Initial and Maintenance Naltrexone Treatment for Alcohol Dependence Using Primary Care vs Specialty Care

A Nested Sequence of 3 Randomized Trials

Stephanie S. O’Malley, PhD; Bruce J. Rounsaville, MD; Conor Farren, MD, PhD; Kee Namkoong, MD; Ran Wu, MS; Jane Robinson, PsyD; Patrick G. O’Connor, MD, MPH

Background: Naltrexone may improve success in primary care treatment of alcohol dependence (AD). This study tests naltrexone and primary care management (PCM) vs naltrexone and cognitive behavior therapy (CBT) and tests naltrexone maintenance among patients who respond to an initial course of naltrexone combined with PCM vs CBT.

Methods: A nested sequence of 3 randomized trials was conducted. In study 1, 197 subjects with AD participated in a 10-week comparison of PCM and naltrexone (50 mg/d) vs CBT and naltrexone (50 mg/d). In study 2, 53 PCM responders from study 1 continued in a 24-week placebo-controlled study of maintenance naltrexone. In study 3, 60 CBT responders from study 1 continued in a 24-week placebo-controlled study of maintenance naltrexone and CBT.

Results: Study 1: No difference in the response to treatment; 84.1% (74/88) of the PCM patients and 86.5% (77/89) of the CBT patients avoided persistent heavy drinking. Percentage of days abstinent (PDA) declined over time for PCM vs CBT (P = .03). Study 2: Higher response maintenance for PCM and naltrexone (21/26, 80.8%) vs PCM and placebo (14/27, 51.9%; P = .03) and PDA declined more for the placebo group (P = .02). Study 3: The differences between naltrexone vs placebo on maintenance of response (25/30, 83.3% vs 21/30, 70.0%) or PDA did not reach statistical significance.

Conclusions: Naltrexone yielded comparable results during the initial 10 weeks of treatment when combined with PCM or CBT. Maintenance of improvement was enhanced by continued naltrexone treatment in the PCM but not in the CBT arm.

Arch Intern Med. 2003;163:1695-1704

Problem drinking is prevalent in primary care settings, and general internists and other primary care physicians are uniquely suited to identify and treat problem drinkers.1,2 In one study3 of primary care patients, 1 of 6 were problem drinkers, and in another study,4 30% of drinkers met criteria for alcohol dependence. Strategies for addressing alcohol problems in primary care have focused on screening and referral to treatment.5 Research6,7 suggests that primary care physicians may help nondependent patients reduce alcohol consumption by using brief counseling techniques. A recent randomized trial8 performed in physicians’ offices demonstrated that drinking and health resource utilization can be decreased with the use of brief physician advice. Although these studies showed the benefits of brief counseling for nondependent problem drinkers, alcohol-dependent patients were generally excluded. Thus, the role of general internists and other primary care physicians in the treatment of alcohol dependence is uncertain.

New medications to treat alcohol dependence may support effective treatment of alcohol dependence in primary care.2 Naltrexone, an opioid antagonist, was approved by the Food and Drug Administration in 1994 for use in the treatment of alcohol dependence. Two randomized trials9,9 demonstrated that naltrexone therapy is superior to placebo use in decreasing the risk of heavy drinking. These findings have largely been replicated in subsequent published studies of naltrexone and nalmefene.10-17 Although there are published exceptions,18-21 although most previous studies of naltrexone treatment incorporated traditional specialty alcohol behavioral interventions, a preliminary analysis22 of 29 alcohol-dependent individuals in the present study who received naltrexone and brief primary care counseling suggested that this approach is feasible and that it is associ-
ated with reductions in drinking from pretreatment levels. This preliminary study, however, did not compare the effectiveness of this approach, which is based on techniques such as support and advice, with more standard specialty alcoholism treatment such as cognitive behavior therapy (CBT), which strives to teach the patient new skills for coping without the use of alcoholism. Given the emerging role of general internists and other primary care providers in treating alcohol problems and the availability of naltrexone as a Food and Drug Administration–approved treatment for alcohol dependence, the effectiveness of a primary care approach to the management of alcohol dependence with naltrexone therapy is an important question.

Because previous efficacy studies of naltrexone therapy have been limited to 12 weeks, its effectiveness for long-term treatment is unknown. Two follow-up studies23,24 revealed that the benefits of treatment declined after discontinuation of therapy, suggesting the need for longer treatment. An understanding of the long-term effectiveness of naltrexone therapy is particularly important for patients cared for by primary care physicians given the ongoing relationship that these physicians tend to have with their patients. In previous studies9,23 of specialty behavioral therapies, CBT has been found to have an advantage over supportive therapies after discontinuation of treatment.

