Cognitive Therapy and Pharmacotherapy for Depression

Singly and in Combination

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• Cognitive therapy and imipramine hydrochloride tricyclic pharmacotherapy, each singly and in combination, were compared in the treatment of nonpsychotic, nonbipolar depressed outpatients. One hundred seven patients were randomly assigned to 12 weeks of active treatment; 64 patients completed the full course of treatment. Rates of attrition were high but not differential. Cognitive therapy and pharmacotherapy did not differ in terms of symptomatic response, either in the primary analyses or in secondary analyses restricted to more severely depressed outpatients. Initial severity did predict response within pharmacotherapy alone, but not within cognitive therapy. Combining cognitive therapy with pharmacotherapy did not markedly improve response over that observed for either modality alone, although such nonsignificant differences as were evident did favor the combined treatment. Two patients died as a consequence of suicide attempts, both of which involved study medication.

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Questions still remain as to the efficacy of cognitive therapy relative to pharmacotherapy in the treatment of depression.[1] Although some trials have found cognitive therapy to be superior to tricyclic pharmacotherapy,[2,3] others have not.[4,5] Similarly, although combined treatment has been found to be superior to pharmacotherapy alone in some studies,[2,6] that has not been the case in several others.[5,7,8] In general, those studies that have most adequately operationalized pharmacotherapy have tended not to find differences favoring cognitive therapy or combined treatment over pharmacotherapy alone.[1] In fact, in the recently published National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDCRP), there were indications that cognitive therapy might even be less effective than imipramine hydrochloride pharmacotherapy among more severely depressed outpatients.[4]

The present study was originally intended to replicate and extend a study by Rush and colleagues[3] that found that cognitive therapy was superior to imipramine tricyclic pharmacotherapy. Although that earlier study generated considerable interest, it was flawed in several respects. Raters were not "blind" to treatment condition, and the adequacy of the pharmacotherapy provided was marginal at best (eg, dosage levels were low, plasma drug levels were not checked, and medication withdrawal was begun 2 weeks before the posttreatment assessment). These problems were compounded by the fact that the study was conducted at the center at which cognitive therapy was developed. If patient referral or institutional allegiance factors operated to bias the project, they were likely to have favored the cognitive modality. Many of these concerns could be raised about a subsequent study at that same site in which the addition of amitriptyline hydrochloride was found to add little to the efficacy of cognitive therapy alone.[7]

See also p 802.

The present study was designed to address each of these concerns. It was conducted at a center with no previous association with cognitive therapy, but with a history of involvement in pharmacologic trials.[9] Raters were blind to treatment condition, and pharmacotherapy was more aggressively pursued (ie, dosage levels were more consistent with current practice, drug plasma levels were monitored throughout treatment, and medication was maintained at full dosage levels up through the posttreatment assessment). As in the several other studies initiated in the aftermath of the original Philadelphia trials (most of which have now been published),[2,4,5] our intent was to ensure that pharmacotherapy was adequately operationalized as a known standard against which cognitive therapy (or combined treatment) could be compared.

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PATIENTS AND METHODS

Patients

The sample consisted of 107 nonpsychotic, nonbipolar depressed outpatients. All patients met the following criteria at intake: (1) major depressive disorder, as defined by the Research Diagnostic Criteria (RDC)[10]; (2) a Beck Depression Inventory (BDI) score of 20 or greater[11]; and (3) a Hamilton Rating Scale for Depression (HRSD, 17-item version) score of 14 or greater.[12] Exclusion criteria were as follows: (1) past or current RDC schizophrenia, bipolar I affective disorder, organic brain syndrome, somatization disorder, antisocial personality, or schizotypal features (two or more); (2) current generalized anxiety disorder, panic disorder, phobic disorder, or obsessive-compulsive disorder, if predominant over and not coterminous with the current episode of depression; (3) RDC diagnosis of alcoholism or drug use disorder within the last year; (4) hallucinations, delusions, or stupor; (5) suicide risk necessitating immediate hospitalization; (6) medical history or results of current laboratory tests (ie, thyroxine level, electrocardiogram, automated chemical analysis, or urinalysis) contraindicating imipramine treatment; (7) recent (within 3 months) history of nonresponse to an *adequate* trial of imipramine hydrochloride (ie, 150 mg/d for at least 2 weeks); or (8) IQ less than 80. Patients were not excluded who met RDC for minor depressive disorder, bipolar II affective disorder, or labile or cyclothymic personality, as long as they currently met criteria for major depressive disorder.

Recruitment and Screening

All patients were drawn from persons seeking treatment from either of two allied psychiatric treatment facilities serving metropolitan St Paul, Minn: the Department of Psychiatry at the St Paul–Ramsey Medical Center and the Ramsey County Mental Health Center. Patients were admitted to the trial beginning in 1980. Potential participants were initially screened by triage personnel in those facilities and informed about the nature of the study. Persons interested in participation were referred for intake evaluation within 7 days. The evaluation consisted of an interview with an experienced research clinician based on the Schedule for Affective Disorders and Schizophrenia–Lifetime Version,[13] along with a battery of self-report measures. All intake interviews were videotaped. One of us (W.M.G.), an experienced diagnostic interviewer, reviewed the tapes for all patients meeting inclusion criteria and concurred with the initial diagnosis in 96% of the cases. Only those patients who passed both screenings were included in the sample.

