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Efficacy of Acamprosate for the Treatment of Alcohol Dependence Long After Recovery From Withdrawal Syndrome: A Randomized, Double-Blind, Placebo-Controlled Study Conducted in Japan (Sunrise Study)

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ABSTRACT

Objective: To undertake a double-blind, randomized, placebo-controlled trial to examine the efficacy of acamprosate in maintaining complete abstinence in Japanese patients with alcohol dependence.

Method: We enrolled 327 patients with *ICD-10*–defined alcohol dependence and randomly assigned them to treatment with either acamprosate (1,998 mg/d orally) or placebo for 24 weeks. The primary endpoint was complete abstinence after 24 weeks of administration. The study was performed at 34 medical institutions between 2009 and 2011.

Results: The acamprosate group demonstrated significantly superior efficacy versus the placebo group on the primary endpoint: the proportion maintaining complete abstinence in the acamprosate group was 47.2% (77/163 subjects), compared with 36.0% (59/164 subjects) in the placebo group ($P = .039$). The difference in complete abstinence rates between the 2 groups was 11.3% (95% CI, 0.6%–21.9%).

Conclusions: Acamprosate is superior to placebo in maintaining abstinence in Japanese patients with alcohol dependence. These findings concur with 11 randomized, blinded, placebo-controlled clinical trials conducted in Europe. This study was designed to reflect clinical practice in Japan and is therefore a meaningful addition to the available evidence in this field.

Trial Registration: JapicCTI identifier: 090694

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Acamprosate was originally synthesized in the laboratories of the French pharmaceutical company Meram and was first approved for clinical use in France in 1987. It is currently licensed for use in 25 countries, including Japan. There have been several meta-analyses of studies that have examined the clinical effectiveness of acamprosate.[1–5] In patients with alcohol dependency, the drug inhibits elevated glutamatergic neurotransmission, suppressing alcohol craving[6–11]; however, the exact mechanism of action has not been completely identified.[8,10]

Alcohol dependence and the inability to overcome the urge to drink[12] have substantial mental, physical, and social costs.[13,14] The prognosis for patients is poor, as current treatments have limited efficacy, and there is an urgent need for better therapeutic options.[15] Achieving and maintaining abstinence are crucial to a successful outcome.[16,17]

In our previous study[18] of the efficacy of inpatient treatment, we found that 55.4% (160/351) of subjects maintained complete abstinence 3 months after discharge, a figure that declined to 38.4% (76/351) after 1 year. The abstinence rates were 48.2% and 25.9%, respectively, if those lost to follow-up were excluded from the analysis. As it is extremely difficult to recover from alcohol dependence, and recovery rates have failed to improve despite significant efforts in the field,[15] it is vitally important to find new ways of helping patients to maintain abstinence. Acamprosate has recently been approved for clinical use in Japan, offering a new drug treatment option where such options had previously been limited to disulfiram and cyanamide.

We conducted a randomized, double-blind study comparing acamprosate with placebo in Japanese patients, the design of which differs from studies undertaken in the United States and European Union in 2 respects. First, we designed the study to reflect routine clinical practice for the treatment of alcohol dependence in Japan, which differs substantially from practice in the European Union and United States. In Japan, patients are hospitalized for about 2 months for treatment of withdrawal symptoms followed by rehabilitation therapy, with drug treatment being initiated on the day of hospital discharge. By contrast, in EU studies, patients are discharged soon after treatment for withdrawal symptoms, with drug treatment initiated upon discharge or after several days. Studies in the United States focused on outpatients only, with alcohol withdrawal symptoms treated in the community if necessary.[19] Second, it is important to advise subjects to keep a diary every day and to confirm abstinence by interviewing a cooperative attendant, as this gives the data greater credibility. In EU[20–31] and US[19] studies, family and friends were interviewed about the subject's use of alcohol when possible, but in the present study a more rigorous methodology was used.

Clinical Points

- In a study designed to reflect clinical practice in Japan, acamprosate was superior to placebo in maintaining abstinence in patients with alcohol dependence.
- The study findings concur with those of 11 randomized, blinded, placebo-controlled clinical trials of acamprosate conducted in Europe.

This study is the first in which such a design has been implemented, and thus our aim was to provide a meaningful addition to the literature on the efficacy of acamprosate in the context of medical practice in Japan and worldwide.

