Cognitive-Behavioral Therapy, Imipramine, or Their Combination for Panic Disorder

A Randomized Controlled Trial

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Context Panic disorder (PD) may be treated with drugs, psychosocial intervention, or both, but the relative and combined efficacies have not been evaluated in an unbiased fashion.

Objective To evaluate whether drug and psychosocial therapies for PD are each more effective than placebo, whether one treatment is more effective than the other, and whether combined therapy is more effective than either therapy alone.

Design and Setting Randomized, double-blind, placebo-controlled clinical trial conducted in 4 anxiety research clinics from May 1991 to April 1998.

Patients A total of 312 patients with PD were included in the analysis.

Interventions Patients were randomly assigned to receive imipramine, up to 300 mg/d, only (n=83); cognitive-behavioral therapy (CBT) only (n=77); placebo only (n=24); CBT plus imipramine (n=65); or CBT plus placebo (n=63). Patients were treated weekly for 3 months (acute phase); responders were then seen monthly for 6 months (maintenance phase) and then followed up for 6 months after treatment discontinuation.

Main Outcome Measures Treatment response based on the Panic Disorder Severity Scale (PDSS) and the Clinical Global Impression Scale (CGI) by treatment group.

Results Both imipramine and CBT were significantly superior to placebo for the acute treatment phase as assessed by the PDSS (response rates for the intent-to-treat [ITT] analysis, 45.8%, 48.7%, and 21.7%; $P=.05$ and $P=.03$, respectively), but were not significantly different for the CGI (48.2%, 53.9%, and 37.5%, respectively). After 6 months of maintenance, imipramine and CBT were significantly more effective than placebo for both the PDSS (response rates, 37.8%, 39.5%, and 13.0%, respectively; $P=.02$ for both) and the CGI (37.8%, 42.1%, and 13.0%, respectively). Among responders, imipramine produced a response of higher quality. The acute response rate for the combined treatment was 60.3% for the PDSS and 64.1% for the CGI; neither was significantly different from the other groups. The 6-month maintenance response rate for combined therapy was 57.1% for the PDSS ($P=.04$ vs CBT alone and $P=.03$ vs imipramine alone) and 56.3% for the CGI ($P=.03$ vs imipramine alone), but not significantly better than CBT plus placebo in either analysis. Six months after treatment discontinuation, in the ITT analysis CGI response rates were 41.0% for CBT plus placebo, 31.9% for CBT alone, 19.7% for imipramine alone, 13% for placebo, and 26.3% for CBT combined with imipramine.

Conclusions Combining imipramine and CBT appeared to confer limited advantage acutely but more substantial advantage by the end of maintenance. Each treatment worked well immediately following treatment and during maintenance; CBT appeared durable in follow-up.

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PANIC DISORDER (PD) IS A chronic condition associated with substantial reduction in quality of life,[1] and lifetime prevalence rates are approximately 3%.[2,3] Role functioning is substantially lower in patients with PD than in patients with diabetes, heart disease, or arthritis.[4] Individuals with PD frequently use both emergency department and general medical services,[5] presenting with high rates of unexplained cardiac symptoms,[6,7] dizziness, and bowel distress.[6,8] These patterns continue indefinitely.[9,10] The social and economic costs of PD are considerable.[11-13] Successfully treating PD can produce medical cost offsets as high as 94%.[12] Thus, efforts to ascertain effective treatments or a combination of treatments for PD are important.

Earlier psychosocial treatments were directed specifically at unexpected panic attacks and associated anxiety.[14,15] A growing number of studies support the effectiveness of these psychosocial approaches for PD compared with no treatment or credible psychosocial placebos.[16] By the 1980s, the efficacy of pharmacological treatment with imipramine in patients with PD had been well established.[17-21] Imipramine was regarded as the pharmacological criterion standard for the treatment of PD for more than 20 years,[22-24] until the emer-

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gence of the selective serotonin reuptake inhibitors (SSRIs).