Assignment

Patients who met all inclusion and exclusion criteria were randomly assigned to one of four conditions: (1) pharmacotherapy without continuation; (2) pharmacotherapy plus continuation; (3) cognitive therapy; or (4) combined cognitive-pharmacotherapy. All pretreatment measures were completed before randomization. Patients were stratified before randomization with respect to sex, age (≤35 years vs >35 years), and chronicity of the index episode (≤6 months vs >6 months). In all instances, treatment was begun within 1 week of randomization. Randomization continued until 16 patients had completed treatment in each condition, with the constraint that no further assignments be made to a given condition once that number of protocol completers had been achieved (less than 1 month passed from the time the first condition was filled until the last patient was assigned). Noncompleters were replaced on an ongoing basis from within strata. This was intended to offset the potential biasing effects of differential attrition among the treatment completers (S.D.H., unpublished data, January 1992).

Assessment

After the intake interview, all patients were reexamined at 6 weeks (midtreatment) and 12 weeks (posttreatment) by study evaluators blind to treatment condition. In addition to the HRSD, all patients were rated on the Raskin Depression Scale (RDS),[14] another index of depression, and the Global Assessment Scale (GAS),[15] a measure of general level of psychosocial functioning. All reevaluations were videotaped and rated by additional raters; interrater reliabilities between the live interviewers and the average of the videotape raters were acceptable in all instances (all $r \geq .80$, with all $P < .0001$, N=125). Patients completed the BDI at each treatment session and at each reevaluation. They also completed the Minnesota Multiphasic Personality Inventory (MMPI) at both intake and posttreatment.[16] Scale 2 of the MMPI provided yet another measure of depression (MMPI-D). To provide a single index of depression, an unweighted composite was constructed by first normalizing each measure individually and then averaging across the four indexes of depression (HRSD, RDS, BDI, and MMPI-D). Such a composite not only provides a more valid measure of the construct of interest, but it also provides one means of reducing the experiment-wise error rate, since it replaces four sets of analyses with a single, more powerful one.[17]

Treatment Modalities

Cognitive Therapy.—Cognitive therapy is a structured, partially didactic approach to the treatment of depression in which patients are trained to identify and modify negative beliefs and maladaptive information processing proclivities in an effort to produce symptom relief.[18] Patients assigned to cognitive therapy (either alone or in the combined treatment) were seen for a maximum of 20 sessions, each 50 minutes, during a 12-week period. (Patients assigned to the combined condition also met separately with a pharmacotherapist.) Protocol called for two sessions per week during the first 4 weeks, either one or two sessions per week during the middle 4 weeks, and one session per week during the last 4 weeks. Missed sessions could be rescheduled at any time during the 12-week active treatment period. Patients who completed cognitive therapy averaged 14.9 sessions during 11.5 weeks of treatment, with no differences between patients assigned to cognitive therapy only vs those assigned to the combined treatment.

The cognitive therapists were four experienced psychotherapists (8 to 20 years of experience) with little previous familiarity with cognitive therapy. One was a male PhD clinical psychologist (M.J.W.); two men and one woman were ICSW clinical social workers. Training was provided by three of us (S.D.H., R.J.D., and M.D.E.) and consisted of up to 14 months of weekly training sessions, plus supervision of practice cases. Ongoing 90-minute group supervision sessions were provided twice weekly during the first two thirds of the study. Supervision sessions were tapered to once-weekly meetings during the last third of the study.

Selected therapy sessions were rated by independent judges on the Cognitive Therapy Scale[19] and the Minnesota Therapy Rating Scale.[20] Four audiotaped sessions were rated for each cognitive therapy completer (including those in the combined treatment); one session was rated for each pharmacotherapy completer (including those in combined treatment). Ratings of the quality of execution (Cognitive Therapy Scale) and adherence to the model (Minnesota Therapy Rating Scale) with respect to cognitive therapy for treatment completers showed clear differentiation between cognitive therapy sessions vs pharmacotherapy sessions, with means of 40.8 vs 14.0 on Cognitive Therapy Scale total scores and 51.4 vs 40.9 on the Minnesota Therapy Rating Scale CB T-score (both $P < .001$, n=46). There were no differences between cognitive therapy alone and the cognitive therapy component of combined treatment.

Pharmacotherapy.—Patients assigned to pharmacotherapy (either alone or in the combined treatment) attended once-weekly sessions with a psychiatrist. (Patients assigned to the combined condition also met separately with a cognitive therapist.) Initial sessions typically lasted about 50 minutes, whereas subsequent sessions lasted about 30 minutes. Treatment was focused on (1) *pharmacotherapy management,* which involved educating patients about medications, adjusting dosage and dosage schedules,

and inquiring about and dealing with side effects, and (2) *clinical management*, which involved a review of the patient's functioning in major life spheres, brief supportive counseling, and limited advice giving. Patients who completed pharmacotherapy averaged 8.8 sessions during 11.4 weeks of treatment, with no differences between patients assigned to pharmacotherapy only vs those assigned to the combined treatment.