METHOD

We undertook a randomized, double-blind, placebo-controlled trial of acamprosate for the maintenance of abstinence at 34 medical institutes, enrolling subjects who were diagnosed with alcohol dependence according to *ICD-10* criteria and who expressed a desire to abstain. Investigators specializing in the treatment of alcohol dependence came from the 34 medical institutions participating in this clinical study. Each of these institutions has both a department of psychiatry and inpatient facilities. Subjects were selected from among patients hospitalized in these institutions. They progressed to the rehabilitation phase after completing treatment for withdrawal symptoms. The main inclusion and exclusion criteria are summarized in Figure 1. The investigator and clinical research coordinator (CRC) explained the study procedures to each subject. At each visit, they also provided details of the schedule for the next visit. An independent investigational drug allocation controller, who was affiliated neither with a participating medical institution nor with the sponsor, carried out blinding of the investigational drugs. The investigational drugs were numbered and then delivered to the participating institutions. At each institution, the investigational drugs in press-through-package sheets were handed in numerical order to the subjects at the time of discharge and at each visit (Table 1). Subjects were administered acamprosate 1,998 mg/d or placebo orally for 24 weeks beginning on the day of discharge after completion of inpatient therapy, followed by a further 24-week follow-up period. Two tablets of the investigational drug (333 mg of placebo) were to be administered after meals 3 times per day. The primary endpoint was complete abstinence. The investigators remained blinded to the group allocation of those who dropped out throughout the study. Figure 1 shows the study schedule, including study visits and observational parameters. The study was performed between 2009 and 2011.

The study was reviewed and approved by the institutional review board (IRB) at each site or the central IRB and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent before any study-related procedures were performed. The study was registered with Japan Pharmaceutical Information Center—Clinical Trials Information (JapicCTI identifier: 090694). A complete list of the study investigators is available in eAppendix 1 at PSYCHIATRIST.COM.

Evaluation of Efficacy

The primary endpoint was complete abstinence maintained for the 24-week study drug treatment period. Secondary endpoints were cumulative days of abstinence during the 24-week study drug treatment period, time elapsed between initiation of study drug treatment and first relapse regardless of the type or amount of alcohol consumed, and time elapsed between initiation of study drug treatment and the third day of 3 or more consecutive days of heavy drinking (defined as equivalent to 60 g/d or more of pure alcohol).

Psychosocial Therapy

The investigators provided subjects with psychosocial therapies including individual psychotherapy, individual and group psychotherapy, and participation in a self-help group. For the individual psychotherapy, therapeutic intervention focusing on counseling for individual subjects was provided by a psychiatrist. For the group psychotherapy, a group of health care providers led by a psychiatric specialist such as a psychiatrist or a clinical psychologist provided group therapy for several patients. Cognitive-behavioral therapy or similar therapies were used in group psychotherapy sessions. The subjects were advised to participate in the meetings of self-help groups including abstinence groups and Alcoholics Anonymous. Because these therapies differed among the subjects, the types and frequency of psychosocial therapies were not considered in this study. The investigators provided all subjects with counseling at the time of their visit. At every visit, a CRC checked the contents of the subject's diary and medication compliance. The CRC informed the investigator of the information obtained from the subject. The investigator then considered the information and provided the subject with counseling.