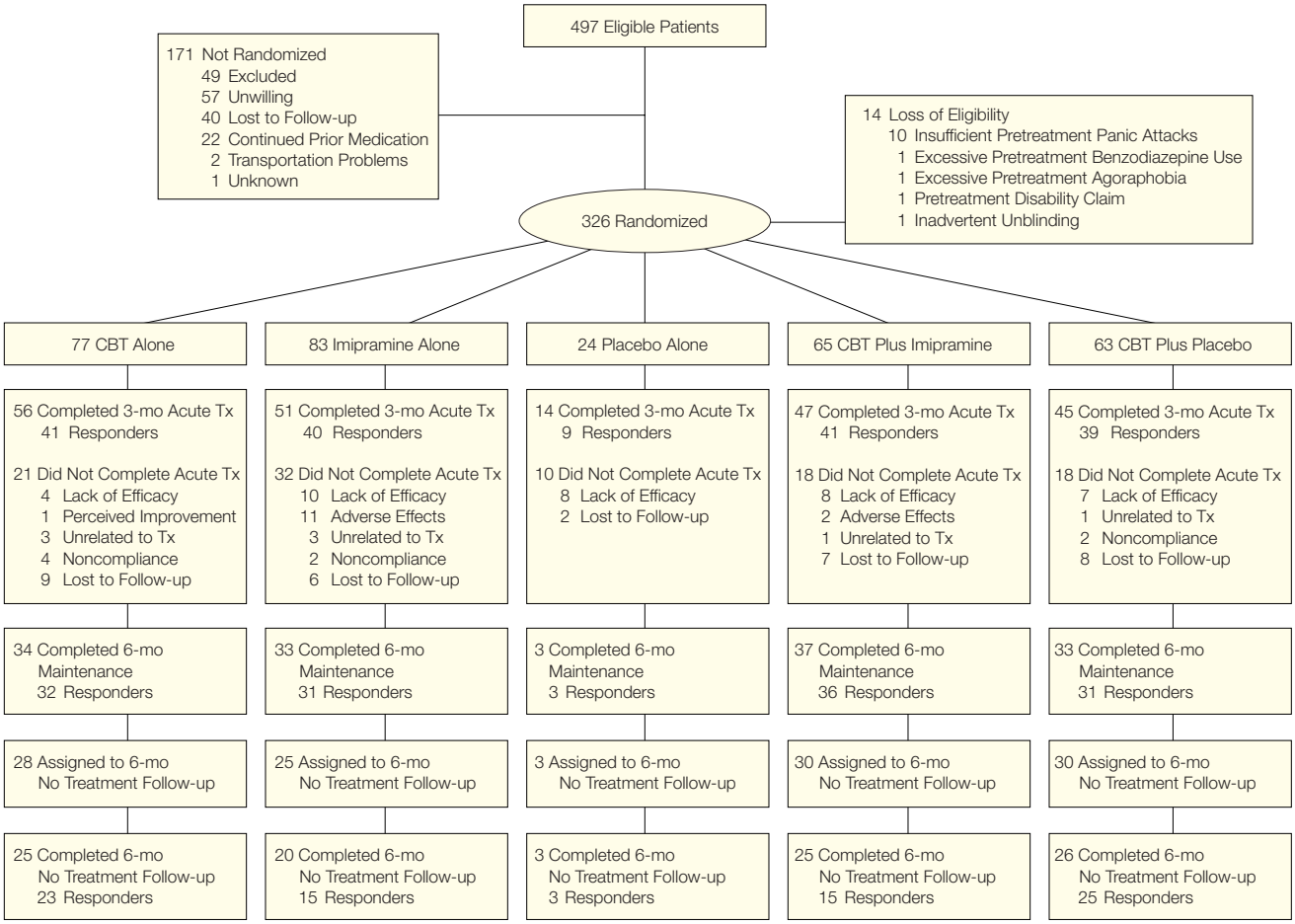
Despite the proven efficacy of both drug and psychosocial treatments for PD and some emerging evidence on the possible synergistic effects of these approaches, particularly on phobic behavior,[25] studies of medication and psychosocial approaches have, until recently, run on parallel and sometimes hostile tracks.[15,26-29] We assembled a team of 4 investigators, 2 committed to each approach, to undertake a comparative study that would determine optimal treatment for PD.

METHODS

Study Design

We conducted a randomized controlled trial comparing cognitive-behavioral therapy (CBT), imipramine plus medical management, the combination of CBT and imipramine (CBT+imipramine), pill placebo plus medical management, and CBT+placebo for PD (FIGURE). Randomization was stratified by site and presence of *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*–defined current major depression and was blocked within stratum. To improve trial efficiency,[30] unequal numbers of patients were randomized to the treatments (6 CBT, 6 imipramine, 5 CBT+imipramine, 25 CBT+placebo, and 2 placebo per block of 24) based on expected pairwise comparison effect sizes. The acute treatment phase consisted of 11 sessions during 12 weeks. Each CBT session lasted approximately 50 minutes and each drug treatment session approximately 30 minutes. Patients in combined treatment saw 2 therapists for a total of about 75 minutes per week. Responders to acute treatment entered a 6-month maintenance phase without breaking the study blind. Maintenance-phase treatment consisted of 6 monthly appointments in which treatment similar to the acute treatment was continued. After 9 months of treatment (3 months acute and 6 months maintenance), patients were assessed again. Responders to maintenance treatment were then assigned to discontinuation of treatment, except for 17 patients who were randomized to an extended maintenance pilot project. Remaining patients were assessed again after 6 months of follow-up (15 months after

Figure. Flow Diagram



CBT indicates cognitive-behavioral therapy; Tx, treatment. Responders are defined in the "Assessment" section.