The pharmacotherapists were four male board-certified psychiatrists (including M.J.G.). Since all had previous experience in controlled drug trials,[9] no formal preproject training was provided. The pharmacotherapists met periodically under the supervision of the project's medical director (V.B.T.) to review protocol execution and treatment-related issues.

The medication used was imipramine hydrochloride, provided in flexible daily dosages, typically taken at bedtime. Treatment protocol called for a beginning dose of 75 mg/d, increasing to 150 mg/d by the end of week 1200 mg/d by the end of week 2, and reaching 200 to 300 mg/d in week 3 and remaining at that level through the end of week 12. Dosages were raised for any patient with a plasma imipramine/desipramine level less than 180 ng/mL at midtreatment. Three patients were maintained at doses below 200 mg/d. These patients evidenced an adequate clinical response and imipramine/desipramine plasma levels in excess of 180 ng/mL but were troubled by side effects at higher dosage levels. Several patients had their doses raised above 300 mg/d after initial nonresponse (the maximum dose used was 450 mg/d). For these patients, imipramine/desipramine plasma values were monitored to ensure no risk of toxic reactions. Maximum daily doses averaged 232 mg/d, with no differences between pharmacotherapy alone vs combined treatment. Imipramine/desipramine plasma levels averaged 312 ng/mL at week 6 and 304 ng/mL at week 12, with values (nonsignificantly) higher in the pharmacotherapy-alone condition. Three patients in the combined-treatment condition discontinued medications due to side effects but were considered treatment completers because they completed cognitive therapy. A fourth patient in the combined-treatment condition was largely noncompliant with cognitive therapy but was considered a treatment completer because he completed pharmacotherapy.

Analytic Strategy

All analyses were conducted on (1) the subset of patients who completed all 12 weeks of protocol treatment (*completers*) and (2) the full sample of all patients initially assigned to treatment (*all assigned*). For noncompleters included in the latter analyses, the last available score on each measure was carried forward as the termination score. Since replacing noncompleters can introduce bias into "intent to treat" analyses, secondary analyses were also conducted in which data for "excess" replacement patients (those patients who increased disproportionality among the conditions on one or more of the stratification variables) were deleted (S.D.H., unpublished data, January 1992).

The unweighted additive composite served as the primary measure of the severity of depressive symptoms. Secondary analyses were applied to the four univariate depression indexes and to the measure of general adjustment. In each instance, analyses of variance were conducted on pretreatment depression scores to assess the comparability of the respective conditions before treatment. A variety of demographic, history of illness, depression subtype, family history, personality, biologic, and cognitive indexes were also examined as potential confounds, with the use of analyses of variance for the continuous variables and χ^2 for the categoric ones. A variable was considered a confound if it both differentiated among the conditions and predicted subsequent response. Even with the use of liberal criteria ($P<.10$), none of the 48 indexes examined met criteria as a confound. Within-condition t tests were conducted on the outcome measures to assess change over time. Analyses of covariance, with pretreatment scores on the respective measures used as the covariate, were applied to the midtreatment and posttreatment scores for the completer sample and to the end-point scores for the full sample. (In instances in which heterogeneity of regression was evident as a function of treatment condition, pretreatment scores were not used as covariates.) Significant treatment effects were followed by Bonferroni t tests, which adjust the type I error rate for the three multiple comparisons among the treatment conditions.[21] We also analyzed response categorically, by means of Brunden's method of partitioning significance levels after χ^2 tests.[22] Finally, to examine the influence of initial severity on outcome, we conducted additional secondary analyses (analyses of covariance and χ^2) within level of severity.

RESULTS

Patient Characteristics

A total of 322 patients were referred, of whom 70 declined participation or could be excluded on the basis of information discerned before evaluation. Of the 252 patients examined, 145 were excluded at intake, typically because they were not sufficiently depressed or because they met criteria for another axis I disorder. The remaining 107 patients were randomly assigned to treatment.

The sample was predominantly female (80%) and white (91%). The average (±SD) age was 32.6±10.8 (range, 18 to 62 years). Twenty-six percent were single, 32% were married or cohabiting, and 42% were separated, divorced, or widowed. Sixty-two percent were employed outside the home, 13% were housepersons, and 25% were unemployed. The sample was characterized by a moderate level of education; 14% were college graduates, 34% had some college education, 32% were high school graduates, and 20% had only partial high school or less. Intelligence, as measured by the Shipley-Hartford scale,[23] was slightly above average (mean±SD, 112.2±13.0). The sample as a whole could be categorized as being lower middle class. Categorization in accordance with Hollingshead and Redlich's two-factor index[24] indicated that 1% of the patients represented socioeconomic status level 1, 12% level II, 22% level III, 36% level IV, and 28% level V.