Thus, the aims of this study are (1) to compare the effectiveness of a primary care model of counseling (PCM) incorporating naltrexone therapy with the effectiveness of specialized alcoholism counseling (CBT) in conjunction with naltrexone therapy for 10 weeks; (2) to determine whether continued naltrexone use for an additional 6 months is efficacious in maintaining the initial response to a short-term trial of naltrexone therapy and PCM; and (3) to determine whether continued naltrexone use for an additional 6 months is efficacious in maintaining the initial response to a short-term trial of naltrexone therapy and CBT.

METHODS

OVERVIEW

Using a single sample of patients, this study is composed of a nested sequence of 3 randomized clinical trials (Figure 1). After baseline assessment, 197 alcohol-dependent patients were randomized to receive 10 weeks of open-label naltrexone treatment and either PCM or CBT. At the end of 10 weeks, individuals in both groups meeting criteria as “responders” were eligible to continue in the maintenance studies. In these studies, responders were randomly assigned to receive 6 months (24 weeks) of treatment comprising either naltrexone maintenance or placebo combined with a less frequent, “maintenance” version of the original behavioral treatment (PCM or CBT).

The design yields 3 related studies aimed at 3 distinct research questions. Study 1, the naltrexone initiation trial, compared PCM and CBT as combined interventions with naltrexone therapy. Study 2, the PCM naltrexone maintenance trial, compared an additional 24 weeks of naltrexone maintenance
therapy with placebo use for responders to the PCM arm of study 1. Study 3, the CBT naltrexone maintenance trial, compared an additional 24 weeks of naltrexone maintenance therapy with placebo use for responders to the CBT arm of study 1.

PARTICIPANTS

Participants were recruited from 1993 through 1997 and were aged 18 to 65 years and met criteria for current DSM-III-R alcohol dependence. Participants were recruited through newspaper advertisements or from patients seeking treatment at the outpatient Alcohol Treatment Unit of the Connecticut Mental Health Center in New Haven, a state-supported mental health center affiliated with Yale University. Written informed consent was obtained at the beginning of the first intake appointment. The protocol was approved by the Yale Human Investigations Committee. At the time of treatment initiation, patients were required to be abstinent from alcohol for 5 to 30 days.

Of 425 patients meeting initial eligibility criteria, 107 were excluded, 121 either declined participation or dropped out before eligibility determination or randomization, and the remaining 197 were randomly assigned to treatment conditions. Reasons for exclusion included the following: no telephone or stable residence (n=9); current DSM-III-R criteria for cocaine abuse or dependence for substances other than alcohol (n=21); current DSM-III-R abuse criteria for opiates or currently using opiates (n=3); significant psychiatric problems (eg, suicidal, psychosis, and current manic episode) or unstable pharmacological treatment for psychiatric disorders (n=20); unstable or significant medical conditions (n=9); evidence of severe hepatocellular injury (eg, aspartate aminotransferase or alanine aminotransferase values >3 times the reference range) (n=17); abstinent more than 30 days (n=2); required more intensive treatment (n=8); more than 5 previous treatment episodes (n=9); or unable to abstain for 5 days (n=10). Although patients receiving other substance abuse treatment were excluded (n=3), those receiving stable pharmacological or behavioral treatment for other nondisabling mental disorders were eligible. Entrance into the study took place only after a psychiatric examination, a physical examination, urine drug screen, and laboratory tests were completed.

Of the 197 patients in study 1, one protocol violation was excluded owing to enrollment in other alcoholism treatment. A total of 190 individuals attended the first session of counseling, at which time study medications were dispensed, and these individuals were considered evaluable for the purpose of these analyses. The number of individuals who did not attend the initial session was comparable for the PCM (n=4) and CBT (n=2) conditions.

To be eligible for the maintenance studies, participants had to have had no more than 2 heavy drinking days in the last 28 days of study 1 and to have taken at least 60% of their study medications during that period. Fifty-three patients continued in the CBT naltrexone maintenance trial (study 2), and 60 patients continued in the CBT naltrexone maintenance trial (study 3). Rates of treatment enrollment and completion for the 3 studies are displayed in Figure 1.

TREATMENTS

Naltrexone

Open-label naltrexone tablets (50 mg) were dispensed biweekly for 10 weeks during study 1. Patients were instructed to take half a tablet (25 mg) on day 1, followed by 1 tablet (50 mg) every day thereafter. After 10 weeks, responders in either behavioral condition were eligible to be randomly assigned to receive an additional 24 weeks of naltrexone (50 mg/d) or identical placebo in studies 2 and 3. Individuals were assigned to receive active or placebo medication by the pharmacist using a computer-generated schedule. All other staff remained masked to treatment assignment. Medication was dispensed biweekly for 1 month and monthly thereafter. Medication compliance was measured using a Medication Event Monitoring System cap (MEMS SmartCap, Aprex Corp, Union City, Calif) that contained a microcomputer chip that recorded the date and time that the pill bottle was opened.26 Two measures of medication compliance were computed for the analyses.27 Percentage of days medication compliant equalled the number of cap openings divided by the total number of days in the study (ie, 70 days for the initial trial and 168 days for the 2 maintenance studies). Duration of medication treatment was the number of days between randomization and the last cap opening during the study.

