Treatment of Men With Major Depression: A Comparison of Sequential Cohorts Treated With Either Cognitive-Behavioral Therapy or Newer Generation Antidepressants

Michael E. Thase, M.D.; Edward S. Friedman, M.D.; Amy L. Fasiczka, M.A.; Susan R. Berman, B.A.; Ellen Frank, Ph.D.; Eric A. Nofzinger, M.D.; and Charles F. Reynolds III, M.D.

Objective: This report compares response to cognitive-behavioral therapy (CBT) and pharmacotherapy in sequential cohorts of men with DSM-III-R major depression.

Method: Patients were enrolled in consecutive standardized 16-week treatment protocols conducted in the same research clinic. The first group (N = 52) was treated with Beck's model of CBT, whereas the second group (N = 23) received randomized but open-label treatment with either fluoxetine (N = 10) or bupropion (N = 13). Crossover to the alternate medication was permitted after 8 weeks of treatment for antidepressant nonresponders. The patient groups were well matched prior to treatment. Outcomes included remission and nonresponse rates, as well as both independent clinical evaluations and self-reported measures of depressive symptoms.

Results: Despite limited statistical power to detect differences between treatments, depressed men treated with pharmacotherapy had significantly greater improvements on 4 of 6 continuous dependent measures and a significantly lower rate of nonresponse (i.e., 13% vs. 46%). The difference favoring pharmacotherapy was late-emerging and partially explained by crossing over nonresponders to the alternate medication. The advantage of pharmacotherapy over CBT also tended to be larger among the subgroup of patients with chronic depression.

Conclusion: Results of prior research comparing pharmacotherapy and CBT may have been influenced by the composition of study groups, particularly the gender composition, the choice of antidepressant comparators, or an interaction of these factors. Prospective studies utilizing flexible dosing of modern antidepressants and, if necessary, sequential trials of dissimilar medications are needed to confirm these findings.

(J Clin Psychiatry 2000;61:466–472)

Received Aug. 19, 1999; accepted Feb. 15, 2000. From Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Supported in part by National Institute of Mental Health grants MH-40023 (Dr. Reynolds), MH-41884, (Dr. Thase), and MH-30915 (Mental Health Clinical Research Center, Pittsburgh, Pa.).

Reprint requests to: Michael E. Thase, M.D., Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara St., Pittsburgh, PA 15213.

A number of controlled studies of depressed outpatients have found that antidepressants and cognitive-behavioral therapy (CBT) have comparable acute-phase treatment efficacy.[1–7] Not all investigators agree that these treatments are equally effective, however, and a spirited debate has developed.[8–12] Some researchers, for example, assert that pharmacotherapy was not adequately conducted in the earlier controlled trials.[8] Others point out that these studies are flawed because it is not appropriate to continue an ineffective antidepressant for 12 to 16 weeks, i.e., a time frame during which 2 trials could be conducted.[9] Importantly, all 7 controlled studies cited above were initiated before 1988 and, hence, tricyclic antidepressants (TCAs) were used as the standard comparators. To date, no published studies of major depressive disorder have compared CBT and newer generation antidepressants, which have generally replaced the TCAs as first-line medications.[13–16]

Although the TCAs and the newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) have comparable efficacy in studies of depressed outpatients, the TCAs have a greater average daily side effect burden, and pharmacotherapy is more likely to be compromised by prescription of subtherapeutic dosages.[13,15] Further, attrition from TCA therapy due to intolerable side effects is about 5% to 10% higher when compared with that from SSRI therapy.[16] The TCAs also are relatively ineffective treatments for patients with atypical or reverse neurovegetative symptoms.[17–20] Together, these factors may have significant impact on the results of comparative clinical trials. Stewart et al.,[20] for example, rean-

alyzed the results of the National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP)[4] and found that imipramine was significantly less effective than CBT among the subset of patients with atypical depression, whereas a strong trend favored imipramine over CBT among the remainder of the sample. Results of the series of comparative trials may thus have underestimated the value of pharmacotherapy *as it is currently practiced*.

Given the ongoing controversy about the relative efficacy of psychosocial and pharmacologic treatments of major depressive disorder, studies using newer generation antidepressants as comparators are sorely needed. Although several such studies are underway, the results of these trials are unlikely to be available before the year 2003. We therefore compared the outcome of 2 cohorts of depressed men who were treated in consecutive studies with either CBT or pharmacotherapy with 2 newer antidepressants, the SSRI fluoxetine and bupropion, a noradrenergically active aminoketone compound.