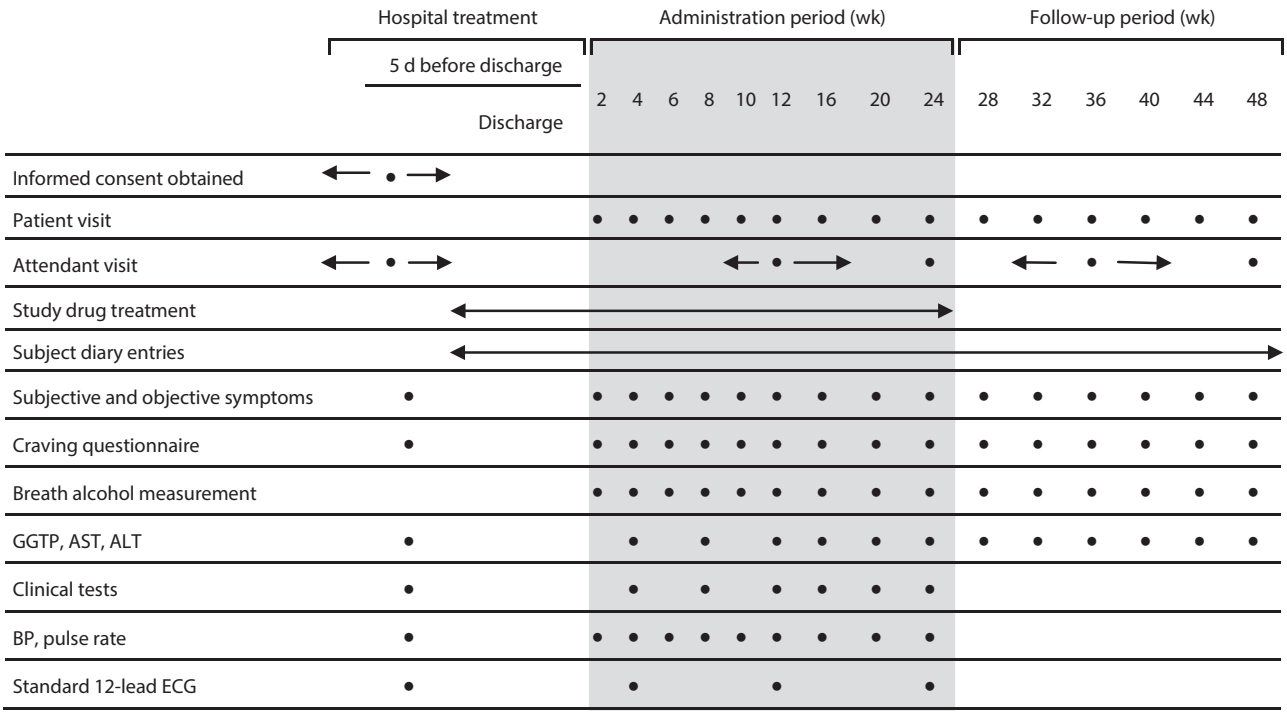
Instructions to Subjects

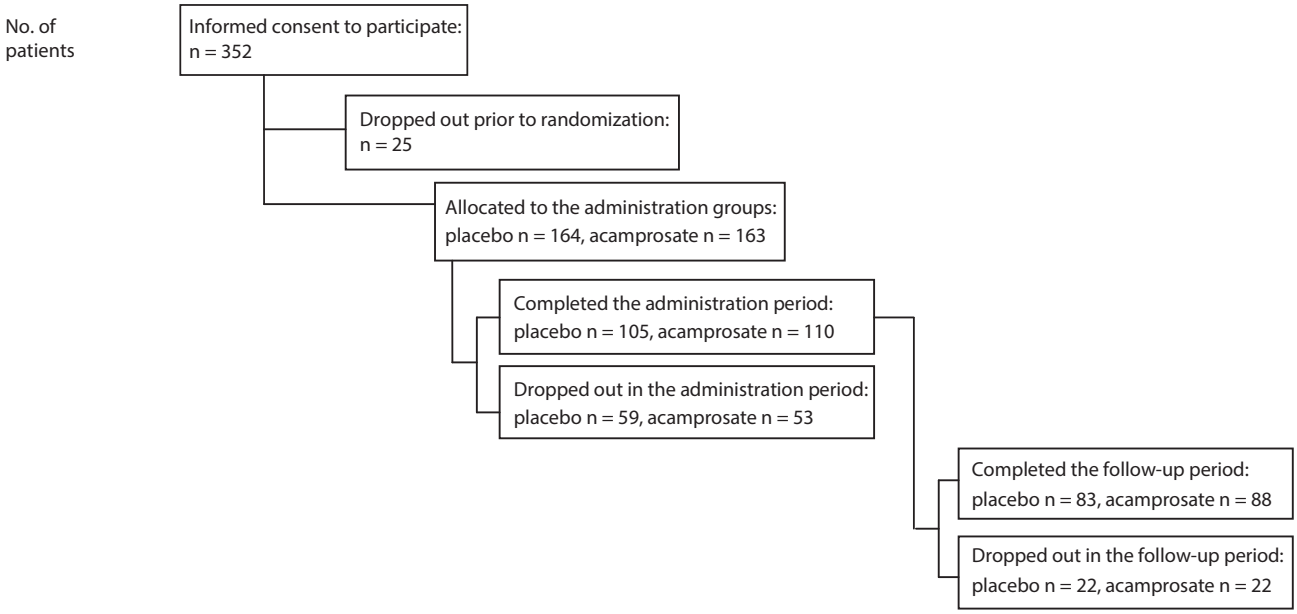
Investigators and CRCs instructed subjects to keep a diary to enhance data integrity, including information about daily dosing, whether or not alcohol was consumed, and, if so, how much and under what circumstances. If errors or omissions were noted during scheduled visits, subjects were asked to correct or make additions to their diary.

