Combination Treatment With Nefazodone and Cognitive-Behavioral Therapy for Relapse Prevention in Alcohol-Dependent Men: A Randomized Controlled Study

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Background: This study evaluated the serotonergic antidepressant nefazodone versus placebo and specific cognitive-behavioral therapy (CBT) versus nondirective group counseling (GC) for relapse prevention in alcohol dependence in a large prospective, randomized, and placebo-controlled double-blind study at 3 German university centers.

Method: 242 male patients fulfilling at least 5 criteria for alcohol dependence according to DSM-IV and ICD-10 were eligible, after detoxification, for one of the following treatment combinations: nefazodone + CBT, nefazodone + GC, placebo + CBT, and placebo + GC. Either nefazodone or placebo was administered throughout the evaluation period of 15 months. Either CBT or GC was applied during the first 12 weeks as group therapy according to operationalized manuals. The main outcome measures (assessed at 3 and 12 months of treatment) were the cumulative number of abstinent days, the amount of ethanol consumed during specified evaluation periods of 3 and 12 months, the number of relapses, and the duration of time until first relapse.

Results: After 12 weeks of treatment, no statistically significant differences were observed between the 4 treatment combinations in any outcome measure. After 52 weeks, the only significant difference was observed in the amount of ethanol consumed, with the nefazodone + GC group showing higher alcohol intake than the other 3 groups.

Conclusions: The results from this carefully designed clinical trial suggest that the 4 treatment combinations do not differ substantially in their efficacy for relapse prevention in nondepressed, severely alcohol-dependent patients. Nefazodone might even increase the risk of consuming a larger amount of ethanol per relapse in a subset of patients. CBT as performed in this study was associated with little additional benefit compared with structured GC.

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The members of the NeVeR Study Group are listed at the end of the article.

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Alcohol dependence is a major medical problem with a high prevalence in Western societies. Prolonged excessive consumption of alcohol is connected to a variety of medical sequelae with possibly devastating outcomes, and the resulting socioeconomic burden for the community is tremendous. Aside from genetic factors, which influence individual vulnerability, the pharmacologic properties of ethanol as well as conditioned learning processes may be involved in the etiology of alcohol dependence. Treatment options for alcohol-dependent subjects are currently being developed by utilizing both pharmacologic and psychotherapeutic strategies. Drugs like the presumptive NMDA (*N*-methyl-D-aspartate) receptor modulator acamprosate[1] or the μ-opioid receptor antagonist naltrexone[2] have been reported to be more effective than placebo for relapse prevention in alcohol dependence. However, the results have not been unequivocal.[3,4] For psychotherapeutic interventions, cognitive-behavioral treatment strategies have a plausible theoretical foundation, as they are based on concepts of conditioned learning processes underlying regular or excessive drinking.[5] Moreover, in clinical practice, many clinicians consider combination treatment of pharmaco-

logic and psychotherapeutic measures adequate for a majority of patients. However, methodologically sound trials for such combination treatments are scarce, as most studies have focused mainly on one treatment component and controlled less for the second.

Serotonergic dysfunctions have been reported in alcohol-dependent patients.[6] Consequently, drugs affecting serotonergic neurotransmission have been hypothesized to possess therapeutic value for relapse prevention in alcohol dependence.[7] However, serotonergic drugs have yielded conflicting results in reducing alcohol consumption. Selective serotonin reuptake inhibitors like fluoxetine have been found to be effective in depressed alcohol-dependent subjects.[8] Their therapeutic value in nondepressed alcoholics, however, is still a matter of debate.[9–11] Nefazodone is a drug that moderately inhibits serotonin (and to a lesser degree norepinephrine) reuptake and has potent 5-hydroxytriptamine $(5\text{-HT})_2$ receptor blocking effects. It has also been reported to treat major depression effectively in alcohol-dependent patients.[12]