METHOD

Patients

Seventy-five men with DSM-III-R major depression were enrolled into the Men's Depression Study[21,22] during a 5-year period. Diagnosis was confirmed by an independent interview (Schedule for Affective Disorders and Schizophrenia [SADS][23]/Research Diagnostic Criteria [RDC][24]), and good physical health was established by a comprehensive medical evaluation. All patients had a minimum score of 14 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D)[25] after a 14-day drug- and alcohol-free "washout." Exclusion criteria included bipolar disorder, history of any psychotic mental disorder, Axis II diagnoses of severe borderline or antisocial personality disorder, unstable or life-threatening general medical disorders, active drug- or alcohol-abuse disorders, sleep apnea, and ongoing treatment with medications that may cause depression, distort polysomnographic profiles, and/or adversely affect sexual functioning (e.g., corticosteroids, antihypertensives, or anticonvulsants). All patients provided explicit written informed consent for research participation. The principal results of this study, which addressed the relationship between depression and sexual function, have been reported previously.[21,22]

During the first 30 months of enrollment, 52 patients were treated with CBT. Therapy was conducted by experienced therapists according to the manual of Beck et al.[26] During the following 18 months, 23 unduplicated patients were treated with either fluoxetine or bupropion. The shift in treatment modalities reflected our interest in studying the effects of these then-novel antidepressants on sexual function. The 2 antidepressants were chosen specifically because of their presumedly different modes of action and their dissimilar effects on sexual function.[27,28]

Post hoc comparisons of completed data sets may be biased by many factors, including changes in staff or procedures, cohort effects (i.e., changing patient characteristics over time), and rater drift. Ensuring the comparability of study groups and assessment methods is therefore an important prerequisite before contrasting outcomes. Table 1 summarizes pretreatment demographic, clinical, and selected polysomnographic characteristics of the CBT and pharmacotherapy groups. Despite performing 20 two-tailed univariate comparisons, only 1 characteristic differed between study groups at the $p < .05$ level (i.e., the exact number expected by chance). The single difference was a 3-point lower score on the Global Assessment Scale (GAS)[29] in the CBT group (out of a functional range of about 30 points), which we did not consider to be clinically significant. Although there is no substitute for randomization to parallel treatment groups, it appears that these patient groups did not differ in a meaningful way prior to treatment.

Rater drift is another potential cohort effect that could bias comparisons. The possibility of rater drift was estimated by comparing the ratio of the self-reported Beck Depression Inventory (BDI)[30] scores divided by the evaluator-rated HAM-D. Downward or upward drifts in evaluators' ratings would result in significant differences in this ratio between the 2 patient groups. As shown on Table 1, the ratio values were virtually identical in the CBT and pharmacotherapy (Rx) groups. Similarly, the correlations between HAM-D and BDI scores at pretreatment were very similar in the 2 groups (CBT: $r = 0.53$, $p = .0001$; Rx: $r = 0.51$, $p = .01$).

Treatment Conditions

The study was conducted in the Cognitive Therapy Clinic of the University of Pittsburgh Medical Center. More detailed descriptions of the CBT protocol and the quality-control procedures used to maintain treatment integrity have been presented in previous publications.[31,32] Briefly, therapy was conducted by certified therapists who received ongoing supervision. The first 16 weeks of therapy could include up to 20 individual sessions, lasting 45 to 60 minutes each. Although some patients received longer courses of therapy to try to achieve a complete remission, we analyzed the data from only the first 16 weeks to ensure comparable lengths of treatment in the 2 groups.

Pharmacotherapy was provided by a team consisting of a nurse clinical specialist and a board-certified psychiatrist (E.S.F.). Patients were randomly assigned to open-label (unblinded) therapy with either fluoxetine (N = 10) or bupropion (N = 13). Pharmacotherapy patients were seen for weekly 30-minute visits until they achieved remission, and every other week thereafter until week 16. If intolerant or not responsive to the initial study medication by week 8,

Table 1. Demographics and Pretreatment Clinical and Polysomnographic Characteristics of the Study Group[a]

