study medication. In order to start on sertraline, subjects had to continue to meet diagnostic criteria for a depressive disorder at the time of starting sertraline. Of note, no subjects had resolution of depression by the end of the first week of treatment, and, thus, all were started on sertraline. Primary major depression required the diagnosis of depression starting before the alcohol dependence or persisting during a 3-month period of alcohol abstinence. Subjects were not included if they had a current DSM-IV diagnosis of any psychoactive substance dependence other than alcohol or nicotine or had evidence of opioid use in the past 30 days, as assessed both by self-report and/or urine drug screen at admission to treatment. Subjects also could not have severe medical or physical illnesses, such as AIDS or active hepatitis, and could not have significant hepatocellular injury, as evidenced by elevated total bilirubin levels. The study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania and the Philadelphia VAMC, and all subjects provided written informed consent before study participation.

Study Design

After completing alcohol detoxification, subjects were randomly assigned to receive either naltrexone (50 mg) or placebo in addition to compliance-enhancement therapy (BRENDA).[40] (The acronym stands for Biopsychosocial evaluation, Report to the patient, Empathetic approach, Needs assessment, Direct advice to the patient, and Assessment of progress.) Randomization was stratified by gender and recruitment site in a block design. After 1 week of naltrexone or placebo, subjects were started on sertraline 50 mg/day for 1 week, increasing to 100 mg/day, as tolerated. Outcome assessments were collected during the 12 weeks of treatment. Study medication was provided in blister cards to assist in measuring adherence and as an aid for patients.

Psychosocial Treatment

In addition to receiving medication, each subject was seen regularly by a nurse to support abstinence and assist in treatment. The supportive therapy (BRENDA) was conducted by a nurse (R.N. or Master's level), with sessions lasting 20 to 30 minutes.[40] BRENDA is a manualized compliance-enhancement therapy based on the six-stage acronym framework described above: Biopsychosocial evaluation, Report to patient on assessment, Empathetic

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understanding of the patient's situation, Needs that must be addressed, Direct advice to patient on how to meet those needs, and Assessment of reaction/behaviors of the patient to advice and adjustment as necessary for best care. Each session focused on progress made toward the goal of reducing alcohol consumption and improving depression. Although abstinence is the stated goal for each patient, reductions in drinking are encouraged while working toward this goal. Sessions were initially weekly for 8 weeks, then biweekly.

Assessment Instruments

Adherence to the study medication regimen was monitored by self-report of medication use and by pill counts, and therapy attendance was tracked by each nurse. Adverse events were monitored weekly by the nurse and reviewed with the principal investigator. Adverse-event reports were collected at baseline and at each clinical visit by use of the Systematic Assessment for Treatment Emergent Effects (SAFTEE).[41] Symptoms were considered adverse events during the trial if they were new or represented worsening of a baseline complaint. Standard research assessments measured psychiatric symptoms, alcohol use, and depressive symptoms. The instruments included 1) the Hamilton Rating Scale for Depression (Ham-D);[42] 2) the Mini-Mental State Exam (MMSE);[43] 3) the Time-Line Follow-Back (TLFB) method of assessing alcohol consumption;[44,45] 4) the Addiction Severity Index (ASI);[44–47] and 5) the Medical Outcomes Study Short Form (SF-36).[48] The Ham-D and TLFB were administered at each visit, and the ASI and SF-36 were administered monthly.

The Ham-D is a 17-item scale used as a marker of severity of depressive symptoms and also as an outcome measure. The MMSE is a cognitive screening instrument. The TLFB is a semistructured interview that uses a calendar format to record the quantity and frequency of drinking during a stated period of time. In this instance, drinking reports were recorded for the 90 days preceding detoxification, as well as during the treatment period. Quantity of alcohol was recorded in standard drinks (e.g., a 12-oz beer, a 6-oz glass of wine, or a 1½-oz shot of hard liquor = one standard drink). The ASI is a 45-minute, structured interview that measures the lifetime and recent (past 30 days) severity of problems in seven areas of biopsychosocial functioning (represented by component scores): medical status, employment and self-support, alcohol use, drug use, legal status, family and social relationships, and psychiatric symptoms. The SF-36 is a measure of quality-of-life outcome, divided into major subscales such as physical functioning, role functioning, and social functioning.