Role of Attendants

Accurate information about subjects' abstinence is essential to allow valid conclusions about the efficacy of acamprosate to be drawn. For this reason, the study protocol included the requirement for each participant to have a cooperative attendant aged 20 years (the age of majority in Japan) or over who lived with the subject and had the capacity to constantly observe the subject and attend the planned visits during the study period.

Figure 1. Study Schedule, Numbers of Patients, and Inclusion and Exclusion Criteria





Inclusion criteria	Those who (1) met the diagnostic guidelines of dependence syndrome specified in *ICD-10* and were diagnosed with alcohol dependence, (2) were willing to remain abstinent, (3) were 20 years or older, (4) had a fixed address, and (5) could have constant contact with the medical institution during the clinical study period.
Exclusion criteria	Those who (1) had a history of use of stimulants, cannabis, or narcotics (excluding therapeutic use); (2) had a history of abuse of psychotropic drugs, organic solvents, or antipyretic/analgesic/antiphlogistic drugs; (3) also suffered from a psychiatric disorder requiring treatment with antidepressants, antipsychotic drugs, antiepileptic drugs, or antimanic drugs; (4) had epilepsy; (5) had a history of attempted suicide; (6) also suffered from a serious renal disorder or hepatopathy; (7) had undergone intestinal resection; (8) had chronic pancreatitis; or (9) had been admitted to a transitional facility.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = blood pressure, ECG = electrocardiogram, GGTP = γ-glutamyl transpeptidase.

Table 1. Demographic and Other Baseline Characteristics of the Efficacy Analysis Set

Characteristic	Placebo (n = 164)	Acamprosate (n = 163)
Age, mean ± SD, y	53.1 ± 12.2	51.7 ± 12.4
Sex, n (%)		
Male	145 (88.4)	141 (86.5)
Female	19 (11.6)	22 (13.5)
Length of dependence, n (%)		
Under 10 y	89 (54.3)	88 (54.0)
10 y or more	75 (45.7)	75 (46.0)
History of inpatient treatments for alcohol dependence, n (%)		
Once	93 (56.7)	107 (65.6)
Twice	36 (22.0)	24 (14.7)
Three times or more	35 (21.3)	32 (19.6)
Delirium tremens, n (%)	51 (31.1)	39 (23.9)
Withdrawal spasms, n (%)	25 (15.2)	23 (14.1)
GGTP,[a] mean ± SD, U/L	59.2 ± 61.6	50.7 ± 45.5
AST,[a] mean ± SD, U/L	24.5 ± 10.4	23.7 ± 13.5
ALT,[a] mean ± SD, U/L	23.8 ± 14.4	24.5 ± 24.2

[a]Placebo group: n = 161.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGTP = γ-glutamyl transpeptidase.

During the planned visits, investigators and CRCs interviewed attendants about subjects' drinking, and attendants were asked to make corrections or add to subjects' diaries if any discrepancies emerged. Study visits were undertaken once during the treatment period (10–16 weeks), at completion of study drug administration (24 weeks), once during the follow-up period (32–40 weeks), and at the end of the study (48 weeks).