Variable	CBT (N = 52)	Pharmacotherapy (N = 23)	Significance Test t or χ^2	df	p
Age, mean (SD), y	38.4 (10.5)	40.0 (11.1)	–0.59	73	.55
Education, mean (SD), y	15.6 (2.6)	15.9 (2.1)	–0.50	69	.62
Race (white/other)	50/2	21/2	0.74	1	.39
Duration of current episode, mean (SD), wk	41.7 (47.2)	40.3 (34.3)	0.13	72	.90
Recurrent (yes/no)	25/26	15/8	1.68	1	.20
RDC endogenous (yes/no)	30/21	17/6	1.56	1	.21
Chronic (yes/no)[b]	23/29	12/11	0.40	1	.53
Reverse vegetative signs (yes/no)[c]	31/21	11/12	0.90	1	.34
BDI score, mean (SD)	24.9 (9.1)	26.2 (8.6)	–0.56	73	.58
HAM-D score, mean (SD)	19.2 (3.8)	19.0 (4.0)	0.15	73	.88
BDI/HAM-D ratio, mean (SD)	1.30 (0.43)	1.39 (0.40)	–0.81	73	.42
Global Assessment Scale score, mean (SD)	53.4 (6.4)	56.8 (4.6)	–2.33	72	.02
Automatic Thoughts Questionnaire score, mean (SD)	0.32 (0.18)	0.39 (0.18)	–1.41	59	.17
Affects Balance Scale score, mean (SD)	0.33 (0.15)	0.32 (0.13)	0.10	68	.92
Dysfunctional Attitudes Scale score, mean (SD)	151.8 (27.2)	145.8 (31.5)	0.81	68	.41
Selected polysomnographic characteristics (2-night mean values)					
Sleep efficiency, mean (SD), %[d]	86.7 (8.7)	82.8 (11.3)	–1.73	73	.09
Slow wave sleep, mean (SD), %[e]	9.3 (8.2)	7.6 (7.8)	0.78	73	.44
REM latency, mean (SD), min[e]	67.5 (18.0)	73.3 (23.8)	–1.08	73	.29
REM density, mean (SD), units/min	1.53 (0.45)	1.52 (0.37)	0.17	73	.87
Normal/abnormal classification[f]	22/30	9/14	0.07	1	.80

[a]Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, HAM-D = Hamilton Rating Scale for Depression, RDC = Research Diagnostic Criteria, REM = rapid eye movement.
[b]Chronicity defined by an index episode of ≥ 2 years' duration *or* antecedent DSM-III-R dysthymic disorder.
[c]Scores of 5 or greater on the Pittsburgh Reverse Vegetative Symptom Scale.[43]
[d]Statistical test performed on log transformation (100 – SE + 1).
[e]Statistical test performed on square root transformation.
[f]See Thase et al.[31] for description of this classification, which is based on a discriminant index score derived from REM latency, sleep efficiency, and REM density.

patients could be withdrawn from that antidepressant over 1 week and crossed over to the alternate compound for a second 8-week trial. Nineteen patients received only 1 medication trial (in 4 of these cases, the patients dropped out), 3 patients were switched from bupropion to fluoxetine, and 1 patient was switched from fluoxetine to bupropion. The dosage of fluoxetine ranged from 20 mg/day to 60 mg/day (mean ± SD = 23 ± 8 mg/day), and the bupropion dosage ranged from 300 mg/day to 450 mg/day (mean ± SD = 395 ± 100 mg/day).

Assessment of Outcome

An independent clinical evaluator completed the HAM-D and GAS every other week from week 0 through week 16. Patients completed the BDI at the same time points. A full remission[33] was defined as HAM-D scores ≤ 6 for at least 2 consecutive visits *and* sustained through week 16. A stable response was defined by either a remission *or* a 50% reduction of HAM-D scores with a HAM-D score ≤ 10 sustained until week 16. Nonresponse was defined by a reduction of less than 50% of the pretreatment HAM-D score or a final HAM-D score > 10.

A secondary set of self-report measures was obtained at pretreatment and again at week 16 or endpoint. These measures, which included the Automatic Thoughts Questionnaire,[34] the Dysfunctional Attitudes Scale,[35] and the Affects Balance Scale,[36] were used to compare the impact of CBT and pharmacotherapy on cognitive symptomatology. The Automatic Thoughts Questionnaire was added to the battery about 9 months after the study began, and, as a result, data were collected for only 60 patients.

Statistical Tests

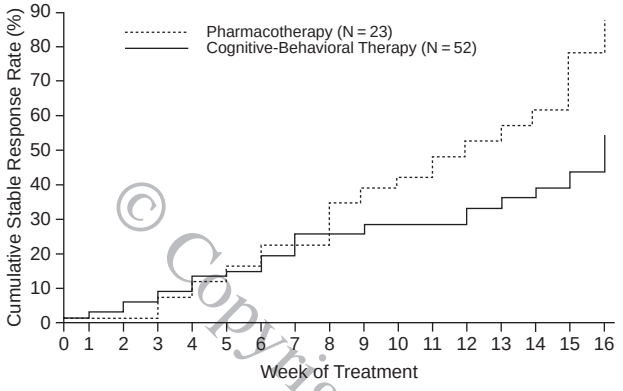
We anticipated that there would be no significant differences between treatments. The principal contrasts between the pharmacotherapy and CBT conditions were 2-tailed chi-square tests of attrition, remission, and treatment failure rates. Time to stable response was compared using survival analysis, with curves plotted by a modification of the Kaplan-Meier method[37] and tested for significance by the log-rank chi-square test.