Statistical Analysis

Statistical analyses used SPSS Version 11.5 for Windows. Descriptive analyses included means and standard deviations (SD) for continuous variables and frequencies for categorical variables. For comparisons between groups, continuous variables were compared by Student *t*-test, and categorical variables were compared by chi-square test. Logistic-regression analyses were applied to assess the relationship between treatment response (remission of depression and lack of drinking relapse) and treatment assignment (naltrexone versus placebo). Pretreatment clinical characteristics that differed significantly between treatment groups were used as covariates; these included pretreatment drinking variables and depression severity (Ham-D score). To assess the effect of drinking during treatment on depression response, logistic-regression models were constructed, with pretreatment variables entered as well as drinking during treatment (measured both as a dichotomous variable relapsed/not relapsed and as the log-transformed value of the percent days of heavy drinking during the trial). Cox regression analyses were constructed to assess the effects of the treatment assignment on the time-to-relapse to significant drinking. Definitions used for response measures included depression remission (Ham-D <10) and relapse to heavy

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drinking (drinking more than 4 standard drinks in 1 day for men or more than 3 for women). Subjects who withdrew from the study were considered in the primary outcome analysis as having a poor treatment response.

Results

A total of 74 subjects were recruited for participation and were randomized. Table 1 presents the baseline demographic, psychosocial, depression severity, and drinking severity information of the treatment sample. The sample consisted primarily of white men (79.7% of the sample was male, and 66.2% of the sample was white). The average age was 63.4 (SD: 6.3) years, and 44.6% of the sample were currently married. There were no significant differences between treatment groups on any of the demographic variables.

Participants had an average of 39.6 (SD: 10.8) years of alcohol use and an average of 17.3 (SD: 9.9) years of drinking-to-intoxication. Subjects drank alcohol heavily on 67.5% (SD: 33.3%) of the 90 days preceding the detoxification period. Given concerns about the potential confounds of cognition on self-reported drinking over a period of 90 days, we also analyzed drinking during the 30 days before treatment. There were no differences in the interpretation of the outcomes using this shorter time period; therefore, the more traditional 90-day time period was reported. Of all subjects randomized into the study, 51.4% had no previous formal treatment for alcohol dependence; 17.6% had participated in one treatment episode; and 29.7% had been in more than one previous treatment. Moreover, only 27.0% had ever participated in outpatient mental health treatment, whereas 25.7% were receiving an antidepressant at the time of screening, and 8.1% had a lifetime suicide attempt. Independent major depression was diagnosed in 31.1% of the sample, with the remaining cases being alcohol-induced (63.5%) or indeterminate (5.4%). As shown in Table 1, those randomized to naltrexone were less depressed, had fewer drinks on a given drinking day, and had fewer days of heavy drinking before randomization.

Adherence was measured both for attendance to treatment sessions and adherence to prescribed study medication. Overall, 83.8% of subjects completed 3 months of psychosocial treatment, as defined by attending at least 80% of the weekly therapy visits. There was no difference between treatment groups in the proportion of subjects completing treatment (89.2% for the placebo group and 81.1% for the naltrexone group; Wald $\chi^2_{[1]}$=0.042; odds ratio (OR): 1.16; 95% confidence interval (CI): 0.28–4.91; p=0.838). Subjects took naltrexone/placebo on 83.3% of the study days and sertraline on 79.1% of the study days. Sertraline adherence was measured only after the first week of treatment. There was no difference between treatment groups in the proportion of subjects adherent to naltrexone/placebo (Wald $\chi^2_{[1]}$=0.029; OR: 1.11; 95% CI: 0.32–3.84; p=0.864) or sertraline (Wald $\chi^2_{[1]}$=0.511; OR: 1.54; 95% CI: 0.47–5.07; p=0.475). Reporting of new or worsening of adverse events during treatment was common, with 58.1% of the sample complaining of headache; 51.4%, anxiety; 41.9%, nausea; 39.2%, decreased sexual functioning; and 24.3%, vomiting. However, none of these adverse events were more common in the naltrexone combination group than the placebo group, and none of these symptoms were related to either completion of the trial or adherence to medication. These results are not presented in detail but are available from the author.