Here we report results from a randomized, controlled, multicenter clinical trial that investigated the effect of nefazodone in combination with highly structured cognitive-behavioral therapy (CBT) for relapse prevention in alcohol-dependent patients. Control conditions were placebo for nefazodone and group counseling (GC) for CBT. In a 2×2 factorial study design, we aimed to evaluate the effects of nefazodone, CBT, and their combination on alcohol consumption in recently detoxified alcohol-dependent patients. The key outcome criteria for efficacy were the cumulative number of days without any alcohol intake and the amount of ethanol consumed during specified evaluation periods of 3 and 12 months. Secondary outcome parameters were the number of alcohol relapses at evaluation endpoints of 3 and 12 months and the duration of time until the first relapse occurred.

METHOD

Patients

The study was conducted from 1996 through 2000 as a tricentric clinical trial at 3 university sites in Germany (Departments of Psychiatry at the Universities of Mainz, Rostock, and Homburg/Saar). The acronym "NeVeR" was chosen to summarize the main goal of the study: to evaluate the combination treatment of **Ne**fazodone and **Ve**rhaltenstherapie (i.e., the German term for cognitive-behavioral therapy) for **R**elapse prevention in alcohol dependence. The study was approved by the local ethics committees of all participating centers.

Male patients, who fulfilled at least 5 criteria of alcohol dependence according to both ICD-10 and DSM-IV, aged 18 to 65 years, were eligible to participate. Patients could be enrolled after clinical detoxification, which was performed on an inpatient basis. During the study, patients were treated mainly as outpatients. For inclusion in the study, patients needed to declare their commitment to the goal of total abstinence. Before beginning the trial, all participants gave their written informed consent after full explanation of the study procedures.

Patients were excluded if they had a current relevant major Axis I disorder requiring treatment (except social phobia and nicotine dependence, which were allowed as concomitant psychiatric disorders). For depressive disorders, there was the additional requirement that a major depressive episode had to be remitted for at least 2 years. Patients with alcohol-induced persisting amnestic disorder, psychotic disorder, or dementia were also excluded. Any relevant neurologic or general medical condition requiring acute treatment or severe chronic diseases like liver cirrhosis, epilepsy, or carcinoma were also excluded. Further exclusion criteria were homelessness, persistent unemployment for at least 5 years, delinquency during the last 5 years with pending legal charges, and more than 2 unsuccessful therapies for relapse prevention. No concomitant psychotropic treatment was allowed except promethazine as a hypnotic.

Diagnostic Instruments and Protocol

Axis I diagnoses were obtained using the DIA-X computer program,[13] and Axis II diagnoses were determined using the Structured Clinical Interview for DSM-III-R (SCID-II). Severity of alcohol dependence was assessed using the German version of the structured clinical interview ASI (Addiction Severity Index).[14] Drinking patterns and amounts of consumed alcohol were assessed using the Form 90 interview.[15] Drinking urges were measured using the Obsessive-Compulsive Drinking Scale (OCDS).[16] Raters were blinded to treatment during the whole study. All participating raters were trained in the use of the following diagnostic instruments: DIA-X, SCID-II, EuropASI, and Form 90. Interrater reliabilities were calculated for SCID-II, EuropASI, and Form 90 across all study sites.

After detoxification, participating patients were randomly assigned to one of the following treatment combinations: nefazodone + CBT, nefazodone + GC, placebo + CBT, or placebo + GC. Medication (nefazodone or placebo) was administered throughout the evaluation period of 15 months. CBT or GC was applied during the first 12 weeks as group therapy according to operationalized manuals (see Psychotherapeutic Intervention section below). For safety evaluations, laboratory markers like ASAT (aspartate aminotransferase), ALAT (alanine aminotransferase), γ-GT (gamma-glutamyl transferase), MCV (mean corpuscular volume), and CDT (carbohydrate-deficient transferrin) were measured repeatedly during the study course. Compliance was checked by pill count and by measurement of serum nefazodone levels in nefazodone-treated patients. Sobriety was checked reg-

ularly at the visits by measurement of breath alcohol concentration.