Improvements of the continuous measures of depressive and cognitive symptoms were compared using analyses of covariance (ANCOVAs). The ANCOVAs were performed on week 16 or endpoint scores of each dependent measure. Baseline scores on these measures served as covariates. The Bonferroni corrected critical p value for each set of ANCOVAs was p = .017 (i.e., .05/3).

RESULTS

No difference was found in the length of treatment received by patients in the 2 groups (CBT mean ± SD = 15.6 ± 2.3 weeks; Rx mean ± SD = 16.5 ± 2.7 weeks; t = 1.11, df = 73, p = .27). Dropout rates were low in both groups and did not differ significantly (CBT: 5/52 [10%],

Figure 1. Life Table Analysis of Time to Stable Response Among Depressed Men Treated With Cognitive-Behavioral Therapy or Antidepressant Medications



Rx: 4/23 [17%]; $\chi^2 = 0.91$, df = 1, p = .34). The proportion of patients in the CBT and pharmacotherapy groups who remitted also did not differ significantly (20/52 [38%] vs. 12/23 [52%]; $\chi^2 = 1.23$, df = 1, p = .27). However, a significantly greater proportion of CBT-treated patients had failed to respond to treatment at week 16 (24/52 [46%] vs. 3/23 [13%]; $\chi^2 = 7.59$, df = 1, p = .006). Pharmacotherapy was also significantly more effective than CBT on the survival analysis of time to stable response (Figure 1; log-rank $\chi^2 = 8.08$, df = 1, p = .005).

On the continuous measures, the ANCOVA assumptions of homogeneity of slopes were not violated, and the covariates were retained in the analyses. Pretreatment scores (covariates) were weakly related to outcome. In each case, a more pathologic score at pretreatment was associated with poorer outcome at posttreatment. However, only pretreatment Dysfunctional Attitudes Scale scores were significantly related to posttreatment scores after Bonferroni adjustment of p values.

The effect for treatment group did not reach statistical significance on the HAM-D (p = .09), although large differences favored the pharmacotherapy condition on the GAS and BDI (Table 2). The ANCOVAs on the Automatic Thought Questionnaire and the Affects Balance Scale similarly documented better outcomes for the pharmacotherapy condition (see Table 2). The difference between treatments on the Dysfunctional Attitudes Scale did not reach statistical significance (p = .11)

As we had previously found that the men with chronic depressive syndromes were less responsive to CBT than those with more acute episodes,[38] the ANCOVAs were recomputed after stratifying for chronicity (yes vs. no). On this reanalysis, no significant main effects were found for chronicity. However, the chronicity-by-treatment interaction terms on the HAM-D (F = 5.40, df = 1,70; p = .023) and the GAS (F = 3.47, df = 1,69; p = .067) suggested differential response. As illustrated in Figure 2, these findings were accounted for by the better response of the chronically depressed men treated with pharmacotherapy. The chronicity-by-treatment interaction terms did not, however, approach significance for any of the self-report measures.

DISCUSSION

This is the first comparison of CBT and newer generation antidepressants in patients with major depression. Pharmacotherapy was significantly more effective than CBT on 4 of 6 dependent measures, and the differences on the GAS and the BDI were both large and clinically meaningful. Although remission rates did not differ significantly, the difference in nonresponse rates was clinically and statistically significant. Results of the survival analysis indicated that the advantage for pharmacotherapy emerged during the latter half of the treatment protocol.

These findings are at variance with those of earlier trials comparing CBT and the TCAs.[1–7] Among those studies, only the TDCRP found some evidence of an advantage for pharmacotherapy, and those differences were limited to a more rapid effect and a better outcome for patients with more severe depressions.[4,39,40] When comparing across studies, our findings are attributable to the relatively good outcome of the pharmacotherapy group, not the poor outcome of the CBT group. In fact, the CBT response rate in this study was within 10% of those observed in all but one of the published comparative studies.[2–5,7]