In total, 52.7% of the sample had a remission from depression, 66.2% did not have an alcohol relapse, and 48.6% were abstinent for the 12 weeks. As shown in Table 2, there were no differences in improvement from the combination of naltrexone+sertraline +psychosocial support, compared with the combination of sertraline+placebo+psychosocial support on either depression or drinking responses or the combination of responses. Time to the first day of heavy drinking (relapse) was also not significantly different between

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treatment groups (Wald $\chi^2_{[1]}$=0.041; β=0.090; p=0.839). In a post-hoc analysis of the differences between men and women, there was a suggestion of differential response (Wald $\chi^2_{[1]}$=3.91; OR: 13.95; 95% CI: 1.02–190.30; p=0.048). For women, 25.0% of those treated with naltrexone+sertraline+psychosocial support had an overall favorable response, compared with 71.4% of those treated with sertraline+psychosocial support. Comparable figures for men were 44.8% and 36.7%, respectively. Among women receiving naltrexone/sertraline who experienced a reduced overall response to treatment when compared with women who received only sertraline, lesser improvement in depression, not alcohol consumption, was the main contributing variable. There were no main effects of treatment assignment within each gender group.

The secondary objective for this study was to examine the mediation effect of drinking during the trial on final depression outcomes. As shown in Table 3, any relapse to heavy drinking was associated with a reduction in response to depression treatment as measured by remission of depression or as measured by absolute improvement in symptoms. Complete abstinence was not associated with improvement in depression. Similar findings were found when considering the percentage of days of heavy drinking. More frequent bouts of heavy drinking during the trial were associated with lower rates of improvement in depression (Wald $\chi^2_{[1]}$=9.32; OR: 2.29; 95% CI: 1.34–3.90; p=0.02) and reduction in Ham-D scores (β=2.49; 95% CI: 1.26–22.86; p <0.001). To increase sensitivity in examining the association between drinking during treatment and improvement in depression, a post-hoc analysis was conducted, using a criterion of any drinking on more than 2 days of the study. Even using this more inclusive criterion, there was a significant association between drinking and poor depression response (Wald $\chi^2_{[1]}$=7.14; OR: 4.00; 95% CI: 1.44–10.82; p=0.008).

Discussion

Results from this trial indicate there was no evidence that naltrexone enhanced treatment responses either for depression or for alcohol consumption when combined with sertraline and individualized psychosocial support. There was evidence supporting the role of elimination of heavy drinking during treatment in order to improve depression-treatment responses. Because this is one of the first clinical trials examining the efficacy of combination treatments for those with alcohol dependence and depression, it is difficult to compare the outcomes of this trial with other trials, including those using monotherapy. However, we note that overall drinking outcomes improved substantially for all subjects, with 66% having a favorable change in drinking behavior. This rate of remission for drinking is similar to the positive results from naltrexone in previous placebo-controlled trials for alcohol dependence and may relate to the effects of the psychosocial intervention and sertraline.[33,49–52] However, this trial was not designed to establish the efficacy of sertraline or the psychosocial intervention, and thus statements regarding the efficacy of these treatments cannot be made. Moreover, previous trials of antidepressants in depressed, alcohol-dependent subjects have shown mixed results in reducing alcohol use.[24–27]