Psychotherapeutic Intervention

Cognitive-behavioral therapy and nondirective group counseling were implemented according to operationalized manuals (available upon request). Both treatments comprised 24 group therapy sessions, with 6 sessions within the first 2 weeks, followed by 10 sessions during week 3 and week 4 and weekly sessions thereafter until week 12. Most of the patients were discharged from inpatient treatment within the first 3 weeks.

Treatments were delivered by 2 therapists per group. All therapists had several years of clinical experience and were trained and experienced in CBT. All received special training for both interventions (two 2-day training workshops at the beginning and around the middle of the study) to familiarize therapists with both interventions and to assure treatment integrity. Ongoing clinical supervision was performed throughout the trial. All sessions were videotaped, and 3 tapes were randomly selected and evaluated by independent and blinded evaluators for adherence to protocol. Patients were considered psychotherapy completers after attending at least 18 (75%) of the sessions.

Cognitive-Behavioral Therapy

A social learning model[5,17] served as theoretical background. Sessions lasted 90 minutes and started with motivational enhancement,[18] including assessing the risks and benefits of further drinking; recognizing the existence of an alcohol problem; establishing the goal of total alcohol abstinence; developing individual models of etiologic conditions, triggers, and maintaining factors for alcohol consumption; and deriving therapeutic objectives that facilitate total abstinence.

After patients were provided with a habituation-extinction rationale for craving, they participated in 10 cue-exposure sessions (third and fourth weeks). The daily sessions lasted as long as patients reported elevated subjective craving, which was at least 90 minutes. In addition to patients' favorite alcoholic beverages, used at the beginning of each exposure session, other alcoholic beverages and imagination of positive and negative drinking situations were used as cues.

The remaining 8 sessions were dedicated to 4 intervention modules. Depending on the needs of individual patients and specific groups, each module comprised 1 or 2 sessions: (1) coping with craving and strategies to overcome urges, (2) developing an individual relapse model (elaborating several possible individual conditions and protective aspects for relapse and challenging associated dysfunctional expectations), (3) social competence and skills to resist alcohol consumption in social situations by means of alcohol-specific role plays, and (4) planning the future, including the development of an individual emergency plan. Between all sessions, patients had homework assignments such as completing work sheets or practicing specific skills.

Group Counseling

This intervention (24 sessions) was considered to be a nonspecific group intervention to facilitate insight, self-help potentials, and support. The theoretical background was nondirective and client-oriented, with the therapist acting as moderator of the group discussion. Topics for discussion were determined by the wishes and needs of the participants except at the beginning of treatment, when health-relevant information about alcoholism and alcohol-related somatic diseases was given. Issues raised by participants during sessions involved biographical aspects, the development and consequences of addiction, the possibility of controlled drinking, and the discussion of problems with employer, wife, and family. In the event that a group discussion did not evolve, therapists referred to topics suggested in the treatment manual, e.g., watching parts of a movie about alcoholism and relapse with subsequent discussion. Therapists were not allowed to structure the discussion, to focus on specific themes other than those raised by the participants during the session, or to employ any specific psychotherapeutic (e.g., cognitive or behavioral) intervention.

To control for the high-frequency cue-exposure sessions during weeks 3 and 4 of treatment, relaxation techniques were taught with the same daily session frequency. This procedure was chosen to ensure treatment credibility, since it seemed doubtful that patients could be motivated for daily nondirective therapy sessions only.

Pharmacotherapy (Nefazodone, Placebo)

Patients took either nefazodone or placebo (up to 600 mg per day, starting with 200 mg per day and increased thereafter in 100-mg steps) following a double-blind protocol. To remain in the study, patients had to be receiving a dose of at least 300 mg per day by week 3. Both study medications contained riboflavin to control for medication compliance by urine samples without breaking the blind. In addition, urine samples allowed us to control for taking other medications (e.g., benzodiazepines), which would violate the study protocol. All medications were prepared in identical capsules by an independent university pharmacy.