Criteria for Judging Abstinence

Abstinence was judged according to subjects' diaries, interviews with subjects and their attendants, breath alcohol concentration, and laboratory liver function tests (γ-glutamyl transpeptidase [GGTP], aspartate aminotransferase [AST], and alanine aminotransferase [ALT]). A breath alcohol concentration ≥ 0.05 mg/L resulted in an entry of "consumed alcohol" for the previous day. If the investigator found abnormally high values exceeding the site-specific standard ranges in the liver function test (GGTP, AST, and ALT), the investigator checked the subject for hepatopathy and ascertained the use of other concomitant drugs. If the investigator suspected that the subject had been drinking, the investigator interviewed the subject or his/her cooperative attendant and made a judgment as to whether the subject had been drinking, taking into account interview results, other test results, and the subject's general condition. It is known that drinking tends to cause a marked increase in GGTP, AST, and ALT. However, the extent of the increase differs from individual to individual, and no cutoff value was defined. If it was determined on the basis of the test results that alcohol had been used, the first day of alcohol use was identified from information in the subject's diary and the results of an interview with the subject and his/her cooperative attendant. In ambiguous cases, subjects were assumed to have consumed alcohol. Days for which a missing value was detected and days on which it was unknown if the subject drank alcohol were treated as days of alcohol use.

RESULTS

Informed consent to participate was originally obtained from 352 patients, of whom 25 dropped out prior to randomization; the remaining 327 subjects were randomly allocated to the acamprosate group (163 subjects) or the placebo group (164 subjects). Of the 163 subjects in the acamprosate group, 110 completed the administration schedule, while 53 dropped out (3 experienced adverse events, 27 relapsed, 9 were not compliant with the protocol, 11 requested withdrawal, and 3 were withdrawn by the investigator). Of the 164 subjects in the placebo group, 105 completed the administration schedule, while 59 dropped out (10 experienced adverse events, 22 relapsed, 13 were not compliant with the protocol, 13 requested withdrawal, and 1 was withdrawn by the investigator). Finally, of subjects who completed the administration schedule, 88 in the acamprosate group completed the 24-week follow-up period, while 22 dropped out (4 experienced adverse events, 12 relapsed, 4 were not compliant with the protocol, and 2 requested withdrawal), and 83 in the placebo group completed the follow-up period, while 22 dropped out (1 experienced an adverse event, 13 relapsed, 3 were not compliant with the protocol, 4 requested withdrawal, and 1 was withdrawn by the investigator). Figure 1 shows the study flowchart. The full analysis set (FAS) was used mainly to evaluate the efficacy of the study drug. The characteristics of subjects in the efficacy analysis set, which includes all 327 subjects (163 in the acamprosate group and 164 in the placebo group), are shown in Table 1. In both the acamprosate group and the placebo group, 91.7% of the subjects (300/327) visited the medical institutions on the scheduled dates, while 99.1% of their cooperative attendants (324/327) visited or had contact with the medical institutions on the scheduled dates. The acamprosate and placebo groups each included 7 subjects whose adherence rate was below 70%, and there was no intergroup difference. All subjects underwent treatment for withdrawal symptoms. Benzodiazepines were preferentially used as drug therapy. Antidepressants and major tranquilizers were also administered to some subjects.

Endpoint

The proportion of subjects achieving complete abstinence was 47.2% (77/163) for the acamprosate group and 36.0% (59/164) for the placebo group, demonstrating the superiority of the study drug ($P = .039$; χ^2 test). The difference in complete abstinence rates between the 2 groups was 11.3% (95% CI, 0.6%–21.9%; Table 2).

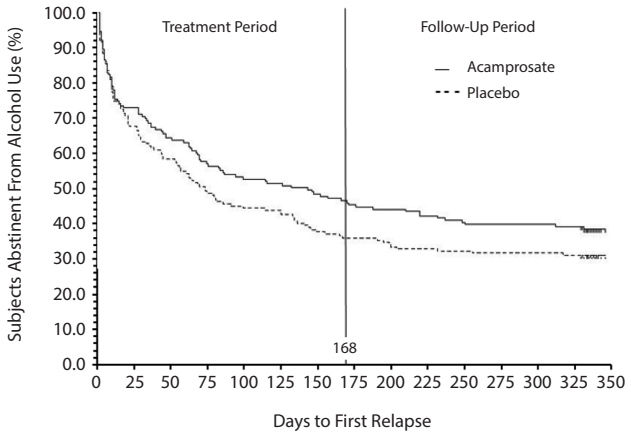
Figure 2 shows a Kaplan-Meier analysis with a log-rank test for one of the secondary outcome measures: the time elapsed from initiation of the study drug to the first relapse. Although no significant difference was observed between the 2 groups, a higher proportion of subjects in the acamprosate group maintained complete abstinence

Table 2. Complete Abstinence Rates

Treatment	Complete Abstinence n	Complete Abstinence %	Relapse n	Relapse %	Unknown[a] n	Unknown[a] %	Difference in Complete Abstinence Rates %	Difference in Complete Abstinence Rates 95% CI	χ^2 Test (complete abstinence vs relapse)
Placebo (n = 164)	59	36.0	98	59.8	7	4.3	11.3	0.6–21.9	$P = .0388$
Acamprosate (n = 163)	77	47.2	79	48.5	7	4.3			

[a]Subjects who dropped out without relapse.