Behavioral Treatments

Each of the study treatments was manually guided and delivered to patients in individual sessions. During study 1, PCM was provided in an initial 45-minute visit, followed by 15 to 20-minute sessions in weeks 1, 2, 3, 4, 6, 8, and 10; CBT was offered in an initial 1.25-hour session followed by 30-minute sessions weekly during the first 10 weeks. During studies 2 and 3, the frequency of sessions was biweekly for the first month of the maintenance phase and monthly thereafter. Patients in either condition could receive up to 1 emergency session in the initial study and 2 emergency sessions during the maintenance phase.

Therapists for PCM were 2 primary care nurse practitioners, 3 primary care physician assistants, and 1 internist supervised by a general internist (P.G.O). Therapists in the CBT condition were 5 doctoral-level psychologists and 2 masters-level social workers supervised by a clinical psychologist (J.R.). The mean ± SD number of patients seen by each therapist was 15.1 ± 11.8. All therapists attended a didactic seminar, at which the treatment manual, study aims, and procedures were reviewed, and completed at least 1 training case. Therapists met regularly with supervisors to discuss case material and review session audiotapes. After each appointment, therapists recorded the therapeutic strategies used during the session using a checklist. An analysis of these data indicated that the PCM therapists had significantly higher scores on the factor related to PCM and that the CBT therapists had significantly higher scores on the factor related to CBT (P<.01 for both).

Primary Care Management

This condition was developed around advice and clinical management techniques commonly used by primary care providers. The initial visit was designed to be comparable in scope and duration to a “new patient visit” in a primary care setting, and it began with a review of the medical and substance abuse history, followed by a detailing of the substance abuse episode and a review of complications of substance abuse. The provider and patient then worked together to develop a treatment plan, review medication issues, and review advice and goals for subsequent sessions. All patients were referred to Alcoholics Anonymous (AA). The follow-up visits included a review of alcohol use since the last visit and medication issues such as compliance and adverse effects. The provider also discussed symptoms and complications related to alcohol use, efforts to attend AA meetings, and advice and goals for subsequent weeks and visits.

Cognitive Behavioral Therapy

The CBT approach was similar to that used in Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity).28 The treatment uses didactic presentations, cognitive and behavioral rehearsal during sessions, and homework exercises.
Patients learn to identify and handle situations that place them at high risk for resumption of drinking. Omitted from this version of the treatment was advice about the abstinence violation effect in which a “slip” or initial lapse to drinking is followed by negative self-evaluations that exacerbate the relapse process. Instead of instructing patients in strategies for preventing a slip from evolving into a full-blown relapse, emphasis was placed on preparing patients for high-risk situations and unanticipated threats to abstinence. Participation in AA was recommended during the first session.

ASSESSMENTS

During study 1, an independent evaluator assessed patients at intake, weekly for weeks 1 through 4, and biweekly for weeks 5 through 10. During the 2 maintenance studies, assessments were made biweekly for the first 4 weeks and every 4 weeks thereafter.

Psychiatric and substance use diagnoses were made according to DSM-III-R criteria using the Structured Clinical Interview for DSM-III-R. Alcohol use from 90 days before study entry through the end of the study was measured using the Timeline Follow-Back assessment method. Breathalyzer tests were administered at all assessment sessions. Alcohol craving was measured using a modified version of the Obsessive Compulsive Drinking Scale that omitted 4 items asking about drinking. Serum aspartate aminotransferase, γ-glutamyltransferase, and alanine aminotransferase levels were measured at baseline; at 4, 8, and 10 weeks; and monthly during the maintenance studies using a single laboratory. Finally, adverse events were monitored at baseline and at each research appointment using the SAFFTEE GI (Systematic Assessment for Treatment Emergent Events—General Inquiry).

STATISTICAL ANALYSIS

Data analyses were carried out separately for the 3 studies. Percentage of days abstinent (PDA) measured drinking frequency and was 1 of the 2 primary outcomes. In study 1, drinking was summarized by 2-week period. In the 2 maintenance studies, drinking was summarized by month. The classification of patients responding to treatment was the second primary outcome measure. In study 1, patients who had no more than 2 days of heavy drinking in the final 28 days of the 10-week treatment were considered responders. In the 2 maintenance studies, response to treatment was defined as no more than 2 days of heavy drinking during any 28-day period. A day of heavy drinking was one in which a man consumed 5 or more drinks and a woman consumed 4 or more drinks.

Additional variables were examined in secondary analyses. Drinks per drinking day (DDDs) provided a measure of drinking intensity averaged over each period of observation as discussed for PDA (abstinent individuals received a score of 0). Relapse to a single day of heavy drinking was analyzed to permit comparisons to other studies of naltrexone therapy. Change in γ-glutamyltransferase level from baseline provided a biological marker sensitive to alcohol consumption, and the Obsessive Compulsive Drinking Scale provided a measure of craving.