Outcome Measures and Statistical Evaluation

The main outcome measures (assessed at 3 and 12 months of treatment) were the cumulative number of abstinent days and the amount of ethanol consumed during the specified time periods. Secondary measures included the number of relapses, the duration of time until first relapse, the average amount of alcohol consumed during a

Figure 1. Flow Diagram of the Progress of Alcohol-Dependent Men Through the Phases of the Trial

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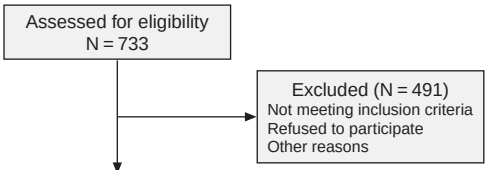


	Total	Nefazodone + CBT	Nefazodone + GC	Placebo + CBT	Placebo + GC	Test Statistics χ^2	df	p
Allocation to treatments	N = 242	N = 63	N = 58	N = 60	N = 61	0.215	3	.975
Received allocated intervention	N = 200	N = 53	N = 50	N = 50	N = 47	0.360	3	.948
Did not receive allocated intervention	N = 42	N = 10	N = 8	N = 10	N = 14	1.810	3	.613

Completers, N (%)	Total	Nefazodone + CBT	Nefazodone + GC	Placebo + CBT	Placebo + GC	Test Statistics χ^2	df	p
Completed intervention	102 (51.0)	30 (56.6)	17 (34.0)	28 (56.0)	27 (57.4)	7.73	3	.052
Completed pharmacotherapy	102 (51.0)	30 (56.6)	17 (34.0)	28 (56.0)	27 (57.4)	7.73	3	.052
Completed psychotherapy	143 (71.5)	43 (81.1)	29 (58.0)	33 (66.0)	38 (80.9)	9.644	3	.022
Lost to follow-up month 3	59 (29.5)	12 (22.6)	21 (42.0)	18 (36.0)	8 (17.0)	9.490	3	.023
Lost to follow-up month 12	138 (69.0)	36 (67.9)	38 (76.0)	33 (66.0)	31 (66.0)	1.558	3	.662

Abbreviations: CBT = cognitive-behavioral therapy, GC = group counseling.

relapse, and the OCDS scores at 3 and 12 months. A relapse was defined as consumption of at least 60 g of pure ethanol per occasion or a hospitalization because of alcohol drinking. We performed χ^2 statistics, variance analyses (4 groups, 2 points in time), and survival analysis (criterion: relapse).

Randomization was performed to allocate patients in a balanced manner to the possible treatment combinations. Randomization followed a centralized assignment procedure independent of responsible or treating clinicians and hospitals.

RESULTS

A total of 733 patients were screened for their eligibility to participate in the study. A total of 242 patients gave written informed consent for enrollment in the study and were randomly assigned to 1 of the 4 possible treatment combinations. The remaining 491 patients were not enrolled in the study for various reasons (mainly because of fulfilling an exclusion criterion or not being willing to participate in the proposed study). The numbers of patients in each treatment group as well as the completers for each treatment modality are given in Figure 1. Interrater reliabilities for the different instruments were as follows: ranges of kappa values for SCID-II, .59 to .84; Pearson correlation coefficients for EuropASI, .69 to .93; and percent agreement for Form 90, .84 to .91.

A randomized compliance check using the measurement of serum nefazodone levels was performed in a total of N = 247 samples. Of these, noncompliance with medication was found in 14.5%.

The essential characteristics of the patient sample are summarized in Table 1. There were no statistically significant differences between the treatment groups with regard to age, demographic characteristics, psychopathology, and comorbidity or items related to alcohol dependence. There was a tendency ($p < .11$) for lifetime comorbidity of social phobia, which was overrepresented in the nefazodone + CBT group.

After 12 weeks of treatment, no statistically significant differences between the treatment groups were detected for the outcome measures relapse rate (using different criteria for relapse), cumulative duration of abstinence, drinking days, number of relapses, or the total amount of alcohol consumed. The results are given in Table 2.