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treatment was initiated). The trial was conducted between May 1991 and April 1998 and was approved by institutional review boards at each site.

Subjects

All patients passing diagnostic screening for a principal diagnosis of PD with or without mild agoraphobia (N=497) were entered in the pretreatment phase after signing written, informed consent. Pretreatment included drug washout for patients taking anxiolytic or antidepressant medication. Patients were permitted up to 10 doses of benzodiazepine (0.5 mg of alprazolam-equivalent) in the 2 weeks before the first treatment visit and up to 20 doses during baseline and acute treatment combined. During the 2 weeks prior to the first treatment visit, patients underwent physical and laboratory examinations, and diagnosis was confirmed using the Anxiety Disorders Interview Schedule-Revised (ADIS-R).[31,32] Mild agoraphobia was operationally defined as a score less than or equal to 18 on the ADIS-R avoidance scale. In addition, inclusion required at least 1 full or limited panic attack in the 2 weeks before the first treatment visit.

Exclusion criteria were psychotic, bipolar, or significant medical illnesses, suicidality, significant substance abuse, contraindications to either treatment, prior nonresponse to similar treatments, and concurrent competing treatment or pending disability claims. More details are available on request from the authors. Patients with comorbid unipolar depression were not excluded unless suicidal. A detailed analysis of reasons for pretreatment attrition is provided elsewhere.[33]

Therapists

Therapists providing CBT were doctoral-level clinicians who underwent extensive training and certification supervised by the Boston site prior to treating study patients. Clinicians were not required to have prior training in cognitive-behavioral procedures. Pharmacotherapists were experienced psychiatrists who underwent additional training and certification in the study protocol under the direction of the Columbia/Hillside site. All CBT therapists and pharmacotherapists received ongoing supervision of their cases from the responsible site during biweekly telephone calls, and adherence and competence ratings were routinely collected after listening to a sample of audiotaped sessions.

Treatment Conditions

Cognitive-behavioral therapy for PD, developed at the Boston site, combines interoceptive exposure, cognitive restructuring, and breathing retraining. This treatment was described in a manual containing detailed instructions for the conduct of each session.[34]

The imipramine and placebo interventions were administered in a double-blind, fixed flexible-dose design, according to a manual developed for this study. Both the imipramine and placebo arms included a medical management component, specified in the manual. The purpose of medical management was to monitor adverse effects, clinical state, and the patient's physical/mental condition; maximize compliance with the pharmacological treatment protocol; and proscribe specific interventions included in CBT (eg, cognitive restructuring of anxiety and panic symptoms). Patients who experienced clinical deterioration were removed from the study and offered alternative treatment for 3 months free of charge.

Starting dosages of imipramine were 10 mg/d (or pill placebo equivalent), increased every other day by 10 mg until 50 mg/d was reached. The dosage was then increased more rapidly, with an effort made to reach 100 mg/d by the end of week 3 and 200 mg/d by week 5, even if the patient became symptom-free earlier, unless adverse effects became intolerable. If the patient was not symptom-free, the dosage could be increased up to 300 mg/d by week 5. Blood levels of imipramine were assessed at 6 and 12 weeks and benzodiazepine screening of urine samples performed by local commercial laboratories.

The combined treatment conditions were administered according to a manual essentially consisting of the CBT and the imipramine manuals.

Assessment

Prior to beginning the study, independent evaluators participated in training and certification on the rating instruments, supervised by the Pittsburgh site. Bimonthly conference calls were held for evaluators to discuss any questions and/or discrepancies among sites, and regular, random interviews were monitored for continued reliability of diagnosis and ratings. Reliability on main measures remained above 90%. Evaluator assessments occurred at baseline and after acute, maintenance, and follow-up phases, and evaluators were blind to treatment assignment.

The primary continuous outcome measure was the average item score for the Panic Disorder Severity Scale (PDSS), a clinician-rated scale of PD severity.[35] We also present results for a 40% reduction from baseline on PDSS. The primary categorical outcome measure involved determination of a responder based on the Clinical Global Impression Scale (CGI),[36] consisting of 7-point scales rating overall improvement and severity. We added specific PD-based anchor points for rating the CGI in this study. To be a responder, a patient needed to achieve a score of 2 (much improved) or better while being rated as 3 (mild) or less on CGI severity. Receipt of nonstudy treatment was evaluated at each assessment point. Patients who received nonstudy treatment for anxiety or panic were determined to be nonresponders, both for PDSS and CGI responder definitions.