Figure 2. Time to First Relapse in the Full Analysis Set Including the Follow-Up Period[a]



[a]Treatment period: $P = .060$, treatment period + follow-up period: $P = .123$ (log-rank test).

throughout the study period (treatment period, $P = .060$; follow-up period, $P = .123$; log-rank test).

There was no significant difference between the groups in terms of the number of days of cumulative abstinence in the 24-week treatment period (73.86 ± 36.22% for the acamprosate group compared with 74.16 ± 33.31% for the placebo group; $P = .310$; Wilcoxon rank sum test). Kaplan-Meier survival analysis of the time elapsed between study drug initiation and the third day of 3 or more consecutive days of heavy drinking showed that nonrelapse rates at the end of the administration period were broadly similar (58.9% for the acamprosate group compared with 57.3% for the placebo group; $P = .961$; log-rank test).

GGTP, AST, and ALT values were consistent with the drinking status ascertained by investigators in almost all of the subjects.

Complete Abstinence Rates According to Psychosocial Therapy

Table 3 shows the proportion of subjects achieving complete abstinence according to the type of psychosocial therapy received. The larger proportion of subjects achieving complete abstinence in the acamprosate group appeared to be independent of the type of psychosocial therapy received.

Safety

Adverse drug reactions observed in either group with an incidence of ≥ 1% were diarrhea (12.9% in the acamprosate group compared with 4.9% in the placebo group), abdominal swelling (0.6% and 2.4%, respectively), constipation (0% and 1.8%, respectively), and vomiting (1.2% and 0%, respectively).

The results of clinical tests, monitoring of blood pressure and pulse rate, and standard 12-lead electrocardiogram conducted during the administration period were examined, and abnormal changes for which a causal relationship to the investigational drug could not be ruled out were seen in 1 subject in the acamprosate group (increase in GGTP) and 5 subjects in the placebo group (increase in blood triglyceride [1], increase in GGTP [1], decrease in blood phosphate [1], increase in percentage of neutrophils [1], first-degree atrioventricular block [1]). In the various examinations conducted during the administration period, abnormal changes for which a causal relationship to the investigational drug could not be ruled out were seen in 1 subject in the acamprosate group and 5 subjects in the placebo group. No changes specifically associated with the administration of acamprosate were observed.

The incidence of adverse drug reactions was 17.2% (28/163) in the acamprosate group and 13.4% (22/164) in the placebo group. There was no intergroup difference between these incidences (χ^2 test; $P = .3444$).

DISCUSSION

Eleven double-blind studies in the European Union have demonstrated the superiority of acamprosate over placebo for the treatment of alcohol dependence.[20–27,29–31] The results of our study, conducted in Japanese patients, concur with these findings.

The main goal of treatment for alcohol dependence is escape from an alcohol-centered lifestyle and reintegration into healthy social and familial activities without alcohol use. Most patients who are dependent on alcohol find controlled drinking after relapse difficult to achieve[12]; complete abstinence allows recovering patients to maintain a stable and healthy lifestyle. We therefore adopted complete abstinence as our primary outcome measure, as it is considered to be the optimal treatment goal for alcohol dependence.[16,17]

In Japan, the rehabilitation period of inpatients is divided into early-stage and late-stage. Most alcohol withdrawal symptoms are treated on an inpatient basis, after which early-stage inpatient rehabilitation is undertaken. After about 2 months of early-stage rehabilitation, patients are discharged to undergo late-stage rehabilitation treatment as outpatients. In contrast, in the European Union and United States, there is no division into early- and late-stage rehabilitation after

Table 3. Proportion of Subjects Achieving Complete Abstinence According to Type of Psychosocial Therapy Received in the Treatment Period