After 52 weeks of treatment, no statistically significant differences between the treatment groups were detected for the outcome measures relapse rate (using different criteria for relapse), cumulative duration of abstinence, drinking days, or number of relapses. For the total amount of alcohol consumed, patients treated with nefazodone and GC had much higher mean values as well as more drinks per drinking occasion. No such effect was observed in patients treated with nefazodone and CBT or in either medication placebo group. The results are given in Table 3.

When a survival analysis with regard to the time to the first relapse was performed, no statistically significant differences were observed between the treatment groups. The results are plotted in Figure 2.

Table 1. Characteristics of Alcohol-Dependent Male Patients at Baseline[a]

Characteristic	Total N = 200	Nefazodone + CBT N = 53	Nefazodone + GC N = 50	Placebo + CBT N = 50	Placebo + GC N = 47	Statistical Significance F	χ^2	df	p
Age, y	42.8 (8.4)	43.2 (8.8)	40.9 (7.4)	42.9 (8.6)	44.3 (8.5)	1.44		3,196	.231
Marital status, %									
Single	20.3	19.2	24.5	22.4	14.9		3.27	6	.78
Married or living with partner	58.9	55.8	59.2	61.2	59.6				
Divorced, separated, or widowed	20.8	25.0	16.3	16.3	25.5				
Education, y	9.8 (1.5)	9.7 (1.4)	9.8 (1.5)	9.9 (1.5)	9.8 (1.8)	0.182		3,196	.908
No. of DSM-IV criteria fulfilled for alcohol dependence									
Mean	6.1 (0.9)	6.2 (0.9)	6.2 (0.8)	6.1 (0.9)	6.0 (0.9)		1.98[b]	3	.578
Median	6	6	6	6	6				
Age when started getting intoxicated regularly, y	19.0 (5.8)	19.2 (7.0)	17.7 (3.6)	19.0 (4.6)	20.4 (7.2)	1.74		3,193	.160
Age when first had difficulty stopping before intoxication, y	26.3 (9.9)	27.1 (10.6)	23.8 (8.0)	27.6 (10.2)	26.5 (10.5)	1.45		3,190	.231
History of alcoholism in first-degree relatives, %	48.5	55.8	42.9	42.9	52.2		2.598	3	.458
History of paternal alcoholism, %	31.0	35.4	37.0	22.9	28.9		2.76	3	.430
Lifetime DSM-IV diagnosis, %									
Major depression	18.9	24.0	15.6	17.4	18.2		1.26	3	.739
Social phobia	8.1	16.0	6.7	4.3	4.5		5.93	3	.115
Generalized anxiety disorder	0.5	0.0	0.0	2.2	0.0		3.04	3	.386
Substance use disorder	4.9	4.0	4.4	6.5	4.5		0.38	3	.944
Antisocial personality disorder	7.7	3.8	10.2	8.5	8.7		1.62	3	.655
Current smoker, %	82.3	78.7	93.5	75.6	81.4		5.793	3	.122
Laboratory markers of excessive alcohol consumption									
ALAT	52.5 (38.8)	52.5 (41.8)	47.4 (31.8)	52.7 (39.9)	57.5 (41.4)	0.28[c]		3,190	.843
ASAT	60.7 (74.8)	66.6 (108.3)	49.5 (42.4)	67.1 (72.9)	59.2 (56.6)	0.47[c]		3,192	.703
γ-GT	219.8 (639.6)	137.7 (168.1)	190.0 (326.6)	192.8 (308.1)	371.2 (1213.2)	0.77[c]		3,189	.512
MCV	95.0 (6.2)	94.8 (5.3)	94.4 (9.2)	95.0 (5.1)	95.7 (4.2)	0.35		3,189	.788
CDT,[d] μ/L	25.0 (19.6)	31.7 (25.2)	19.1 (9.1)	23.9 (15.7)	26.7 (27.4)	1.31[c]		3,59	.278
Patient subset	n = 63	n = 14	n = 16	n = 21	n = 12				
CDT,[d] %	9.7 (11.1)	11.0 (16.8)	9.3 (7.1)	9.8 (10.0)	8.7 (8.1)	0.09[c]		3,69	.964
Patient subset	n = 73	n = 20	n = 19	n = 15	n = 19				
Drinking days in previous 90 d, %									
Mean	70.8 (31.1)	68.4 (32.5)	74.2 (30.9)	65.1 (32.4)	75.0 (27.3)	1.11		3,184	.346
Median	85.6						2.21[b]	3	.531
Mode	100	100	100	100	100				
No. of drinks per drinking day in previous 90 d	14.7 (8.9)	14.0 (8.0)	16.7 (9.9)	15.0 (10.2)	13.0 (7.1)	1.483		3,184	.221