Analyses of variance, χ² tests, or Fisher exact tests (2-tailed) were used where appropriate to examine between-group differences on baseline variables. χ² Tests or Fisher exact tests were used to analyze categorical outcomes (response to treatment, relapse to heavy drinking). Analyses of variance were used to analyze continuous outcomes. Longitudinal outcomes with repeated measures (PDA, DDDs, and Obsessive Compulsive Drinking Scale score) were analyzed with random coefficient regression using the PROC MIXED procedure (SAS Institute Inc, Cary, NC) after testing of statistical assumptions. In study 1, summary scores from the 90-day alcohol timeline were treated as point 0 for the models testing PDA and DDDs. In studies 2 and 3, data obtained from the last 28 days of study 1 were treated as point 0. Significant treatment interactions with time were tested on a period by period basis to evaluate how they changed over time. Given that the distribution of scores on number of DDDs was highly skewed, these scores were square root transformed before conducting the analyses.

All outcome analyses were based on observed data. The completeness of data for the groups was similar (Figure 1). In the random coefficient models, it is assumed that individuals’ missing data would have followed the same linear trajectory as their observed data.  

RESULTS

STUDY 1: NALTREXONE INITIATION TRIAL

Sample Characteristics

The demographic and clinical characteristics of the 190 participants who were considered evaluable in the comparison of PCM and naltrexone therapy vs CBT and naltrexone therapy are given in Table 1. Patients randomized to the 2 behavioral treatment conditions (PCM and CBT) did not differ in demographic and clinical characteristics or in the mean±SD number of days abstinent from alcohol before treatment (PCM group: 11.8±7.9 days; P=.29 and CBT group: 12.9±7.4 days).

Treatment Exposure

Measures of exposure to the study treatments, medication, and counseling are given in Table 2. There were no significant differences in medication compliance or in the duration of participation in the medication components of the study. The number of sessions attended was significantly higher for CBT participants than for PCM participants (P=.02), in keeping with the design of CBT as a more intensive intervention with more sessions offered. Conversely, PCM participants were more likely to attend AA meetings (34 [38%] of 90 vs 20 [22%] of 89, χ²=5.00, P=.03), consistent with the greater focus on AA participation in the PCM approach.

Treatment Effectiveness

χ² Analysis of the percentage of patients classified as responding to initial treatment based on drinking criteria—no more than 2 days of heavy drinking during the last 28 days of study 1—did not yield statistically significant differences between the 2 behavioral treatment groups. Overall, 85.3% (151/177) of the patients responded to the initial treatment combining naltrexone (50 mg) and 1 of 2 behavioral counseling methods. However, the proportion of responders who were abstinent during the last 28 days was significantly higher in the CBT group (59 of 77 patients) than in the PCM group (43 of 74 patients) (χ²=5.9; P=.02).

The results of the random-effects regression model analyzing PDA revealed a significant therapy × time interaction (F1,710=4.60; P=.03). Both groups evidenced high levels of abstinent days after enrollment into treatment,
but this rate was better maintained in the CBT group than in the PCM group (Figure 2). The effectiveness of naltrexone when provided in combination with PCM vs CBT was not significantly different on any of the secondary outcomes obtained during the initial treatment (Table 2).

**STUDY 2: PCM NALTREXONE MAINTENANCE TRIAL**

**Sample Characteristics**

Of the 74 PCM patients who were classified as responders based on drinking criteria, 53 entered the maintenance study. The remainder were not enrolled for the following reasons: 8 had discontinued treatment before the end of the initial study, 8 did not meet the medication compliance criterion, 3 declined further treatment, and 2 were excluded for other reasons. The randomized patients were predominantly men (68%), white (96%), employed (74%), and unmarried (51%) and had a mean ± SD age of 46.5 ± 7.8 years. Patients assigned to discontinuation vs maintenance naltrexone did not differ significantly on initial demographic or clinical indices.

**Treatment Exposure**

There were no significant differences between patients who continued taking naltrexone and those who switched to placebo use in medication compliance, duration of participation, or attendance at counseling sessions (Table 3). In addition, attendance at AA meetings was similar for naltrexone (12 [46%] of 26) and placebo (10 [37%] of 27) patients (χ² < 1, P = .50).

**Treatment Efficacy**

The 2 primary outcome measures—maintenance of response and PDA—revealed an advantage of continued naltrexone use over placebo use in patients initially responding to naltrexone therapy and PCM (Table 3). Among patients who were classified as maintaining their response, the proportion remaining continuously abstinent was similar for the naltrexone (9 of 21 patients) and placebo (5 of 14 patients) groups. A benefit of continued naltrexone therapy was also demonstrated by the random-effects regression model analysis of PDA by month. Specifically, a significant medication × time interaction was found (F = 5.52; P = .02) in which the PDA declined over time to a greater degree in the placebo group (last 28 days of study 1, 92.1% ± 22.6%; month 6, 72.2% ± 36.0%) in contrast to the naltrexone group (last 28 days of study 1, 95.2% ± 7.1%; month 6, 88.9% ± 19.0%).