Statistical Analyses

The study was designed to address if both CBT alone and imipramine alone performed better than placebo; if either CBT or imipramine performed better relative to each other; and if there was an advantage to combining CBT and imipramine as evidenced by superiority of CBT+imipramine to CBT+placebo, imipramine alone, and CBT alone. These questions were addressed at each of 3 assessment points: postacute, postmain-

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tenance, and follow-up. At each point, we performed an intent-to-treat (ITT) analysis, using an early-termination assessment. The baseline was carried forward as an assumption of nonresponse or return to baseline if the early-termination assessment was missing or contaminated by nonstudy treatment. Similarly, the baseline was also carried forward in follow-up analyses for the same reasons. Intent-to-treat analyses included all randomized patients except those discovered to be ineligible after randomization (Figure). At postmaintenance and follow-up assessments, we also conducted intent-to-continue (ITC) analyses, restricted to patients completing the preceding phase as responders. At postacute assessment, we present results for completers only.

Data were subjected first to omnibus testing of all 5 treatments and then to pairwise post hoc testing when the omnibus test indicated statistical significance. The Freeman-Halton and Fisher exact tests were used for categorical measure analyses, analysis of variance for PDSS baseline analysis, and analysis of covariance for subsequent analyses using baseline as the covariate. When analyses indicated a significant baseline-by-treatment interaction on the dependent measure, analysis of covariance was replaced by repeated-measures analysis of variance, with treatment assignment as the independent (between groups) variable and time as the dependent (within groups) variable. Significance was defined as $P \leq .05$ with a 2-tailed test.

RESULTS

Of the 326 patients randomized, 312 are included in the analysis. Thirteen were excluded following uniform screening for loss of eligibility, and 1 was removed because of inadvertent unblinding. Proportions of excluded patients were not significantly different among treatment assignments.

Baseline, Site, and Stratum Analyses

There were no significant differences on demographic measures or on baseline PDSS score among the 5 randomized groups (TABLE 1). The mean PDSS scores indicate a moderate-to-average severity. No significant site effect, depression stratum effect, site-by-treatment interaction, or stratum-by-treatment interaction was observed in the acute ITT analyses for any of the 3 measures; thus, all data were aggregated across sites and across strata. Similarly, there were no significant interactions between treatment and other baseline variables (Table 1) in multivariate acute ITT analyses for any of the 3 measures. No important differences at baseline were observed between treatment groups entering vs not entering maintenance or follow-up. It has been suggested that when $P < .10$ level heterogeneity of the slope is present across treatments, treatment effects that apply to an important portion of the baseline severity spectrum may be obscured in analyses of covariance.[37] For slope heterogeneity, $P > .25$ for 8 of 9 omnibus PDSS analyses of covariance, suggesting little heterogeneity.

Subject Disposition, Dosing, and Laboratory Analyses

Acute completion rates did not differ significantly across treatment groups. Among the 8 noncompliant patients was 1 patient receiving imipramine alone who violated protocol by using benzodiazepines at rates exceeding those allowed, and 1 patient receiving CBT who began nonprotocol antidepressant treatment during acute treatment. The Figure also shows that 82% to 90% of maintenance-eligible patients completed maintenance across active treatments, compared with 33% of placebo patients. The omnibus test for this analysis was significant. Pairwise comparisons were significant for all active treatments vs placebo, including CBT alone ($P = .006$), imipramine alone ($P = .007$), CBT+imipramine ($P = .001$), and CBT+placebo ($P = .004$).

Patients receiving medication reported taking doses of 175 to 180 mg/d across treatments by week 6 and 214 to 239 mg/d by week 12. Mean (SD) imipramine+desipramine plasma levels at week 6 were 219 (186) ng/dL and 223 (127) ng/dL for CBT+imipramine and imipramine alone, respectively, and 225 (148) ng/dL and 263 (156) ng/dL at week 12.

Rates of urine samples that tested positive for benzodiazepines were low. At week 6, 3 (1.5%) of 197 samples tested positive (1 CBT+imipramine, 1 CBT, 1

Table 1. Baseline Analyses*

Variable	CBT Alone	Imipramine Alone	Placebo Alone	CBT Plus Imipramine	CBT Plus Placebo	Total†	*P* Value‡
No. of subjects	77	83	24	65	63	312	
Female sex, %	63.2	60.2	75.0	64.1	58.1	62.5	.67
Age, mean (SD), y	37.5 (10.9)	35.5 (9.7)	34.2 (9.7)	34.1 (11.4)	37.8 (11.3)	36.1 (10.7)	.23
White race, %	89.0	89.0	91.3	95.3	90.3	90.8	.71
Currently married, %	52.1	45.1	39.1	48.4	58.1	49.7	.45
Duration of illness, mean (SD), y	6.61 (8.55)	6.38 (7.54)	6.64 (10.4)	6.60 (8.99)	5.50 (8.17)	6.33 (8.43)	.96
PDSS average item score, mean (SD)§	1.82 (0.55)	1.88 (0.56)	1.86 (0.52)	1.86 (0.57)	1.74 (0.51)	1.83 (0.54)	.58
Current major depression, %	23.7	30.1	29.2	26.6	27.0	27.1	.92