The association between heavy drinking during treatment and reduced effectiveness of depression treatment substantiates the idea of toxic effects of alcohol in this clinical context. Although complete abstinence was not associated with poor depression response, patients who had more than 2 days of any drinking also demonstrated the poorest depression response. Together, these analyses suggest that both frequency and quantity are important in treating comorbidity. Although there was a strong relationship between drinking and depression outcomes, these data do not distinguish between patients who may have returned to drinking because the depression had not improved versus those whose drinking led to a worsening of depression. Other possible explanations of our findings include reduced

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efficacy of sertraline due to changes in pharmacokinetics/dynamics in the presence of alcohol use, or direct CNS-toxic effects of alcohol that limit improvement in depression symptoms.

The lack of an additive effect of naltrexone should not diminish the estimation of the value of naltrexone for treating alcohol dependence in other settings. The lack of efficacy of naltrexone in the present setting may relate to differing effects of naltrexone on neurotransmission in different populations. The efficacy of naltrexone is understood by the opioid-compensation hypothesis, which posits a dysfunction in opioid neurotransmission after alcohol ingestion, leading to increased drinking. In support of this are several studies demonstrating that response to naltrexone is related to family history of alcoholism and to the presence of a specific polymorphism of the μ-opioid receptor gene ($OPRM_1$) that is known to change the functioning of this receptor.[39,53,54] One-third of the participants in this trial were of African descent and unlikely to have the polymorphism associated with naltrexone response. Unfortunately, subjects in this trial were not genotyped, and family-history data are lacking. Thus, the lack of efficacy of naltrexone suggests that depressed alcohol-dependent patients may have normally functioning μ-opioid receptors and that the mechanism for excessive drinking may relate to dysfunction in another part of the pathway for loss of control of drinking (possibly the serotonergic, GABAergic, or another signaling pathway). It is also noted that although naltrexone has been shown to have a small-to-moderate efficacy in older adults with alcohol dependence, it is also possible that there is an age-related loss of efficacy of the medication, perhaps related to differential drive for alcohol consumption or motivation for quitting.[34,55]

The interaction effect between gender and treatment assignment raises the possibility of differential efficacy by gender. Currently, there are no published results suggesting differential response in women, although this difference is being examined in several ongoing trials. It is possible that the potential “toxic” effect seen in women relates to greater adverse effects of the combination of medications or a direct adverse effect of naltrexone on depression for women, given that the effect for women seemed mostly driven by a lack of improvement in depressive symptoms. However, there was no evidence of greater reporting of adverse events among women. Despite this finding and the lack of evidence from other clinical trials, heuristic clinical opinion suggests that women may not tolerate as high a dose of naltrexone as men.

One limitation of the trial was the adoption of a relatively conservative measure of response in this study, by examining the percentages of patients who improved to the point of remission of depression and lack of relapse to heavy drinking for alcohol use. This was based on the need to have a common standard of improvement across the two types of behavioral health problems we examined. The strength of this approach was the reference to meaningful standards of severity namely the use of relapse-to-heavy-drinking and a Ham-D score of ≤10. Other limitations of the study include the modest sample size, inclusion of a limited number of women, and the restricted age-range of the participants. To better understand the differential effects of combination treatments across the lifespan, a more inclusive trial should be attempted that targets young, middle-aged, and older adults with representation across gender and ethnicity.

The results of this trial also raise questions about the methods used for determining the efficacy of combination treatments. In all likelihood, a substantial proportion of subjects may be best treated with monotherapy in combination with psychosocial support. This is clearly supported by the results of this trial, in which half the patients responded favorably to the monotherapy; and even though recruitment for the trial met the estimated sample size requirements, with 80% power to detect differences of 30% or more in response, these

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estimates were based on the expectation of the full treatment package having moderate-to-large effects and monotherapy having modest effects. Future trials should consider alternative design strategies that may maximize differences in effect from combination treatments. Namely, future trials should consider the merits of using adaptive treatment designs or stepped-care approaches. In these approaches, standard treatment, such as monotherapy plus psychosocial support, is begun, and combination treatment is added to a random subset of those who do not respond to the initial treatment efforts. A comparison group of patients continuing on monotherapy plus psychosocial support is also maintained. This type of design would not only match clinical practice, but may also reduce exposure and the expense of combination treatments that may be unnecessary or carry additional patient burden.