With regard to RDC subtypes of depression (combining probable and definite designations), 64% of the sample met criteria for recurrent depression (27% had no previous episodes of major depressive disorder, whereas 37% had a history of three or more [mean±SD, 2.3±2.2 episodes]). Twenty-four percent of the sample met criteria for "double depression" (an episode of major depressive disorder superimposed on an RDC minor depression, cyclothymia, or labile personality). Sixty-four percent met criteria for RDC endogenicity. The mean age at the first episode of major depressive disorder was 23.3±9.9 years, and the duration of the current episode was 6 months or less for 79% of the patients. Onset was reported to have been sudden (within 1 day) by 8%, gradual (during the course of a week) by 51%, and insidious by 40%. Sixty-six percent reported an event they considered to be a precipitant. Thirty-three percent had a history of hospitalization, 28% a history of antidepressant medication, and 64% a history of psychotherapy. The mean number of previous therapists was 1.5±1.6 (range, zero to 10), with 29% having had no previous therapists and 18% having had three or more. Sixty-six percent reported suicidal ideation at intake, and 39% reported having made one or more suicide attempts during their lifetime. Thirteen percent had a history of alcoholism, and 8% had a history of other forms of substance abuse. With respect to psychiatric disorder in first-degree relatives, 69% of the sample had relatives with a history of depression, 16% with a history of mania, and 60% with a history of other disorders, typically alcoholism or one of the anxiety disorders.

Attrition

As shown in Table 1, of the 107 patients assigned, 43 (40%) failed to complete 12 weeks of protocol treatment. Of this total, five (5%) failed to initiate treatment (*refusers*), and another 38 (35%) failed to complete treatment after beginning (*noncompleters*). Among the noncompleters, 29 (27%) discontinued against medical advice (*dropouts*) and nine (8%) were withdrawn by the project medical director after complications (*withdrawals*). Rates of

Table 1.—Attrition Status as a Function of Treatment Condition

Treatment Cell	No. Screened in	Completion, No. (%)	Attrition, No. (%)			
			Total	Refusal (0 wk)	Noncompletion: Early (1-3 wk)	Noncompletion: Late (>3 wk)
Drugs (pooled)	**57**	32 (56)	25 (44)	2 (4)	10 (18)*	13 (23)†
Cognitive therapy	**25**	16 (64)	9 (36)	3 (12)	1 (4)	5 (20)‡
Combined cognitive-pharmacotherapy	**25**	16 (64)	9 (36)	0 (0)	6 (24)§	3 (12)
Total	**107**	**64** (60)	**43** (40)	**5** (5)	**17** (16)	**21** (20)

*Includes three patients withdrawn from treatment by the project medical director: one hospitalized after a suicide attempt and two because of severe side effects.

†Includes four patients "withdrawn" from treatment by the project medical director: one after a fatal suicide attempt, two hospitalized because of symptomatic worsening (including increased suicide risk), and one because of severe side effects.

‡Includes one patient withdrawn from treatment by the project medical director after the emergence of a psychotic manic episode.

§Includes one patient "withdrawn" from treatment by the project medical director after a fatal suicide attempt.

Table 2.—Mean Pretreatment (Pre) and Adjusted Midtreatment (Mid) and Posttreatment (Post) Scores*

Index	Time	Drug (Pooled) N	Drug (Pooled) Mean±SD	Cognitive N	Cognitive Mean±SD	Combined N	Combined Mean±SD	Sign Level†
Completers Only (N=64)								
Comp	Pre	32	0.96±0.42	16	0.90±0.32	16	0.88±0.47	.76
	Mid	32	−0.34±0.68	16	−0.48±0.68	16	−0.55±0.68	.57
	Post	32	−0.48±0.68‡	16	−0.53±0.68	16	−0.93±0.68‡	.11
BDI	Pre	32	31.1±7.3	16	30.4±6.5	16	29.9±7.8	.84
	Mid§	32	13.7±9.4	16	11.4±9.4	16	11.3±9.4	.61
	Post§	32	10.5±9.5	16	7.9±9.5	16	6.8±9.5	.39
HRSD	Pre	32	24.0±5.4	16	24.8±3.9	16	23.5±4.5	.74
	Mid	31	9.6±6.4	16	8.5±6.4	16	7.3±6.4	.51
	Post	31	8.4±7.7	16	8.8±7.8	16	4.2±7.7	.17
RDS	Pre	32	10.6±1.6	16	10.6±1.6	16	10.4±2.0	.92
	Mid	31	5.4±2.3	16	5.4±2.3	16	4.9±2.3	.75
	Post	31	5.3±2.4‡	16	5.2±2.4	16	3.7±2.4‡	.08
MMPI-D	Pre	29	84.4±13.4	16	81.5±10.2	16	83.6±10.2	.74
	Mid	...	...	...	...	...	...	...
	Post§	26	72.5±13.8‖	12	71.8±14.5	14	61.4±11.6‖	.04
GAS	Pre	32	44.1±7.2	16	46.4±7.1	16	44.8±8.4	.60
	Mid	31	70.0±13.0	16	70.5±13.0	16	73.6±12.9	.66
	Post	31	73.4±13.8	16	73.0±13.8	16	79.9±13.7	.26
All Patients Assigned (N=107)								
Comp	Pre	57	0.94±0.39	25	0.92±0.35	25	0.97±0.50	.92
	Post	57	0.07±0.83	25	−0.01±0.83	25	−0.30±0.83	.17
BDI	Pre	57	30.3±6.9	25	30.1±5.7	25	32.0±8.3	.54
	Post	57	14.6±12.1	25	13.3±12.0	25	12.9±12.0	.81
HRSD	Pre	57	23.8±5.0	25	24.1±4.3	25	23.7±5.2	.95
	Post	57	14.2±10.0	25	13.3±10.0	25	10.5±10.0	.30
RDS	Pre	57	10.4±1.6	25	10.4±1.6	25	10.5±1.9	.97
	Post	57	7.2±3.3	25	6.8±3.3	25	5.8±3.3	.20
MMPI-D	Pre	52	85.4±12.5	22	85.0±11.2	24	85.3±12.2	.99
	Post	55	80.1±12.8‖	22	79.9±12.8	24	72.2±12.7‖	.04
GAS	Pre	57	45.0±7.2	25	46.3±7.6	25	45.4±8.3	.78
	Post	57	62.8±17.8	25	64.1±17.8	25	70.2±17.8	.23