	Placebo (n = 164)		Acamprosate (n = 163)			
Treatment	%	n/N	%	n/N	Difference (%)	95% CI
Individual psychotherapy	31.3	21/67	36.0	18/50	4.7	−12.7 to 22.0
Individual and group psychotherapy	27.3	3/11	56.3	9/16	29.0	−6.8 to 64.8
Individual psychotherapy and participation in self-help group	37.7	23/61	45.6	31/68	7.9	−9.1 to 24.9
Individual and group psychotherapy and participation in self-help group	48.0	12/25	65.5	19/29	17.5	−8.6 to 43.6

treatment of withdrawal symptoms, and most rehabilitation is undertaken on an outpatient basis, although inpatient treatment remains an option if abstinence proves particularly difficult to achieve or if complications occur.[16,32,33] Our study design reflects Japanese clinical practice, in which drug treatments to achieve maintenance of abstinence are started on the day of discharge from early-stage rehabilitation. Our study is the first to examine the efficacy of acamprosate when administration is commenced after both withdrawal symptom treatment and a period of early-stage rehabilitation have been completed. It is noteworthy that this study, based on Japanese clinical practice, has broadly similar findings to EU studies despite the different timing of drug initiation. The fact that acamprosate appears to be equally effective in different therapeutic environments shows that the drug may be used in accordance with differing patient needs and that initiating treatment at a different stage of the recovery process does not compromise its utility in maintaining abstinence. In this clinical study, the subjects received inpatient treatment before initiation of administration of the investigational drug. This inpatient treatment could have affected the prognosis after discharge.[34]

One double-blind controlled study[19] conducted in the United States evaluated days of cumulative abstinence but showed no significant benefit from acamprosate by this outcome measure. However, subanalysis of subjects with a treatment goal of abstinence did demonstrate significant efficacy compared with placebo. This study provided outpatient treatment for withdrawal symptoms for about 10% of its participants. Furthermore, half of the subjects were not abstinent from alcohol at the start of treatment drug administration, and only 41% had a treatment goal of abstinence. Patient choice is an important factor in assessing the potential benefits of acamprosate treatment, and subjects are likely to require a treatment goal of abstinence. In the present study, we confirmed potential participants' desire to abstain completely before enrollment; we consider patient desire to have been a crucial factor in the efficacy demonstrated in our study, and we believe that this should inform future clinical practice.

Several studies have found acamprosate to be ineffective. In the United Kingdom Multicentre Acamprosate Study, conducted in the United Kingdom, the protocol included a 1-week observation period between discharge following treatment for withdrawal symptoms and initiation of the study drug.[28] Efforts were not made to motivate subjects, 32% of whom were drinking alcohol at the beginning of acamprosate treatment. In one Korean study,[35] 61.4% of subjects in the acamprosate group and 65.2% of subjects in the placebo group were drinking alcohol 2 days before beginning drug treatment. The use of alcohol so close to initiation of acamprosate may explain its apparent lack of effect. These 2 studies illustrate the importance of motivating and educating patients before initiating drug treatment.

Subjects enrolled in the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study in the United States were recruited from advertisements and clinical referrals at 11 academic sites[36]; only 2.3% of those enrolled required treatment for withdrawal symptoms. Similarly, another study performed in Australia mainly enrolled subjects who did not require withdrawal symptom treatment.[37] The proportion of days of abstinence tends to increase in subjects that require no treatment for withdrawal symptoms, including subjects in the placebo group. This aspect of the study therefore raised the possibility that it would be difficult to distinguish any difference in therapeutic effect between acamprosate and placebo in these patients.

Acamprosate inhibits the elevated glutamatergic neurotransmission evident in patients with alcohol dependence.[6–11] Patients without withdrawal symptoms may not have sufficiently elevated glutamatergic neurotransmission for the drug to exert a therapeutic effect.[10] The subjects enrolled in our study did require treatment for withdrawal symptoms, but because acamprosate administration began only after a period of inpatient treatment, glutamatergic activity was likely no longer elevated at this point. Although this aspect of study design is similar to the COMBINE study and the Australian study described above, subjects requiring treatment for withdrawal symptoms are also more likely to suffer occasional cravings even after prolonged periods of abstinence and are at risk of falling into a pattern of pathological consumption after relapse.[38] The degree to which this latent tendency was present in our cohort may have influenced our findings.