In conclusion, this trial has raised many questions for future trials, including the design used for establishing combination treatments, consideration of the rationale for selecting combination treatments, and the caution that simply considering two treatments as better than one is a naive approach to clinical care. Moreover, despite the relatively positive improvement in drinking behavior seen among most participants in this trial, 47% of the sample remained significantly depressed at the end of the trial. Although the modest depression response may relate to the inclusion of patients who remained depressed after detoxification and 1 week of treatment with naltrexone, this again raises important issues with regard to the focus of treatment and sequencing of treatments. Although it was true that reduction in alcohol use was necessary for improvement in depression, this was not sufficient in all participants. The low remittance of depressive symptoms also raises questions about the diagnostic usefulness of “substance-induced depression” in this particular cohort, as we might have expected a greater response to treatment when two-thirds of subjects were judged to have depression related to alcohol use. Further work will be necessary to establish the next line of treatment in patients who decrease or eliminate alcohol use, but continue to have significant depression. It is likely that a continued integration of depression and alcoholism care will be necessary to keep these patients from returning to heavy drinking as we continue to adapt and modify the depression treatment.

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References

1. Kessler RC, Nelson CB, McGonable KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the U.S. National Comorbidity Survey. Br J Psychiatry. 1996; 168(suppl30):17–30.
2. Merikangas K, Gelernter CS. Comorbidity for alcoholism and depression. Psychiatr Clin North Am. 1990; 13:613–632. [PubMed: 2281009]
3. Helzer JE, Pryzbeck TR. The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. J Stud Alcohol. 1988; 49:219–224. [PubMed: 3374135]