Similar findings were obtained for 2 of the secondary outcomes. The random-effects regression analysis of DDDs revealed a significant medication × time interaction. For the placebo group, mean ± SD DDDs increased from 1.2 ± 2.9 during the baseline period (the last month of study 1) to 4.4 ± 5.0 during month 6 of the maintenance study. In contrast, mean ± SD DDDs for the naltrexone group changed little from baseline (2.0 ± 3.9). Consistent with reports of greater drinking, γ-glutamyltransferase levels increased significantly in the placebo group compared with the naltrexone group (P = .03). No differences were observed in continuous abstinence or in Obsessive Compulsive Drinking Scale scores.

### Table 1. Baseline Characteristics of 190 Participants in the Naltrexone Initiation Trial (Study 1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCM Arm (n = 93)</th>
<th>CBT Arm (n = 97)</th>
<th>df</th>
<th>χ²/ F Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No. (%)</td>
<td>65 (70)</td>
<td>70 (72)</td>
<td>1</td>
<td>0.12</td>
<td>.73</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>43.8 ± 8.6</td>
<td>44.5 ± 9</td>
<td>1</td>
<td>0.33</td>
<td>.56</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td>3</td>
<td>2.08</td>
<td>.56</td>
</tr>
<tr>
<td>White</td>
<td>88 (95)</td>
<td>90 (93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status, No. (%)</td>
<td></td>
<td></td>
<td>1</td>
<td>0.07</td>
<td>.79</td>
</tr>
<tr>
<td>Married</td>
<td>43 (46)</td>
<td>43 (44)</td>
<td>3</td>
<td>0.08</td>
<td>.96</td>
</tr>
<tr>
<td>Other</td>
<td>50 (54)</td>
<td>54 (56)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level, No. (%)</td>
<td></td>
<td></td>
<td>3</td>
<td>0.08</td>
<td>.96</td>
</tr>
<tr>
<td>More than high school</td>
<td>65 (70)</td>
<td>66 (68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>20 (22)</td>
<td>22 (23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>8 (9)</td>
<td>9 (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status, No. (%)</td>
<td></td>
<td></td>
<td>1</td>
<td>1.12</td>
<td>.29</td>
</tr>
<tr>
<td>Employed</td>
<td>75 (81)</td>
<td>72 (74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18 (19)</td>
<td>25 (26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days abstinent, mean ± SD,*</td>
<td>40.2 ± 23.1</td>
<td>35.1 ± 23.2</td>
<td>1</td>
<td>2.30</td>
<td>.13</td>
</tr>
<tr>
<td>Drinks per drinking day, mean ± SD, No.*</td>
<td>9.2 ± 5.5</td>
<td>9.6 ± 6.4</td>
<td>1</td>
<td>0.29</td>
<td>.59</td>
</tr>
<tr>
<td>Days without heavy drinking, mean ± SD, %†</td>
<td>46.9 ± 29.4</td>
<td>42.1 ± 32.4</td>
<td>1</td>
<td>1.02</td>
<td>.31</td>
</tr>
<tr>
<td>γ-Glutamyltransferase level, mean ± SD, U/L</td>
<td>78 ± 97</td>
<td>82 ± 95</td>
<td>1</td>
<td>0.09</td>
<td>.76</td>
</tr>
<tr>
<td>Positive family history of alcoholism in first-degree relatives, No. (%)</td>
<td>66 (71)</td>
<td>70 (73)</td>
<td>1</td>
<td>0.09</td>
<td>.77</td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavior therapy; PCM, primary care management.

*During 90-day pretreatment baseline period.
†Heavy drinking refers to drinking 5 or more drinks for men or 4 or more drinks for women.
STUDY 3: CBT NALTREXONE MAINTENANCE TRIAL

Sample Characteristics

Of the 77 CBT patients who were classified as responders based on drinking criteria, 60 entered the maintenance study. The remainder were not enrolled for the following reasons: 12 had discontinued treatment, 3 did not meet the medication compliance criterion, and 2 declined further treatment. Randomized patients were predominantly men (72%), white (97%), employed (78%), and unmarried (52%) and had a mean±SD age of 45.4±9.2 years. Those assigned to receive discontinuation vs maintenance naltrexone did not differ on initial demographic or clinical indices.

Treatment Exposure

There were no significant differences in medication compliance between the naltrexone and placebo groups or in the duration of participation in the medication or behavioral components during study 3 (Table 4). Attendance at AA meetings was similar for patients treated with naltrexone (10 [33%] of 30) vs placebo (6 [20%] of 30) ($\chi^2 = 1.36; P = .24$).