*Pretreatment scores are means from a one-way analysis of variance. Adjusted midtreatment and posttreatment scores are treatment main-effect least-square mean scores from analyses of covariance with pretreatment scores as covariates. Comp indicates depression composite; BDI, Beck Depression Inventory; HRSD, Hamilton Rating Scale for Depression (first 17 items only); RDS, Raskin Depression Rating Scale; MMPI-D, Minnesota Multiphasic Personality Inventory Depression Scale; and GAS, Global Assessment Scale. Higher scores on the GAS indicate better functioning.

†Probability level for F test comparing the three treatment groups (pooling the two pharmacotherapy-only conditions).

‡Nonsignificant trend, $P<.10$, with Bonferroni's correction (significantly different, $P<.05$, on multiple t test).

§Pretreatment scores not used as covariate because of lack of equality of slopes between pretreatment and midtreatment or posttreatment scores.

‖Significantly different, $P<.05$, with Bonferroni's correction.

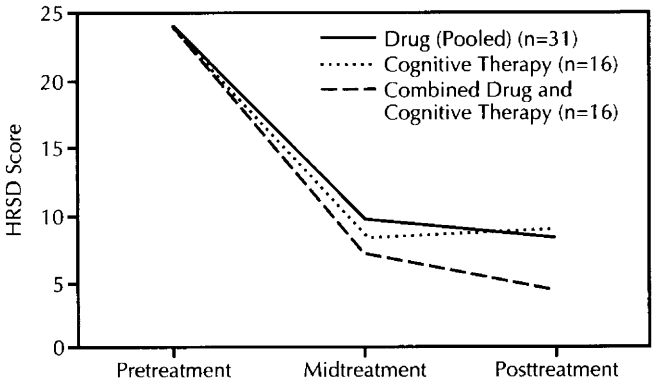

Fig 1.—*Change in depression by condition among treatment completers. Hamilton Rating Scale for Depression (HRSD) scores are least-square mean midtreatment and posttreatment scores from a one-way analysis of covariance with pretreatment severity on the HRSD as the covariate. Data are for treatment completers only.*

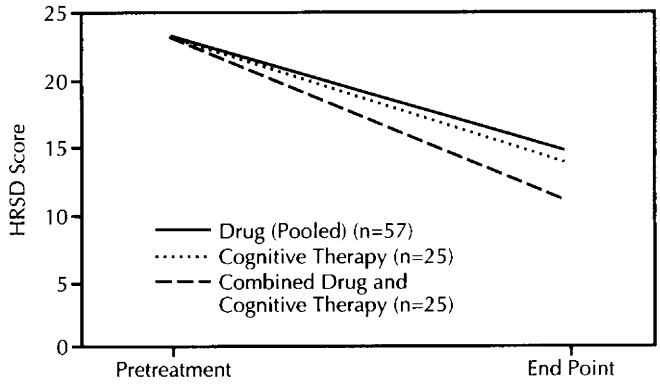

Fig 2.—*Change in depression by condition among all assigned. Hamilton Rating Scale for Depression (HRSD) scores are least-square mean end-point scores from a one-way analysis of covariance with pretreatment severity on the HRSD as the covariate. Data are for the full sample of all assigned.*

attrition did not differ across conditions ($\chi^2_{[3]}=3.58$, not significant). Since patients in the two pharmacotherapy-only conditions received identical treatment during the acute treatment phase and evidenced no significant differences on attrition or any treatment response variable, their data are pooled in Table 1 and throughout the remainder of this article.

Noncompleters did not differ in terms of overall length of treatment as a function of condition, whether assessed by analysis of variance or survival analysis (pharmacotherapy, 3.68 weeks; cognitive therapy, 3.44 weeks; and combined treatment, 4.00 weeks). However, when attrition was divided into "refusal," "early termination" (≤3 weeks), and "late termination" (>3 weeks), a nonsignificant trend was evident for attrition to occur at different points as a function of condition ($\chi^2_{[4]}=9.07$, $P<.06$). As can be seen in Table 1, patients were particularly likely to refuse to enter cognitive therapy and to terminate early from the combined condition.

Twenty-one patients failed to complete for reasons related to treatment: 10 due to medication side effects (including seven dropouts and three withdrawals), six due to noncompliance, and five due to dissatisfaction with the specific nature of treatment or their particular therapist. Six patients were withdrawn from treatment due to symptomatic worsening: one after the onset of a manic episode, three after hospitalization due to symptomatic worsening, and two after completed suicide attempts. Nine patients failed to complete treatment for reasons purportedly unrelated to treatment or lack of response: three due to moving out of town and six due to pressure from significant others. Four patients did not complete due to spontaneous remission, including two of the five patients who failed to begin treatment. The three remaining refusers provided no explanation for failing to begin treatment, but all three were less symptomatic than the average for the sample as a whole. Only medication side effects differentiated among the conditions; all 10 patients failing to complete treatment for this reason came from pharmacotherapy alone ($\chi^2_{[2]}=9.68$, $P<.01$).