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4. Cornelius JR, Bukstein O, Salloum I, et al. Alcohol and psychiatric comorbidity. Recent Dev Alcohol. 2003; 16:361–374. [PubMed: 12638646]
5. Speer D, Bates K. Comorbid mental and substance disorders among older psychiatric patients. J Am Geriatr Soc. 1992; 40:886–890. [PubMed: 1512383]
6. Callahan CM, Hendrie HC, Dittus RS, et al. Depression in late life: the use of clinical characteristics to focus screening efforts. J Gerontol. 1994; 49:M9–M14. [PubMed: 7904281]
7. Blazer D. The diagnosis of depression in the elderly. J Am Geriatr Soc. 1980; 30:587–592. [PubMed: 7108092]
8. Blow F, Cook CL, Booth B, et al. Age-related psychiatric comorbidities and level of functioning in alcoholic veterans seeking outpatient treatment. Hosp Community Psychiatry. 1992; 43:990–995. [PubMed: 1328023]
9. Cook B, Winokur G, Garvey M, et al. Depression and previous alcoholism in the elderly. Br J Psychiatry. 1991; 158:72–75. [PubMed: 2015453]
10. Conwell, Y. Suicide in elderly patients, in Diagnosis and Treatment of Depression in Late Life. Schneider, LS.; Reynolds, CF., III; Lebowitz, BD., et al., editors. Washington, DC: American Psychiatric Press, Inc; 1991. p. 397-418.
11. Schuckit MA, Tipp JE, Bergman M, et al. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. Am J Psychiatry. 1997; 154:948–957. [PubMed: 9210745]
12. Blixen CE, McDougall GJ, Suen LJ. Dual diagnosis in elders discharged from a psychiatric hospital. Int J Geriatr Psychiatry. 1997; 12:307–313. [PubMed: 9152713]
13. Hanna EZ, Grant BF. Gender differences in DSM-IV alcohol use disorders and major depression as distributed in the general population: clinical implications. Compre Psychiatry. 1997; 38:202–212.
14. Hasin DS, Tsai WY, Endicott J, et al. Five-year course of major depression: effects of comorbid alcoholism. J Affect Disord. 1996; 41:63–70. [PubMed: 8938207]
15. Fortney JC, Booth BM, Curran GM. Do patients with alcohol dependence use more services? a comparative analysis with other chronic disorders. Alcohol Clin Exp Res. 1999; 23:127–133. [PubMed: 10029213]
16. Kranzler HR, DelBoca FK, Rounsaville BJ. Comorbid psychiatric diagnosis predicts three-year outcomes in alcoholics: a posttreatment natural history study. J Stud Alcohol. 1996; 57:619–626. [PubMed: 8913993]
17. Hodgins DC, el-Guebaly N, Armstrong S, et al. Implications of depression on outcome from alcohol dependence: a 3-year prospective follow-up. Alcohol Clin Exp Res. 1999; 23:151–157. [PubMed: 10029217]
18. Schutte KK, Hearst J, Moos RH. Gender differences in the relations between depressive symptoms and drinking behavior among problem drinkers: a three-wave study. J Consult Clin Psychol. 1997; 65:392–404. [PubMed: 9170762]
19. Saunders PA, Copeland JR, Dewey ME, et al. Heavy drinking as a risk factor for depression and dementia in elderly men. Br J Psychiatry. 1991; 159:213–216. [PubMed: 1773236]
20. Crum RM, Brown C, Liang KY, et al. The association of depression and problem drinking: analyses from the Baltimore ECA follow-up study: Epidemiologic Catchment Area. Addict Behav. 2001; 26:765–773. [PubMed: 11676386]
21. Oslin DW, O'Brien CP, Katz IR. The disabling nature of comorbid depression among older DUI recipients. Am J Addict. 1999; 8:128–135. [PubMed: 10365193]
22. Partonen R, Sihvo S, Lonnqvist JK. Patients excluded from an antidepressant efficacy trial. J Clin Psychiatry. 1996; 57:572–575. [PubMed: 9010119]
23. McGrath PJ, Nunes EV, Stewart JW, et al. Imipramine treatment of alcoholics with primary depression a placebo-controlled clinical trial. Arch Gen Psychiatry. 1996; 53:232–240. [PubMed: 8611060]
24. Mason BJ, Kocsis JH, Ritvo EC, et al. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA. 1996; 275:761–767. [PubMed: 8598592]