Treatment Efficacy

Responders to initial treatment with naltrexone and CBT had comparable outcomes with maintenance CBT irrespective of whether they continued taking naltrexone or switched to placebo (Table 4). The percentage of indi-
individuals who maintained their initial treatment response, defined as no more than 2 days of heavy drinking during any 28-day period during the 6-month maintenance phase, was high in both groups (25 [85%] of 30 naltrexone users and 21 [70%] of 30 placebo users). Although the percentage of patients maintaining response was somewhat higher in the naltrexone group, this difference did not reach statistical significance (\(P = .22\)). Of the 46 responders across the 2 groups, 30 were continuously abstinent. Percentage of days abstinent by month remained high for both groups and did not differ significantly as a function of medication or medication \(\times\) time interaction (placebo group: last 28 days of study 1, 98.6%±3.7%; month 6, 90.1%±22.2%; naltrexone group: last 28 days of study 1, 98.2%±4.9%; month 6, 91.0%±17.9%). Other secondary outcome measures did not reveal significant effects of medication or medication \(\times\) time interactions.

**LONG-TERM SAFETY: NALTREXONE VS PLACEBO**

During initial therapy with naltrexone in study 1, 76% (143/189) of the patients reported experiencing 1 or more symptoms potentially related to naltrexone use, with nausea being the most common complaint (40 patients [21%]), consistent with our previous study\(^{36}\) on a subsample of patients. Collapsing across studies 2 and 3, the number of patients reporting 1 or more symptoms during maintenance treatment did not differ significantly between the naltrexone group (14 [25%] of 56 patients) and the placebo group (16 [28%] of 57 patients). Five of 56 naltrexone-treated patients experienced fatigue, and a similar proportion reported abdominal cramps, whereas no placebo-treated patients had these complaints (\(P = .02\)). No other symptoms distinguished naltrexone- and placebo-treated patients. Two deaths were reported. One patient died as a result of a perforated colon secondary to pancreatic cancer that was diagnosed after week 26 of naltrexone therapy. The second death occurred 3 months after the patient withdrew from the study (after taking naltrexone for 12 weeks), due to causes presumed to be related to alcoholism.

Alanine aminotransferase levels measured at baseline, at the end of week 10, and monthly during the study were analyzed as the primary marker for hepatotoxicity for the 113 patients who participated in the maintenance studies. Analyses of variance of alanine aminotransferase levels at each of these points did not detect any significant differences between the active medication and placebo groups. Findings from analyses of aspartate aminotransferase levels paralleled those described for alanine aminotransferase.

### Table 3. Treatment Utilization and Efficacy in the PCM Naltrexone Maintenance Trial (Study 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Naltrexone Group (n = 26)</th>
<th>Placebo Group (n = 27)</th>
<th>df</th>
<th>(\chi^2/F) Test</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed treatment, No. (%)</td>
<td>17 (65)</td>
<td>13 (48)</td>
<td>1</td>
<td>1.60</td>
<td>.21</td>
</tr>
<tr>
<td>Weeks in treatment, mean ± SD, No.</td>
<td>18.1 ± 8.8</td>
<td>16.1 ± 9.2</td>
<td>1</td>
<td>0.68</td>
<td>.41</td>
</tr>
<tr>
<td>Therapy sessions, mean ± SD, No.</td>
<td>5.8 ± 2.7</td>
<td>5.3 ± 2.6</td>
<td>1</td>
<td>0.57</td>
<td>.45</td>
</tr>
<tr>
<td>Duration of medication treatment, mean ± SD, d</td>
<td>134.8 ± 51.6</td>
<td>128.4 ± 46.2</td>
<td>1</td>
<td>0.21</td>
<td>.65</td>
</tr>
<tr>
<td>Days medication compliant, mean ± SD, %</td>
<td>64.0 ± 31.2</td>
<td>52.5 ± 32.0</td>
<td>1</td>
<td>1.75</td>
<td>.19</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders, No. (%)(^{†})</td>
<td>21 (81)</td>
<td>14 (52)</td>
<td>1</td>
<td>4.94</td>
<td>.03*</td>
</tr>
<tr>
<td>Days abstinent, %(^{‡})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication, mean ± SD</td>
<td>89.8 ± 17.9</td>
<td>78.4 ± 33.4</td>
<td>1,254</td>
<td>0.77</td>
<td>.38</td>
</tr>
<tr>
<td>Time</td>
<td>1,51</td>
<td>23.9</td>
<td>&lt;.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication (\times) time</td>
<td>1,254</td>
<td>5.52</td>
<td>.02*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinks per drinking day, No.(^{§})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication, mean ± SD</td>
<td>2.1 ± 3.8</td>
<td>3.03 ± 4.8</td>
<td>1,254</td>
<td>0.16</td>
<td>.69</td>
</tr>
<tr>
<td>Time</td>
<td>1,51</td>
<td>11.3</td>
<td>.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication (\times) time</td>
<td>1,254</td>
<td>4.40</td>
<td>.04*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous abstinence, No. (%)(^{∥})</td>
<td>9 (35)</td>
<td>5 (19)</td>
<td>1</td>
<td>1.77</td>
<td>.18</td>
</tr>
<tr>
<td>GGT end point change from week 10, mean ± SD, U/L(^{¶})</td>
<td>0.6 ± 23.25</td>
<td>41.05 ± 88.89</td>
<td>1</td>
<td>4.81</td>
<td>.03*</td>
</tr>
<tr>
<td>OCDS total score(^‡)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication, mean ± SD</td>
<td>5.7 ± 4.9</td>
<td>5.6 ± 4.8</td>
<td>1,226</td>
<td>&lt;1.00</td>
<td>.95</td>
</tr>
<tr>
<td>Time</td>
<td>1,50</td>
<td>1.99</td>
<td>.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication (\times) time</td>
<td>1,226</td>
<td>&lt;1.00</td>
<td>.59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GGT, \(\gamma\)-glutamyltransferase; OCDS, Obsessive Compulsive Drinking Scale; PCM, primary care management.