*CBT indicates cognitive-behavioral therapy; placebo, pill placebo plus medical management; and PDSS, Panic Disorder Severity Scale. No. of subjects for each cell may vary slightly from the number of subjects in each treatment arm due to occasional missing data (exact numbers available on request).
†Total of all 5 treatments combined.
‡*P* value for omnibus analysis of variance (for continuous measures) or 5 × 2 Freeman-Halton exact test (for categorical measures).
§A higher PDSS score indicates greater severity.

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imipramine), and at week 12, 3 (1.8%) of 164 (1 CBT+imipramine, 1 CBT, 1 imipramine) tested positive. Rates of missing urine samples were not significantly different across treatments.

CBT Alone and Imipramine Alone vs Placebo. In the acute ITT analysis, both CBT alone and imipramine alone were superior to placebo for the PDSS continuous measure (TABLE 2). Both treatments had significantly fewer dropouts for lack of efficacy than did placebo (4/18 for CBT and 10/30 for imipramine vs 8/10 for placebo [Figure]), and the imipramine group had significantly more dropouts for adverse effects than did the placebo group. Maintenance ITT analysis (Table 2) confirms the superiority of both CBT alone and imipramine alone to placebo.

CBT vs Imipramine. We found no significant difference between CBT alone and imipramine alone in the acute ITT or completer analyses or in the maintenance ITT or ITC analyses (Table 2). As expected, significantly more patients in the imipramine group than in the CBT group dropped out because of adverse effects (Figure). The follow-up analyses (Table 2) show trends favoring CBT over imipramine.

Combined CBT+Imipramine vs Single Treatment. We hypothesized that CBT+imipramine would be better than all 3 of the relevant comparison groups. Table 2 shows that CBT+imipramine was superior to CBT alone on 1 of 3 ITT analyses and 1 of 3 completer analyses but was not superior to CBT+placebo. In the maintenance ITT analysis (Table 2), combined treatment was better in the PDSS average analysis than in all 3 comparison treatments (thereby meeting our criteria for superiority) and better than CBT and CBT+placebo on ITC analyses.

Intent-to-continue analyses showed that responders to imipramine, with or without CBT, fared significantly worse in the no-treatment follow-up period than those who received either CBT alone or CBT+placebo (Table 2). After treatment discontinuation in the follow-up ITT analyses, the treatments that continued to show evidence of superiority to placebo were CBT alone (Table 2) and CBT+placebo (statistically significant for all 3 measures).

Quality of Response

In a secondary analysis restricted to responders based on the CGI definition (TABLE 3), acute imipramine responders had significantly lower PDSS average scores than acute CBT responders, indicating a higher quality of response. Maintenance responders showed the same pattern at the trend level. Responders to combined CBT+imipramine had higher-quality responses than CBT responders at acute and maintenance points, as well as a higher quality of response than patients taking CBT+placebo at maintenance.

Timing of Loss of Response

Timing of loss of response could be determined in 4 of 5 imipramine follow-up completers, losing response during months 3, 4, 5, and 6 (1 case each) and in 1 of 2 CBT follow-up completers, losing response during month 3. Among 9 CBT+imipramine follow-up completers losing response, relapse occurred during months 2, 4, and 5 (2 cases each), months 1, 3, and 6 (1 case each), and in the CBT+placebo relapser during month 1.

COMMENT

Our results demonstrate that both imipramine and CBT are better than pill placebo for treatment of PD. Imipramine produced a superior quality of response, but CBT had more durability and was somewhat better tolerated.

In our study, ITT placebo response did not differ from active treatment on acute-phase assessment when CGI was used to determine responder status. By contrast, the 7-item PDSS successfully discriminated between conditions. Moreover, the placebo response in the ITT analysis of 37.5% based on CGI criteria after 3 months drops to 13% after 9 months of treatment. Several studies have made similar observations in the treatment of depression and PD.[38-41] While attrition in the placebo group may have compromised comparisons at the end of maintenance, placebo response is weak in magnitude and transient in duration.[1,24]

There are several differences between active treatments. Although no differences emerged on a priori planned completer or ITT analyses, patients treated with imipramine and designated responders based on CGI criteria following the acute phase showed significantly more improvement on the PDSS than patients who responded to CBT. A trend level of significance remained at the end of maintenance. Thus, among those who did well with either treatment, patients receiving imipramine responded more completely. However, at follow-up, patients who had received CBT alone maintained their improvement significantly better (4% relapse) than those treated with imipramine (25% relapse) based on PDSS responder criteria. We discontinued imipramine by tapering during a 1- to 2-week period, following standard practice at the time. Relapses in medication-treated patients appeared to be evenly distributed across follow-up, suggesting that withdrawal played little role in the results. We did not aim to determine optimal tapering strategy or to ascertain the duration of medication maintenance that produces the best long-term outcome. Our results indicate the need for such work.