Noncompleters who, at the time they terminated, scored more than 0.5 SD above the mean for the eventual completers, or who were withdrawn from the project because of clearly negative symptom outcomes (eg, manic episode, psychiatric hospitalization, or completed suicide), were judged to be symptom failures. The rate of symptom failure among the 43 noncompleters (and refusers) was highest in the combined condition ($\chi^2_{[2]}=8.26$, $P=.02$). This suggests that noncompleters in the combined condition were more likely to be doing poorly at the time they terminated than were such patients in either of the two single modalities. However, the bulk of the symptom failures in the combined condition (five of six) occurred before the end of the third week in treatment, before subjects had an adequate exposure to treatment. Thus, although differential attrition did occur (and could have biased the analyses based on the completers only), it did not appear to be a consequence of differential nonresponse to treatment. Patients with a history of hospitalization were more likely to fail to complete cognitive therapy than the other two conditions ($\chi^2_{[2]}=5.98$, $P<.05$). However, they were not more likely to be symptom failures in that condition than in the others. Therefore, it seems unlikely that differential attrition related to previous hospitalization biased the comparisons among the groups.

Treatment Response

Table 2 presents scores on the measures of depression (the composite and each of its constituents) and general adjustment at each of the assessment points for both samples. Scores at midtreatment and posttreatment are adjusted for pretreatment levels on the respective indexes (except in the case of unequal slopes). Secondary analyses excluding the "excess" replacement patients from the full sample or excluding the partial completers in the combined condition from the completers-only sample closely paralleled these findings and will not be reported separately. Similarly, none of the stratification variables predicted response; they will not be considered further.

The sample as a whole was at least as severely depressed as those studied in other comparable trials, including the NIMH TDCRP.[2-8] As can be seen, there were no differences among the treatment conditions on any of the symptom measures at pretreatment in either sample. Within-group t tests indicated that all three treatment conditions evidenced marked symptom reduction from pretreatment to posttreatment in both samples and from pretreatment to midtreatment in the completer-only sample (all $P<.001$). More than 90% of the observed change in each of the two single modalities occurred during the first 6 weeks of treatment. Only the combined condition continued to evidence significant change between midtreatment and posttreatment among the completers.

Differences between the two single modalities were negligible at all assessment points in each sample. Effect sizes on the composite, calculated as Cohen's d,[25] were no greater than 0.10 in either sample. This suggests that the lack of differentiation between pharmacotherapy alone and cognitive therapy alone was not simply an artifact of low design power.[26] Nonsignificant differences at posttreatment appeared to favor the combined condition over either single modality among the completers (effect sizes, 0.66 and 0.59, respectively, for comparisons between the combined treatment vs pharmacotherapy alone and vs cognitive therapy alone). However, an examination of the findings for the full sample suggested that a portion of that advantage was an artifact of the differential loss of patients with symptom failure from the combined condition. Nonetheless, nonsignificant differences favoring the combined treatment remained sufficiently large to be of potential interest even in the full sample of all assigned (effect

Table 3.—Patients Recovered at Termination*

Score	No. (%) of Patients: Drug (Pooled)	Cognitive	Combined	Significance Level†
Completers Only (N=64)				
N	32	16	16	. . .
BDI ≤9	18 (56)	10 (62)	11 (69)	.70
HRSD ≤6	17 (53)	8 (50)	12 (75)	.27
All Patients Assigned (N=107)				
N	57	25	25	. . .
BDI ≤9	23 (40)	11 (44)	12 (48)	.81
HRSD ≤6	19 (33)	8 (32)	13 (52)	.22

*BDI indicates Beck Depression Inventory; HRSD, Hamilton Rating Scale for Depression.

†Probability level for χ^2 test comparing the three treatment groups (pooling the two pharmacotherapy-only conditions).

sizes, 0.44 and 0.35, respectively, for comparisons between the combined treatment vs pharmacotherapy alone and vs cognitive therapy alone). These patterns are depicted in Fig 1 (completers only) and Fig 2 (all assigned). For ease of interpretability, both figures are presented in terms of the HRSD, which closely paralleled the composite.

Patterns of Individual Response

Presentation of group data can mask considerable variability in outcome.[27] Table 3 presents the posttreatment clinical status of individual patients as a function of treatment condition. Levels of depression are classified according to the BDI and HRSD, with cutoffs drawn from recent comparable trials.[3-5] Response status at posttreatment for completers and at termination for noncompleters is reported on both instruments. As can be seen, although the combined condition consistently exhibited the highest rate of full response, there were no significant differences on any of the indexes.