*Statistically significant.

\(^{†}\)Responders had maintenance of initial treatment response as defined by no more than 2 days of heavy drinking during any 28-day period during the 6-month discontinuation study.

\(^{‡}\)Random coefficient model. Baseline is included. The effect of interest is the medication \(\times\) time interaction.

\(^{§}\)Statistics are based on square root–transformed data; means are reported using untransformed data.

\(^{∥}\)During the period when data were available.

\(^{¶}\)Naltrexone group: n = 25; placebo group: n = 22.
The following results emerged from this sequence of studies evaluating naltrexone and behavioral treatments in initial and maintenance treatment of alcohol dependence:

1. Except for PDA, PCM and CBT yielded comparable outcomes during the first 10 weeks of active treatment with naltrexone.

2. After an initial 10 weeks of combined PCM and naltrexone therapy, maintenance naltrexone therapy during the subsequent 6 months vs placebo therapy was significantly more likely to result in sustained improvement among initial treatment responders.

3. After an initial 10 weeks of combined CBT and naltrexone therapy, maintenance naltrexone therapy during the subsequent 6 months conferred no significant advantage over placebo therapy and maintenance CBT counseling among initial treatment responders.

Most previous studies have tested the efficacy of naltrexone therapy combined with specialty alcoholism treatment approaches. Our results suggest that naltrexone therapy shows promise as a therapy that could be used effectively with a PCM model of counseling. During study 1, the overall outcomes of patients receiving PCM and naltrexone were similar to those of patients receiving CBT and naltrexone. In particular, the percentage of patients classified as responding to therapy was comparable (effect size, 0.002). On measures of abstinence, CBT had a small advantage in the later weeks of the initial treatment trial. This difference may have resulted from either the content of the CBT or the fact that the schedule of appointments changed to biweekly in the PCM group after the fourth week of treatment but remained weekly for the CBT group through the end of the 10-week period. There were no differences between the 2 groups on any of the secondary measures. In extending this work, future studies should evaluate the effectiveness of this approach to managing alcohol dependence directly in physicians' offices with typical primary care patients.

The results of the 2 maintenance trials suggest that the value of continued naltrexone use after a positive response to an initial course of naltrexone and counseling may depend on the type of behavioral counseling provided. When the initial counseling approach used a PCM model, continued naltrexone use resulted in greater maintenance of response over continued maintenance counseling appointments and placebo use. Sustained improvements were observed on the 2 primary variables and on several secondary outcomes, including DDDs and γ-glutamyltransferase level, a biochemical marker of heavy drinking. When the initial counseling was CBT, continuous...
used naltrexone therapy did not confer a significant advantage over monthly maintenance counseling appointments and placebo use on any of the primary or secondary outcome measures. However, it is conceivable that different results might have been obtained if patients had discontinued all medication use rather than switching to placebo therapy or in a larger study with greater power to detect true differences between the groups that might be clinically meaningful.

The percentage of participants maintaining their initial response among those receiving continued naltrexone and PCM (80.8%) was comparable to that observed for the participants who received continued naltrexone and CBT (83.3%) and the participants who were switched to placebo and CBT (70.0%). These findings suggest that when using the treatments studied, long-term response may be optimized through either of 2 approaches: (1) short-term naltrexone therapy combined with more specialized alcoholism treatment such as CBT followed by maintenance counseling alone or (2) long-term naltrexone therapy combined with PCM counseling. This is of particular importance given that alcohol-dependent individuals are equally likely to seek treatment from a primary care provider as from a specialty addiction service.