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25. Roy-Byrne PP, Pages KP, Russo JE, et al. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2000; 20:129–136. [PubMed: 10770449]
26. Roy A. Placebo-controlled study of sertraline in depressed, recently-abstinent alcoholics. Biol Psychiatry. 1998; 44:633–637. [PubMed: 9787889]
27. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial. Arch Gen Psychiatry. 1997; 54:700–705. [PubMed: 9283504]
28. Pettinati HM, Volpicelli JR, Luck G, et al. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol. 2001; 21:143–153. [PubMed: 11270910]
29. Volpicelli, JR.; O'Brien, CP.; Alterman, AI., et al. Naltrexone and the treatment of alcohol dependence: initial observations, in Opioids, Bulimia, and Alcohol Abuse and Addiction. Reid, LD., editor. New York: Springer-Verlag; 1990. p. 195-214.
30. Volpicelli JR. Uncontrollable events and alcohol drinking. Br J Addict. 1987; 82:381–392. [PubMed: 3555574]
31. Kreek MJ. Opiates, opioids, and addiction. Mol Psychiatry. 1996:1232–1254.
32. O'Malley SS, Jaffe AJ, Chang G, et al. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry. 1992; 49:881–887. [PubMed: 1444726]
33. Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry. 1992; 49:876–880. [PubMed: 1345133]
34. Oslin D, Liberto JG, O'Brien J, et al. Naltrexone as an adjunctive treatment for older patients with alcohol dependence. Am J Geriatr Psychiatry. 1997; 5:324–332. [PubMed: 9363289]
35. Chick J, Anton R, Checinski K, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol. 2000; 35:587–593. [PubMed: 11093966]
36. Morris PL, Hopwood M, Whelan G, et al. Naltrexone for alcohol dependence: a randomized controlled trial (comment). Addiction. 2001; 96:1565–1573. [PubMed: 11784454]
37. Monti PM, Rohsenow DJ, Swift RM, et al. Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and one-year outcomes. Alcohol Clin Exp Res. 2001; 25:1634–1647. [PubMed: 11707638]
38. Anton RF, Moak DH, Latham PK, et al. Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. J Clin Psychopharmacol. 2001; 21:72–77. [PubMed: 11199951]
39. Monterosso JR, Flannery BA, Pettinati HM, et al. Predicting treatment response to naltrexone: the influence of craving and family history. Am J Addiction. 2001; 10:258–268.
40. Volpicelli, JR.; Pettinati, HM.; McLellan, AT., et al. BRENDA Manual: Compliance Enhancement Techniques with Pharmacotherapy for Alcohol and Drug Dependence. Philadelphia: Guilford Press; 1997.
41. Rabkin J, Markowitz J, Ocepek-Welikson K, et al. General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research. J Clin Psychopharmacol. 1992; 12:3–10. [PubMed: 1552037]
42. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–65. [PubMed: 14399272]
43. Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State:” a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
44. Sobell L, Sobell M, Gloria L, et al. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Br J Addiction. 1988; 83:393–402.
45. Sobell, LC.; Sobell, MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption, in Measuring Alcohol Consumption. Litten, R.; Allen, J., editors. Totowa, NJ: Humana Press Inc.; 1992. p. 41-65.
46. McLellan AT, Lubrosky L, O'Brien CP. An improved evaluation instrument for substance abuse patients: The Addiction Severity Index. J Nerv Ment Dis. 1980; 168:26–33. [PubMed: 7351540]

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47. McLellan A, Alterman A, Cacciola J, et al. A new measure of substance abuse treatment: initial studies of The Treatment Services Review. J Nerv Ment Dis. 1982; 180:101–110. [PubMed: 1737971]

48. McHorney CA, Ware JE, Lu JFR, et al. The MOS 36-Item Short-Form Health Survey (SF-36), III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994; 32:40–66. [PubMed: 8277801]

49. O'Malley SS, Rounsaville BJ, Farren C, et al. Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs. specialty care: a nested sequence of three randomized trials. Arch Intern Med. 2003; 163:1695–1704. [PubMed: 12885685]

50. Gastpar M, Bonnet U, Boning J, et al. Lack of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. J Clin Psychopharmacol. 2002; 22:592–598. [PubMed: 12454559]

51. Guardia J, Caso C, Arias F, et al. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial. Alcohol Clin Exp Res. 2002; 26:1381–1387. [PubMed: 12351933]

52. Latt NC, Jurd S, Houseman J, et al. Naltrexone in alcohol dependence: a randomised, controlled trial of effectiveness in a standard clinical setting. Med J Aust. 2002; 176:530–534. [PubMed: 12064984]

53. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the μ-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology. 2003; 28:1546–1552. [PubMed: 12813472]

54. Jaffe AJ, Rounsaville B, Chang G, et al. Naltrexone, relapse prevention, and supportive therapy with alcoholics: an analysis of patient treatment-matching. J Consult Clin Psychol. 1996; 64:1044–1053. [PubMed: 8916634]

55. Oslin DW, Pettinati H, Volpicelli JR. Alcoholism treatment adherence: older age predicts better adherence and drinking outcomes. Am J Geriatr Psychiatry. 2002; 10:740–747. [PubMed: 12427583]

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TABLE 1
Demographic and Pretreatment Clinical Characteristics of the Randomized Sample