[a]Values are mean (± SD) unless otherwise indicated.
[b]Kruskal-Wallis test.
[c]After normalization.
[d]CDT values have been measured as absolute values (in μ/L) in a subset of patients and as relative values of total transferrin (in %) in the remainder of the patients.
Abbreviations: ALAT = alanine aminotransferase, ASAT = aspartate aminotransferase, CBT = cognitive-behavioral therapy, CDT = carbohydrate-deficient transferrin, γ-GT = gamma-glutamyl transferase, GC = group counseling, MCV = mean corpuscular volume.

DISCUSSION

First, several methodological strengths of this study should be mentioned. Treatment combinations were allocated in a randomized but balanced manner, thus ensuring that in all treatment groups comparable subsamples of patients were treated. Assessment with psychometric and diagnostic instruments was taught, and interrater reliabilities were calculated, indicating good-to-excellent agreement. Psychotherapeutic treatment was manualized for both treatment conditions, and adherence to treatment manuals was checked by videotape assessment. Psychotherapeutic treatments were intensive and comprised individualized cognitive-behavioral or supportive treatment, individual cue-exposure treatment or relaxation therapy, as well as intensive group therapy. Ratings of treatment outcomes were performed by raters blind to the treatment combination. Compliance with medication was checked by serum level assessment for nefazodone. The duration of treatment was long enough to detect even delayed treatment effects. The number of patients included in the study was sufficient to allow the detection of substantial differences between the treatment combinations. The inclusion of severely alcohol-dependent patients (fulfilling at least 5 criteria for alcohol dependence) underscores the clinical importance of the findings. The exclusion of patients with a relevant current depressive episode allowed the assessment of a possible relapse-preventive

Table 2. Outcome of Treatment After 12 Weeks[a]

Outcome	Total N = 200	Nefazodone + CBT N = 53	Nefazodone + GC N = 50	Placebo + CBT N = 50	Placebo + GC N = 47	Significance Group	χ^2	F	df	p
Relapse rate, %										
Any alcohol consumption	48.5	52.8	48.0	48.0	44.7		0.682		3	.877
More than 60 g	45.5	49.1	46.0	48.0	38.3		1.385		3	.709
Cumulative duration of abstinence, % d	78.2 (32.3)	80.2 (30.3)	76.21 (32.8)	73.9 (35.7)	82.7 (30.6)	NEF/PLA		0.00	1,196	.983
						CBT/GC		0.27	1,196	.603
						Interaction		1.92	1,196	.167
Drinking days, % d	21.8	19.8	23.8	26.1	17.3					
No. of relapses	18.0 (27.2)	16.6 (25.4)	19.3 (27.5)	21.9 (30.0)	14.0 (25.8)	NEF/PLA		0.00	1,196	.999
						CBT/GC		0.43	1,196	.513
						Interaction		1.90	1,196	.169
Total amount of alcohol consumed, g	569.8 (1514.0)	404.1 (1032.3)	723.9 (2423.0)	877.6 (1463.0)	376.5 (1024.3)	NEF/PLA		0.055	1,125	.815
						CBT/GC		0.113	1,125	.737
						Interaction		2.32	1,125	.130
Amount ethanol per day	6.8 (18.0)	4.8 (12.3)	8.6 (28.8)	10.5 (17.4)	4.5 (12.2)					
Amount ethanol per drinking day	159.4 (121.0)	137.5 (100.8)	138.3 (91.4)	181.3 (130.8)	174.4 (154.1)	NEF/PLA		0.883	1,35	.354
						CBT/GC		0.005	1,35	.943
						Interaction		0.008	1,35	.929
Mean decrease of OCDS, total score	12.9 (9.9)	15.4 (9.2)	9.6 (10.4)	13.9 (9.6)	11.8 (10.4)	NEF/PLA		0.033	1,96	.856
						[b]CBT/GC		3.92	1,96	.051
						Interaction		0.941	1,96	.334