The treatment of alcohol dependence is broadly similar in different countries and is generally based on psychosocial therapy, including psychotherapy and participation in self-help groups.[33,39–42] A variety of psychosocial therapies is available; the selection and combination of therapies depend on the individual patient and hospital.[43] In our study, the investigators provided counseling for all the subjects, regardless of whether they were in the acamprosate group

or the placebo group. There was no intergroup difference. Our study demonstrated a therapeutic effect of acamprosate comparable to that shown in European studies, and our finding that this difference of the effect of acamprosate and placebo appears to be independent of the psychosocial strategy employed is of great significance. Also noteworthy are our findings that the acamprosate group demonstrated a longer period until first relapse than did the placebo group, as well as its clinical benefit with regard to complete abstinence after 24 weeks of administration. In this study, 91.7% of the subjects visited the medical institutions on the scheduled dates, while 99.1% of their cooperative attendants visited or had contact with the medical institutions on the scheduled dates. These percentages show that the investigators had adequate information to make an accurate assessment of the subject's status, which provides an adequate basis on which to verify the superiority of acamprosate over placebo.

This study failed to demonstrate a significant difference between acamprosate and placebo in terms of the number of days of cumulative abstinence, but clinically this outcome is less important than maintaining complete abstinence or increasing the proportion of abstinent days. Nonetheless, the apparent lack of efficacy of acamprosate in this regard requires further consideration. Both groups demonstrated a high proportion of days of cumulative abstinence during the treatment period (73.9% for acamprosate and 74.2% for placebo). This may be explained by our rigorous efforts to establish abstinence status in order to ensure data integrity, which may have given extra impetus and motivation to the participants. All of the subjects enrolled in this study had cooperative attendants. The subjects consented to keeping a diary and had the ability to make entries in their diaries. These conditions are associated with favorable prognosis after treatment and may have contributed to the high proportion of days of cumulative abstinence in both groups. However, in terms of the rate of complete abstinence, the primary endpoint of this study, a statistically significant difference was found between the 2 groups because a subject who drank alcohol even once was excluded from the abstinent cases even if the proportion of days of cumulative abstinence was high. We used biological markers including GGTP, AST, and ALT to validate the drinking status of the subjects ascertained by investigators. This procedure is considered to increase further the reliability of the drinking outcome in this study.

Acamprosate helps achieve abstinence through controlling alcohol craving, but we did not find a clear effect in terms of suppressing heavy drinking. Even with pharmacologic assistance, patients find maintaining complete abstinence challenging, and relapse rates can be high[41]; these patients should be managed with additional psychosocial support and not discontinuation of drug therapy. In this study, the investigational drug was first administered on the day of discharge so that all the subjects could start treatment at the same time point. In clinical practice, however, early initiation of treatment is recommended, and it should be administered immediately after treatment of withdrawal symptoms is completed. A better therapeutic effect can be expected if the plasma drug concentration has already reached the steady state at the time of discharge. Our study, designed to reflect Japanese treatment protocols, confirmed the clinical benefit of acamprosate and provided insights into how the drug can be used most effectively. Acamprosate is currently used in various countries, and clinical experience is accumulating.[16,17,44,45] Acamprosate will soon be available as a new therapeutic option in Japan. Its use should improve the treatment of alcohol dependence, and experience gained with the drug will likely benefit the development of further novel treatments.

Drug names: acamprosate (Campral), disulfiram (Antabuse).
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Role of the sponsor: Nippon Shinyaku Co Ltd was involved in the study design, data collection, data analysis, and interpretation of the data, but not in the decision to submit the manuscript for publication.
Previous presentation: These findings were presented at the 14th Congress of the European Society for Biomedical Research on Alcoholism; September 8–11, 2013; Warsaw, Poland.
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Supplementary material: A complete list of the Japanese Acamprosate Study Group investigators is available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Addiction section. Please contact Daniel D. Langleben, MD, at dlangleben@psychiatrist.com.

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Supplementary Material

Article Title: Efficacy of Acamprosate for the Treatment of Alcohol Dependence Long After Recovery From Withdrawal Syndrome: A Randomized, Double-Blind, Placebo-Controlled Study Conducted in Japan (Sunrise Study)

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List of Supplementary Material for the article

1. **eAppendix 1** Members of the Japanese Acamprosate Study Group

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

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