Findings of high acceptability and durability of CBT are consistent with previous reports,[16] although attrition in the CBT-alone group was higher than reported previously.[6,14,15,42] Adverse effects with imipramine and relapse following discontinuation are also consistent with previous reports.[38-40] However, our results that show a superior quality of response with imipramine among responders to both treatments in the acute phase underscore the need to reduce attrition and develop optimal maintenance and discontinuation procedures for those receiving medication.

Acute coadministration of imipramine and CBT resulted in limited benefit over monotherapy. Adding medication to CBT achieved significantly better results than CBT alone at postacute assessment on some measures, but this

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combination was never better than CBT+placebo. By the end of maintenance, CBT+imipramine was superior to both CBT alone and CBT+placebo (as well as imipramine alone) on the PDSS average measure. However, this robust combination treatment produced the highest relapse rate at follow-up assessment. Surprisingly, the addition of CBT

Table 2. Treatment and Follow-up Analyses*

Analysis	Measure	CBT Alone	Imipramine Alone	Placebo Alone	CBT Plus Imipramine	CBT Plus Placebo	Total	*P* Value	Pairwise Comparisons† I vs P	C vs P	I vs C	C + I vs C + P‡	C + I vs C‡	C + I vs I‡
					Acute Treatment Analyses									
Acute completers	No. of subjects	56	51	14	47	45	213							
	PDSS average item score, mean (SD)	0.95 (0.65)	0.75 (0.65)	1.15 (0.86)	0.60 (0.61)	0.72 (0.62)	0.79 (0.66)	.003	**.03**	.17	.13	.22	**.002**	.23
	PDSS response rate, %	67.3	74.5	38.5	84.4	80.0	73.7	.01	**.02**	.06	.52	.78	.06	.32
	CGI response rate, %	74.5	78.4	64.3	89.1	86.7	80.6	.13	NA	NA	NA	NA	NA	NA
Acute intention-to-treat	No. of subjects	77	83	24	65	63	312							
	PDSS average item score, mean (SD)§	1.14 (0.74)	1.05 (0.77)	1.52 (0.90)	0.88 (0.74)	0.99 (0.70)	1.06 (0.76)	.003	**.009**	**.02**	.41	.34	**.02**	.15
	PDSS response rate, %	48.7	45.8	21.7	60.3	57.1	50.0	.02	**.05**	**.03**	.75	.86	.18	.10
	CGI response rate, %	53.9	48.2	37.5	64.1	61.9	54.8	.10	NA	NA	NA	NA	NA	NA
					Maintenance Treatment Analyses									
Intention-to-continue in maintenance	No. of subjects	41	40	9	41	39	170							
	PDSS average item score, mean (SD)§	0.76 (0.77)	0.54 (0.72)	1.03 (0.84)	0.29 (0.60)	0.67 (0.67)	0.60 (0.71)	.005	.12	.32	.16	**.006**	**.001**	.07
	PDSS response rate, %	73.2	79.5	37.5	90.0	76.3	77.7	.03	**.03**	.09	.60	.13	.08	.22
	CGI response rate, %	78.0	79.5	37.5	87.8	82.1	79.6	.06	NA	NA	NA	NA	NA	NA
Maintenance intention-to-treat	No. of subjects	77	83	24	65	63	312							
	PDSS average item score, mean (SD)§	1.18 (0.86)	1.14 (0.87)	1.54 (0.83)	0.78 (0.86)	1.08 (0.79)	1.09 (0.86)	.001	**.04**	**.05**	.72	**.04**	**.004**	**.01**
	PDSS response rate, %	39.5	37.8	13.0	57.1	46.8	42.2	.003	**.02**	**.02**	.87	.28	**.04**	**.03**
	CGI response rate, %	42.1	37.8	13.0	56.3	50.0	43.3	.003	**.02**	**.01**	.63	.59	.13	**.03**
					Follow-up Analyses									
Intention-to-continue in follow-up	No. of subjects	28	25	3	30	30	116							
	PDSS average item score, mean (SD)§	0.56 (0.72)	0.81 (0.90)	–0.11 (0)	1.11 (1.02)	0.53 (0.70)	0.71 (0.87)	.02	.20	.10	.23	**.007**	**.01**	.30
	PDSS response rate, %	85.2	60.0	100	50.0	83.3	70.5	.01	.52	1.00	.06	**.01**	**.009**	.58
	CGI response rate, %	82.1	60.0	100	51.7	83.3	70.4	.02	.53	1.00	.12	**.01**	**.02**	.59
Follow-up intention-to-treat	No. of subjects	73	77	24	59	62	295							
	PDSS average item score, mean (SD)§	1.33 (0.93)	1.45 (0.83)	1.62 (0.77)	1.45 (0.90)	1.18 (0.92)	1.37 (0.89)	.12	NA	NA	NA	NA	NA	NA
	PDSS response rate, %	32.4	19.7	9.1	25.0	41.0	27.6	.01	.34	**.05**	.09	.08	.43	.41
	CGI response rate, %	31.9	19.7	13.0	26.3	41.0	28.0	.03	.55	.11	.09	.12	.56	.41