Initial Severity

It has been suggested that cognitive therapy may be less effective than pharmacotherapy in the treatment of more severely depressed outpatients.[4] Therefore, we conducted a number of additional secondary analyses to explore the impact of initial severity on outcome. We first tested for differential relations between initial severity and subsequent response as a function of treatment group. Initial severity did predict poorer response within pharmacotherapy, but not within cognitive therapy. Nonetheless, differences in the slopes between the two single modalities were not significant. Heterogeneity of regression was evident on two of the self-report measures (BDI and MMPI-D) among the treatment completers (Table 2) but was largely a consequence of a superior response among the more severely depressed patients to the combined treatment relative to pharmacotherapy alone. Influence diagnostics[28] suggested that this lack of equality was largely the consequence of a single outlier, a severely depressed patient who showed an unexpectedly good response to combined treatment. Thus, our initial exploration provided little evidence of any robust relationship between initial severity and differential treatment response.

We next divided the sample at the median on each measure. Greater severity was indicated by scores on the depression composite of greater than or equal to 0.87, BDI scores of greater than or equal to 30, HRSD scores of greater than or equal to 25, RDS scores of greater than or equal to 11, and GAS scores of less than or equal to 45. We then conducted analyses of covariance (treating pretreatment severity as the covariate) and χ^2 analyses within each level of severity and found no evidence of any advantage of pharmacotherapy alone among the more severe outpatients. Differences between the two single modalities among the more severely ill patients were negligible (average effect sizes were 0.16

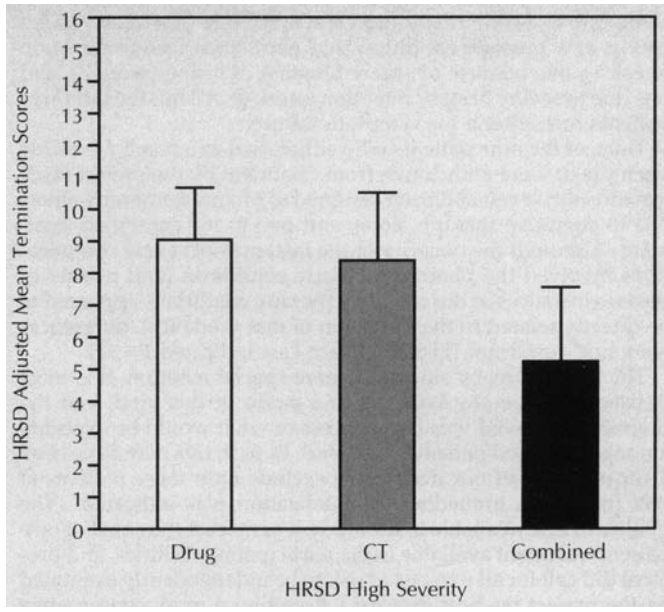

Fig 3.—*Posttreatment depression by condition among high-severity treatment completers. Hamilton Rating Scale for Depression (HRSD) scores are least-square (+SE) treatment scores from a one-way analysis of covariance with pretreatment severity on the HRSD as the covariate. Data are for treatment completers scoring 20 or above at intake on the HRSD (the HRSD criterion used to define high severity in the National Institute of Mental Health Treatment of Depression Collaborative Research Program[4]). Drug indicates the pooled pharmacotherapy-only conditions (n=25); CT, cognitive therapy (n=15); and Combined, the combined condition (n=12).*

among the completers only and 0.04 in the full sample of all assigned) and as often favored cognitive therapy as pharmacotherapy. We also conducted a series of analyses of variance and χ^2 tests, treating severity and treatment condition as the independent variables. None of the analyses produced any indication of an interaction between condition and severity (all $P>.20$). Finally, we repeated both sets of analyses with the use of cutting scores identical to those adopted in the NIMH TDCRP (greater severity was indicated by HRSD scores ≥20 and GAS scores ≤50). We again failed to find any evidence of differentiation. (Figure 3 presents the adjusted posttreatment scores on the HRSD for completers meeting the NIMH TDCRP criterion for high severity on the HRSD at intake; since the bulk of our patients met this criterion, no comparable values are depicted for patients with low severity.) Thus, there was no evidence in our sample that cognitive therapy was less effective than pharmacotherapy in the treatment of more severely depressed outpatients.

Safety

Three patients made suicide attempts during the course of active treatment, and two died as a result. The first of the fatalities involved a patient in her ninth week of pharmacotherapy alone who overdosed on study medications and alcohol after an argument with her boyfriend (this patient had shown a generally good symptomatic response before that time). The second fatality involved a patient assigned to the combined treatment who asphyxiated herself (possibly in combination with an imipramine overdose) the morning after her first pharmacotherapy session. She had not yet met with her cognitive therapist. The third patient, also in pharmacotherapy alone, was hospitalized after a nonlethal overdose of imipramine in the third treatment week.

Two additional patients in pharmacotherapy alone were withdrawn from treatment (weeks 4 and 5, respectively) by the project medical director and hospitalized due to increased risk of suicide. Another patient was withdrawn from cognitive therapy after the emergence of a manic episode in week 6 of treatment. Finally, three other patients were withdrawn from pharmacotherapy

alone due to severe medication reactions: one due to an exacerbation of a prostate condition that necessitated hospitalization (week 1), one because of severe blurring of vision (week 2), and one due to severe urinary retention (week 6). All but the last three patients met criteria for symptom failure.