	Placebo (N = 37)	Naltrexone (N = 37)	Test Statistic	p
Age, years	62.5 (5.6)	64.2 (6.9)	$t = -1.17$	0.248
Male, %	81.1	78.4	χ^2=0.08	0.772
Caucasian, %	64.9	67.6	χ^2=0.06	0.806
Recruitment site, % VA	29.7	32.4	χ^2=0.06	0.802
Ham-D	23.4 (5.0)	20.1 (5.7)	t=2.60	0.011
Days heavy drinking, %	75.8 (29.1)	59.2 (35.6)	t=2.190	0.032
Days drinking, %	82.4 (24.5)	75.5 (29.3)	t=1.11	0.270
Drinks/drinking day	10.2 (6.8)	6.5 (3.9)	t=2.84	0.006
ASI Alcohol Score	0.67 (0.18)	0.64 (0.17)	t=0.79	0.433
PCS	43.8 (8.5)	46.1 (10.3)	$t = -0.99$	0.325
MCS	33.2 (9.6)	38.1 (11.5)	$t = -1.91$	0.061
With primary depression, %	68.6	65.7	χ^2=0.07	0.799

Note: Those subjects randomized to placebo had significantly greater depressive symptoms and pretreatment heavy-drinking days. Values are mean (standard deviation) for continuous measures and percentages for categorical measures.

Ham-D: Hamilton Rating Scale for Depression; ASI: Addiction Severity Index; PCS: Physical Component Score from the Medical Outcomes Scale (SF-36); MCS: Mental Component Score from the Medical Outcomes Scale (SF-36).

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TABLE 2
Clinical Responses Among Those Subjects Assigned to Naltrexone or Placebo

	Placebo	Naltrexone	Regression Coefficient	p
Relapsed, %	32.4	35.1	Wald χ^2=0.159 OR: 1.25 (0.42–3.70)	0.690
Abstinent, %	54.1	43.2	Wald χ^2=0.314 OR=1.34 (0.49–3.68)	0.575
Depression remitted, %	54.1	51.4	Wald χ^2=0.187 OR=1.25 (0.46–3.44)	0.665
Overall improvement, %	43.2	40.5	Wald χ^2=0.381 OR=1.40 (0.48–4.03)	0.537

Note: Ranges are 95% confidence intervals. Overall improvement was defined as: no relapse and depression remitted. Covariates included pretreatment drinking (percent days of heavy drinking and drinks per drinking day) and pretreatment depression severity (Ham-D). All chi-square regressions had 1 df.

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TABLE 3

Relationship Between Drinking During the Trial and Treatment Response (Retention and Depression Remission)

	No Relapse (N = 49)	Relapsed (N = 25)	Regression Coefficient	p
Completed, %	83.7	84.0	Wald χ^2=−0.02 OR: 1.11 (0.28–4.42)	0.886
Depression remitted, %	63.3	32.0	Wald χ^2=6.42 OR: 3.83 (1.36–10.81)	0.011
Ham-D, end of trial	8.8 (6.7)	12.7 (8.2)	β=4.42 (0.94–7.90)	0.013
	Abstinent (N = 36)	**Any Drinking (N = 38)**	**Regression Coefficient**	**p**
Completed, %	86.1	81.6	Wald χ^2=0.15 OR: 0.77 (0.20–2.91)	0.696
Depression remitted, %	55.6	50.0	Wald χ^2=0.17 OR: 1.22 (0.48–3.11)	0.684
Ham-D, end of trial	10.3 (6.6)	11.0 (8.1)	β=0.77 (−2.73 – 4.26)	0.663

Note: Values represent means (standard deviations) for continuous measures and percentages for categorical measures. Regressions were used for responses (95% confidence intervals). Covariates included pretreatment drinking (percent days of heavy drinking and drinks per drinking day) and pretreatment depression severity [Ham-D]). All chi-square regressions have 1 df.