*See first 3 footnotes to Table 1. *P* value for omnibus analysis of the continuous measure used analysis of covariance with baseline as covariate or repeated-measures analysis of variance when analysis of covariance assumptions were not met. CGI indicates Clinical Global Impression Scale; I, imipramine; P, placebo; C, CBT; C + I, CBT + imipramine; and C + P, CBT + placebo.

†Pairwise comparisons are for 2-tailed Fisher exact tests; analyses were for continuous data, as per first footnote. Boldface indicates *P* values significant at ≤.05; gray tint indicates therapy listed on top is better than therapy listed below (consistent with hypotheses); boxed values indicate bottom therapy is better than top therapy (counter to hypotheses) at either significant or trend levels. Exact *P* values are shown, rounded to 2 significant digits when *P*≥.01, otherwise to 3 significant digits. NA indicates post hoc pairwise comparisons not applicable because of nonsignificant omnibus test results.

‡All 3 comparisons of C + I>C + P, C + I>C, and C + I>I were required to indicate superiority of combined treatment.

§Baseline adjusted means.

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Table 3. Analysis of PDSS Average Item Score for Responders*

	Mean (SD)							Pairwise Comparisons					
	CBT Alone	Imipramine Alone	Placebo Alone	CBT Plus Imipramine	CBT Plus Placebo	Total	*P* Value	I vs P	C vs P	I vs C	C + I vs C + P	C + I vs C	C + I vs I
No. of subjects	41	40	9	41	39	170							
Acute	0.69 (0.41)	0.47 (0.45)	0.77 (0.58)	0.48 (0.50)	0.56 (0.43)	0.58 (0.45)	.03	.08	.66	**.01**	.34	**.01**	.83
No. of subjects	32	31	3	36	31	133							
Maintenance	0.49 (0.43)	0.32 (0.42)	0.26 (0.50)	0.19 (0.33)	0.45 (0.42)	0.35 (0.41)	.02	.81	.37	.09	**.006**	**.001**	.11
No. of subjects	23	15	3	15	25	81							
Follow-up	0.26 (0.30)	0.15 (0.21)	−0.05 (0.0)	0.20 (0.26)	0.20 (0.24)	0.19 (0.25)	.39	NA	NA	NA	NA	NA	NA

*First 4 footnotes to Table 2 apply.

to imipramine did not mitigate relapse following medication discontinuation; addition of imipramine appeared to reduce the long-term durability of CBT. More work is needed to elucidate this result. A selection effect may account for the relatively poor outcome of combined treatment after discontinuation. Combined treatment could conceivably select patients who had been in particular need of long-term treatment from the beginning. We have not been able to detect important differences at baseline on variables in Table 1 between patients who did and did not enter the follow-up phase, but these analyses do not exclude the possibility of selection on an unmeasured prognostic factor.

There are several limitations of this study. First, to avoid the complications and possible confounding factors of adding exposure-based interventions to each condition, we enrolled patients with only limited degrees of phobic avoidance, and results are generalizable only to this group. Second, it could be argued that we underestimate the benefits of medication by using a tricyclic antidepressant instead of an SSRI. Current recommendations[43] (not yet in place when this study began) consider SSRIs to be the first-line medication. While there is little question that SSRIs are more convenient and have a more limited adverse-effect profile, studies examining differences from tricyclic antidepressants do not consistently find higher efficacy for SSRIs. In fact, of 4 randomized studies, none found significant differences in the end-of-study acute ITT analyses.[44-47] One study found evidence for a more rapid response for the SSRI,[44] and another found that the tricyclic antidepressant but not the SSRI was more effective than placebo.[46] Moreover, there have also been refinements in CBT since we began our study. Thus, we believe it likely that results of a similar comparative study using an SSRI would not differ substantially from ours. Third, at the time we designed this study, a consensus existed that an adequate dose of imipramine should be at least 200 mg/d. A recent study, however, suggests that imipramine/desipramine plasma levels of about 150 mg/mL may be optimal in treating PD.[48] Hence, it is conceivable that we underestimate the therapeutic potential of imipramine in this study. Finally, the use of nonstudy medication is a possible confounding factor to any anxiety study. We made the decision to permit limited use of benzodiazepines, because we sought to simulate clinical practice. Rates of urine samples that tested positive for benzodiazepine use among the 5 treatments were equivalent and low. Only 1 subject's data were censored because of excessive benzodiazepine use. Thus, we believe benzodiazepine use did not play a significant role in our results.