Thus, of the nine patients who either died as a result of suicide attempts or were withdrawn from treatment by the project medical director, seven had been assigned to pharmacotherapy alone, one to cognitive therapy alone, and one to the combined treatment. Although the majority of the instances of severe complications involved the pharmacotherapy conditions (and neither of the two instances in the cognitive therapy conditions appeared to be directly related to the provision of that modality), differences were not significant (Fisher's Exact Test indicated $P=.17$).

The two deaths by suicide deserve special mention. It is most unusual to have any fatalities in a study of this kind, and the mortality observed was far in excess of what would be expected among depressed patients in general. In part, this may have been a consequence of our decision to exclude only those patients at risk for whom immediate hospitalization was indicated. (The quality of care available in the study was at least the equal of outpatient treatment available in the participating facilities, and protocol did call for all persons at risk to be independently examined by the project medical director.) Adopting a more conservative stance with respect to the inclusion of such patients probably would have reduced the number of fatalities among study participants, although it is not clear that it would have reduced risk for the particular individuals involved.

COMMENT

Cognitive Therapy vs Pharmacotherapy

Cognitive therapy and imipramine pharmacotherapy did not differ in overall efficacy, regardless of the composition of the sample (completers only or all assigned) or initial severity. In all instances, the magnitudes of the differences observed between the two single modalities were negligible, suggesting that this lack of differentiation was not simply a consequence of low design power.[25,26] At the same time, changes were observed over time within each modality that were comparable with those observed in other similar trials.[2-8] This suggests that the lack of differentiation was not an artifact of insensitive measurement. Change did occur and was detected, but there was no indication that it occurred differentially as a function of assignment to the two single modalities. In this sense, our findings do not replicate either the finding of Rush et al[3] of superiority for cognitive therapy or the NIMH TDCRP's suggestion of superiority for pharmacotherapy among more severely ill patients.[4] (It should be noted that this latter finding was not robust even in the NIMH TDCRP, as it held for only one of the three participating sites.)

We think it is unlikely that either modality was inadequately operationalized. Each modality was overseen by knowledgeable advocates, conducted by experienced practitioners, operationalized in a fully representative manner, and monitored in an ongoing fashion. We further think it unlikely that comparisons between the two single modalities were biased, either as a result of a failure of initial randomization or as a consequence of subsequent attrition. Nearly 50 pretreatment indexes (including most of the major correlates of response) were examined as potential confounds; none of the variables that predicted response differentiated between the two single modalities. Attrition was high and could represent a threat to the validity of the conclusions drawn. Nonetheless, it was not markedly higher than has been observed in other comparable trials. (For example, the recently completed NIMH TDCRP reported noncompletion rates of 40% in pharmacotherapy and 35% in cognitive therapy,[4] compared with rates of 44% and 36%, respectively, for those same conditions in the present study.) Finally, the sample studied appeared to be representative of depressed outpatients in general, and at least as severely depressed as those studied in other recent trials, including the NIMH TDCRP.[2-8]

Nonetheless, nonsignificant findings are always open to multiple interpretation. In particular, the absence of any placebo control makes an unambiguous interpretation difficult. In the absence of such a control, it remains possible that the sample was not pharmacologically responsive,[29] or that the pharmacotherapy was not adequately implemented.[30] We think the data are most consistent with the interpretation that both pharmacotherapy and cognitive therapy were effective, and comparably so (even with more severely depressed outpatients), but we think that future studies will need to include minimal-treatment controls if they are to provide the best tests of those hypotheses.

Combined Cognitive Therapy and Pharmacotherapy

It remains unclear whether combining cognitive therapy with tricyclic pharmacotherapy yields any advantage over either single modality alone, at least with respect to acute response. There was some indication of an advantage for the combined modality among the completers only, but the lower magnitude of that effect in the full sample suggests that it was, at least in part, an artifact of differential attrition. Nonetheless, effect sizes of the magnitude observed even among the full sample might still be clinically meaningful and worthy of detection. Combined treatment has typically produced differences of comparable magnitude (whether significant or not) in other similar trials.[2,5-8] We think it is likely that combined treatment does provide some modest advantage over either single modality, but that to detect the effect, larger samples will need to be studied than has typically been the case.[26]

CONCLUSIONS

Overall, results from the present study suggest little difference between cognitive therapy and imipramine pharmacotherapy in the treatment of depressed outpatients. No differences in overall response were observed between the two single modalities, even among the more severely depressed outpatients. Although caution is always required when null findings are interpreted, the minimal differences between the two conditions and the overall level of response to each (combined with the absence of any clear factors that might have biased the comparison) lead us to conclude that the two single modalities were comparably effective. Combined treatment was not clearly superior to either single modality alone, although there were indications of a potential modest advantage that deserves to be explored in subsequent studies with larger samples.

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CORRECTION

Incorrect Word in Text

In the article titled "Neuroendocrine Aspects of Primary Endogenous Depression: XI. Serum Melatonin Measures in Patients and Matched Control Subjects," published in the July issue of the ARCHIVES (1992;49:558-567), an error was made in the "Circadian Pattern of Serum Melatonin" section on page 561. In the left column, paragraph 2, lines 5 through 7 should have read as follows: "This approximated the method that was used by Lewy et al[44,45] to determine the 'dim light melatonin onset' time (dim light defined as <300 lux)." The journal apologizes for the error.