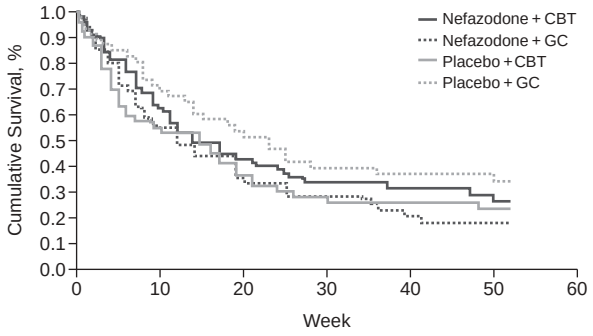
[a]Values are mean (± SD) unless otherwise indicated.
[b]Main effect of psychotherapy was insignificant when baseline OCDS scores were controlled. Analysis of covariance revealed a strong effect of baseline OCDS measure (p = .001), but no differential effect of treatment conditions: NEF/PLA: F = 0.231, df = 1,95; p = .632; CBT/GC: F = 0.068, df = 1,95; p = .795; Interaction: F = 0.074, df = 1,95; p = .786.
Abbreviations: CBT = cognitive-behavioral therapy, GC = group counseling, NEF = nefazodone, OCDS = Obsessive Compulsive Drinking Scale, PLA = placebo.

Table 3. Outcome of Treatment After 52 Weeks[a]

Outcome	Total N = 200	Nefazodone + CBT N = 53	Nefazodone + GC N = 50	Placebo + CBT N = 50	Placebo + GC N = 47	Significance Group	χ^2	F	df	p
Relapse rate, %										
Any alcohol consumption	77.0	77.4	82.0	76.0	72.3		1.314		3	.726
More than 60 g	76.0	75.5	82.0	76.0	70.2		1.858		3	.602
Cumulative duration of abstinence, % d	47.0 (37.8)	47.9 (37.6)	39.3 (34.8)	47.0 (38.9)	54.3 (39.2)	NEF/PLA		1.77	1,196	.185
						CBT/GC		0.015	1,196	.903
						Interaction		2.21	1,196	.138
Drinking days, % d	53.0	52.1	60.7	53.0	45.7					
No. of relapses	191.4 (137.7)	188.5 (138.3)	219.3 (126.4)	192.5 (141.9)	164.0 (142.7)	NEF/PLA		1.74	1,196	.189
						CBT/GC		0.004	1,196	.952
						Interaction		2.33	1,196	.129
Total amount of alcohol consumed, g	4651.5 (10,744.4)	2701.5 (6291.1)	10,007.1 (19,710.1)	4719.4 (7082.3)	2582.4 (4906.2)	NEF/PLA		2.13	1,126	.147
						CBT/GC		1.95	1,126	.166
						Interaction		6.49	1,126	.012
Amount ethanol per day	12.8 (29.5)	7.4 (17.3)	27.5 (54.2)	13.0 (19.5)	7.1 (13.5)					
Amount ethanol per drinking day	171.4 (124.1)	143.3 (93.2)	223.6 (171.5)	178.8 (116.0)	161.0 (124.7)	NEF/PLA		0.180	1,59	.673
						CBT/GC		0.962	1,59	.331
						Interaction		2.36	1,59	.130

[a]Values are mean (± SD) unless otherwise indicated.
Abbreviations: CBT = cognitive-behavioral therapy, GC = group counseling, NEF = nefazodone, PLA = placebo.