There are several limitations to this study. First, the PCM intervention was evaluated using a sample of treatment-seeking alcohol-dependent individuals who received care in a research clinic. Consequently, the results may not generalize to all primary care patients with alcohol dependence but rather to those who are more motivated to change their drinking. On the other hand, the primary care providers were new to the patients, whereas providers in a primary care setting would have an ongoing relationship with the patient, which might increase the effectiveness of the intervention. Finally, the primary care intervention was more intensive than the brief interventions currently used to address hazardous drinking in primary care settings. Given that alcohol dependence is a more serious problem than hazardous drinking, the intervention was intended to approximate the more intensive follow-up used to manage acute exacerbations of other chronic illnesses such as diabetes mellitus and cardiovascular disease, with less frequent follow-up during the maintenance phase. The potential feasibility of incorporating this approach into primary care settings may be increased by using nonphysicians (eg, advanced practice registered nurses, physician associates, and nurses) to provide the counseling. Based on this initial demonstration of the effectiveness of naltrexone therapy using a primary care approach, future research should evaluate the effectiveness of naltrexone therapy with more minimal interventions and with patients recruited from and treated within primary care clinics.

The initial treatment trial did not evaluate the efficacy of naltrexone therapy but rather the effectiveness of 2 models of care that incorporated naltrexone therapy, an approved treatment for alcohol dependence. The efficacy of naltrexone therapy has been demonstrated in other double-blind, placebo-controlled studies of naltrexone therapy combined with specialty counseling, and a meta-analysis of these studies suggests that naltrexone therapy yields a 12% to 19% improvement over placebo therapy and counseling. Although this is a modest difference, it is comparable to that in studies comparing transdermal nicotine replacement therapy with placebo patches. Regardless of whether the improvements observed in the initial phase of our study can be attributed directly to naltrexone pharmacotherapy or to the concurrent counseling, the data suggest that alcoholism treatment incorporating naltrexone and primary care counseling can be effective in selected patients. Bolstering this conclusion, Monterosso and colleagues found a significant advantage of naltrexone use over placebo use in patients who received concurrent therapy with a primary care counseling approach for 13 weeks.

Ultimately, the value of adjunctive pharmacotherapy may be most apparent when the behavioral intervention is less intensive or in patients who are not as responsive to more intensive specialty care interventions, for example, those with a family history of alcoholism. Consistent with this hypothesis, the negative findings of the Veterans Affairs Naltrexone Cooperative Study may be due in part to the good response that the placebo group had to the concurrent behavioral intervention, which used a strongly abstinence-oriented intervention (12-step facilitation) and counseling about medication compliance. The hypothesis that the intensity of the behavioral intervention may affect the efficacy of treatment with naltrexone and acamprosate is being directly tested in an ongoing multisite study sponsored by the National Institute on Alcohol Abuse and Alcoholism.

In conclusion, this 3-part clinical trial of initial and maintenance naltrexone therapy for alcohol dependence suggests that naltrexone therapy can be combined with a primary care counseling approach and be used by general internists and other primary care providers to treat alcohol dependence in selected patients. When used openly during a 10-week initial treatment phase, largely equivalent results were obtained when naltrexone administration was combined with either PCM or CBT, a behavioral treatment designed for use by substance abuse treatment specialists. For 6 months after initial treatment, maintenance of improvement was enhanced by continued naltrexone treatment in responders to PCM, but the effect was not statistically significant in responders to CBT. Thus, when naltrexone is used, a primary care alternative to specialty alcohol dependence treatment may yield similar results if naltrexone use is maintained after the treatment initiation phase in conjunction with monthly follow-up appointments. The major benefit of this may be to increase access to effective treatment for alcohol dependence by enlisting primary care providers into the treatment system. This could not only increase the number of treatment sites for patients with alcohol dependence but also may provide a new site for care that may be more attractive to selected patients with alcohol dependence who would not have otherwise entered treatment. Further research should be directed toward evaluating this model in typical primary care settings. Finally, when initial naltrexone treatment is combined with CBT, treatment gains are likely to be maintained for many in-
individuals who continue in monthly counseling. In the present study, long-term maintenance on active medication did not seem to confer a large additional benefit when provided in the context of maintenance CBT sessions; however, there may be a subset of patients for whom continued naltrexone therapy may be helpful. Future efforts to identify individual differences that predict response should be undertaken to better inform treatment recommendations for naltrexone therapy.

Accepted for publication September 30, 2002.

This study was supported by grants RO1AA09538, KO2AA00171, and KO5DA00089 from the National Institute of Health, Bethesda, Md, and by Veterans Administration New England Mental Illness Research Education and Clinical Center (MIRECC), West Haven, Conn. Naltrexone and matching placebo were supplied by DuPont Pharmaceuticals, Wilmington, Del.

We thank Joel Dubin, PhD, for statistical review of this manuscript; Philip Wirtz, PhD, for statistical consultation; and Ellen Anderson, BA, Elaine Lavelle, MA, and Anna Forselius, MA, for their assistance with the study.

Corresponding author and reprints: Stephanie S. O’Malley, PhD, Department of Psychiatry, Yale University School of Medicine, Connecticut Mental Health Center, 34 Park St, Room S-202, New Haven, CT 06519 (e-mail: stephanie.omalley@yale.edu).

REFERENCES