This study represents, to our knowledge, the first multicenter trial comparing medication and psychosocial therapies and their combination for PD. Prior studies contrasting the 2 approaches have been criticized because of possible investigator-allegiance bias in study design, implementation, and/or analysis. Our study sites included 2 with psychotherapy and 2 with pharmacotherapy expertise. In this context, the absence of site differences in ITT outcome supports the important implication that both types of treatment should be transportable to most clinical settings and confirms the generalizability of the results.

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Table. Recommendations for Improvement of End-of-Life (EOL) Care in Dementia

Palliative Care
Palliative care must be available to persons with advanced dementia earlier than at a point when the person is eligible for inclusion in existing hospice programs.
Health maintenance organizations, assisted-living and nursing facilities must support and provide appropriate EOL care for persons with dementia.
Programs that provide comprehensive and life-long services, such as Programs of All-inclusive Care for the Elderly (PACE), need to be expanded and made more accessible to persons with dementia, including those who do not have family caregivers.
Decision Making
Advance care planning must begin at the point of diagnosis, preferably when the person can still make his or her own decisions.
Ethical principles important for EOL decisions must be incorporated into health care policies and caregiving practices to support good EOL care for persons with terminal dementia.
Acute Care
Hospital and emergency care for persons with advanced or terminal dementia must recognize the specific needs of this population and include presence of a familiar caregiver during the treatment process.
Research and Education
Dementia EOL cooperatives should be created to engage in rapid cycling improvement studies in an effort to improve EOL care for persons with dementia.
Knowledge of EOL care for persons with advanced and terminal dementia must be widely disseminated to professional and lay caregivers.

tual capacity, personality, and the ability to communicate one's wishes for care and produces intense physical, emotional, and financial burden on the family.

Methods. The US Department of Veterans Affairs and the Alzheimer's Association convened an advisory board to examine the current state of EOL care in ADRD and to draft recommendations for improvement of care. A steering committee reviewed published and unpublished data, held focus group meetings with professional caregivers, and conducted a national survey of primary family caregivers of persons who had died from terminal ADRD in the past 6 months to identify elements that either promote or inhibit high-quality care. The committee also convened a panel of experts that participated in a 2½ day meeting in which the available information was summarized, desired outcomes were defined, areas considered deficient for EOL care were identified, and a brainstorming session to identify needed changes to make high-quality care a reality was held. The session concluded with agreement on the policy recommendations through a consensus process.[4]

Results. The panel defined high-quality EOL care for persons with ADRD as care that treats the whole person, reflects the choices and values of the individual, and is provided in a culturally sensitive manner by well-educated and well-supported family members, professionals, paraprofessionals, and volunteers within a seamless network of care. Key elements of high-quality care are resource availability and accessibility; community care settings that meet the needs of patients and families; ongoing processes of educated decision making established early in the diagnosis; and integrated, coordinated provision of care. The opposite—poor quality of care—is characterized by inappropriate interventions, poor symptom management, and inappropriate use of services. The panel formulated 8 recommendations organized into 4 categories (TABLE).

Comment. End-of-life care for persons dying with dementia requires specialized knowledge and service arrangements, education for professional and lay caregivers, and continuing evaluation and improvement. Because persons dying with ADRD are vulnerable and depend on others to meet their needs, the US health care system must attend to these unique needs and develop policies to promote compassionate high-quality care.

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CORRECTIONS

Incorrect Unit of Measure and Numbers: In the Original Contribution entitled "Cognitive-Behavioral Therapy, Imipramine, or Their Combination for Panic Disorder" published in the May 17, 2000, issue of THE JOURNAL (2000;283:2529-2536), the units of measure for imipramine and desipramine should be ng/mL instead of ng/dL on page 2532 and ng/mL instead of mg/mL on page 2535. On page 2530 under "Study Design," patients randomized to CBT+placebo should number 5 per block of 24, not 25. In the "Treatment Conditions" section on page 2531, near the end of the third paragraph, " . . . the dosage [of imipramine] could be increased up to 300 mg/d by week 5" should read "week 7."

Author Omitted: In the Caring for the Critically Ill Patient article entitled "Ketoconazole for Early Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome" published in the April 19, 2000, issue of THE JOURNAL (2000;283:1995-2002), an author was inadvertently omitted from the ARDS Network listing on page 2002. Brian Christman, MD, should have been listed with the Vanderbilt University group and identified as an author.

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