Figure 2. Percentage of Alcohol-Dependent Men Without Relapse (indicated as cumulative survival) During the Treatment Period[a,b]



[a]Relapse was defined as at least 60 g of ethanol per drinking occasion. The analysis comprised patients with documented or assumed relapse (e.g., patients lost to follow-up).
[b]No significant difference was detected between the treatment groups at any time point.

potential of nefazodone without confounding antidepressant effects.

None of the 4 treatment groups differed substantially on a variety of clinically relevant outcome measures after 3 and 12 months of treatment. The only statistically significant difference in any outcome measure was observed after 12 months of treatment, indicating that patients treated with nefazodone and group counseling tended to drink more ethanol when relapsing than those receiving the other treatment combinations.

The absence of a clinically prominent benefit for nefazodone in nondepressed alcohol-dependent subjects is in line with recent findings of other research groups. Kranzler et al.[19] reported no clinical benefit for nefazodone compared with placebo for relapse prevention. However, it may be important to stress that this report does not differentiate outcomes according to subtypes of alcoholism but presents the results of the overall evaluation. From the results of Pettinati and coworkers,[20,21] one may expect that, for a serotonergic drug, stratification according to Babor's Type A/Type B[25] may reveal differential effects. This assumption is corroborated by the findings of Johnson et al.,[22] reporting differential effects with the 5-HT_3-receptor antagonist ondansetron in patients with early versus late onset of alcohol-related problems. Without subtyping alcohol-dependent patients, however, nefazodone does not seem to be of therapeutic value for relapse prevention in alcohol dependence.

A point of major clinical relevance is the finding that CBT including cue-exposure therapy did not lead to a substantially better clinical outcome compared with intensive group counseling with relaxation techniques in this overall analysis. Although it is important to bear in mind that group counseling in this study was an intensive individually tailored psychotherapeutic treatment, one should nevertheless face the fact that specific CBT interventions were not associated with remarkable additional benefit in this rigorously controlled clinical trial. This result resembles to some degree one major finding from the MATCH study,[23] in which specific treatment interventions were not significantly superior to 12-step facilitation therapy or motivational enhancement therapy. Our results also match the conclusion of a recent review of evidence for CBT for alcohol dependence,[24] which found little empirical evidence supporting major assumptions of CBT in the treatment of alcohol dependence.

The fact that there was substantial treatment attrition might have influenced outcome. In fact, group counseling in combination with nefazodone disappointed most patients, leading to the lowest completion rate. Obviously, it is the combination of medication and the kind of psychotherapy that might have influenced outcome. But our results do not support such a conclusion. All results reported here are based on intent-to-treat statistics, and thus no patient included in the study protocol was lost for evaluation. However, a completer analysis (excluding lost subjects) did not show different results.

Additional statistical analyses focusing on proportion of individuals with a lifetime history of antisocial personality disorder, social phobia, or lifetime comorbidity did not result in different outcome. Excluding subjects with 1 or more of these diagnoses did not change the results at all.

It remains an open question if more individualized and more intensive interventions for subgroups of alcohol-dependent patients would show different outcomes than a treatment package that includes lots of methods without enough time to address each intervention element. For example, patients who suffer from cravings might benefit from treatment with intensive cue exposure more than patients without cue reactivity, or patients with obvious skill deficits might need more skill training than was provided during the few sessions of the study treatment. Our results should prompt researchers to reevaluate treatment strategies and underlying major assumptions in a critical manner, as psychotherapeutic interventions (CBT) are often time-consuming and costly.

Drug names: fluoxetine (Prozac and others), naltrexone (ReVia and others), nefazodone (Serzone), ondansetron (Zofran), promethazine (Phenergan, Promethegan, and others).

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