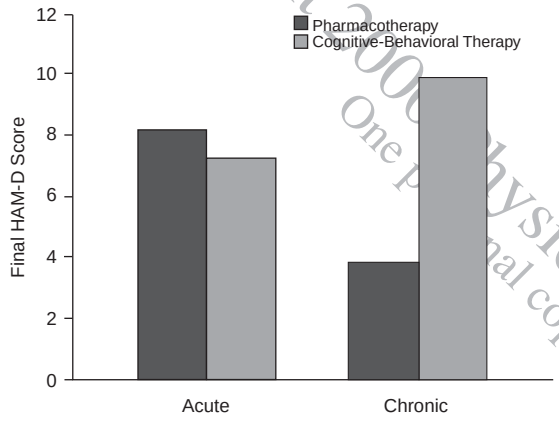
What factors could explain the more favorable outcome of the pharmacotherapy group? First, the pharmacotherapy condition in the current study was not encumbered by poor TCA response among patients with atypical depression.[20] To the contrary, both bupropion and fluoxetine appear to be effective for atypical depressive syndromes.[41,42] This is important because 56% of the patients in our study (42/75) scored 5 or more on a measure of reverse vegetative features, i.e., the "cut-point" for preferential monoamine oxidase inhibitor response.[18,43] Second, our pharmacotherapy protocol had an attrition rate of only 17%, as compared with TCA dropout rates of 28% to 42% in the 6 larger comparative studies.[1–5,7] Third, by permitting nonresponders to "cross over" from one antidepressant to the other, 2 adequate trials were possible during the 16-week treatment study. As 3 of the 4 "crossover" patients responded to the second medication, the cumulative pharmacotherapy response rate rose by 13%. If a larger proportion of our pharmacotherapy patients would have dropped out (as was the case in the TCA-controlled studies) *and* only a single antidepressant trial was permitted, an antidepressant response rate of about 50% would have been observed, i.e., virtually identical to the response rate of the CBT group.

Table 2. Analysis of Covariance (ANCOVA) on Posttreatment Depression and Cognitive Ratings[a]

	CBT (N = 52)				Pharmacotherapy (N = 23)				ANCOVAs[b]					
	Pre		Post		Pre		Post		Covariate			Treatment		
Rating	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p	F	df	p
Primary measures														
HAM-D	19.2	3.8	8.5	6.3	19.0	4.0	5.9	5.9	5.67	1,74	.02	2.87	1,74	.09
GAS	53.4	6.4	73.6	12.0	56.8	4.6	83.3	11.4	3.09	1,73	.08	7.45	1,73	.008
BDI	24.9	9.1	11.9	9.8	26.2	8.6	5.7	5.7	3.85	1,73	.05	8.36	1,73	.005
Secondary measures														
ATQ	0.32	0.18	0.58	0.25	0.40	0.19	0.79	0.20	4.52	1,59	.04	9.82	1,59	.003
ABS	0.33	0.15	0.50	0.20	0.32	0.13	0.73	0.16	3.08	1,67	.08	19.32	1,67	.0001
DAS	151.8	27.2	132.9	26.3	145.8	31.5	117.8	35.7	7.77	1,62	.01	2.69	1,62	.11

[a]Abbreviations: ABS = Affects Balance Scale, ATQ = Automatic Thoughts Questionnaire, BDI = Beck Depression Inventory, CBT = Cognitive-Behavioral Therapy, DAS = Dysfunctional Attitudes Scale, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression.
[b]Bonferroni adjusted, critical p = .017.

Figure 2. Response to Cognitive-Behavioral Therapy and Pharmacotherapy Among Men With Chronic or More Acute Depressions[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. The treatment-by–diagnostic group interaction was statistically significant (p = .023).

Was the all-male composition of our study group a contributing factor to differential treatment response? There is no evidence that depressed men respond poorly to CBT, and, in one report, depressed men with more severe symptoms responded better to CBT than more severely depressed women.[32] Also, there is no evidence that men have particularly favorable responses to fluoxetine or bupropion when compared with TCAs, although this topic has not been researched exhaustively.[44]

The use of a pharmacotherapy crossover after 8 weeks of unsuccessful treatment is consistent with good clinical practice,[14] but it is not representative of the designs used in standard comparative clinical trials. It is problematic to compare treatments with different anticipated time courses using protocols with a fixed length of time. Specifically, it is just as "unfair" to compare 16 weeks of CBT with a single antidepressant trial as it would be to limit the trial to only 6 or 8 weeks, which is presumedly suboptimal for CBT. Switching psychotherapies (i.e., from CBT to interpersonal psychotherapy) at 8 weeks of unsuccessful treatment may provide one alternative, although the utility of this strategy has not been established empirically. Within the CBT strategy, it is feasible to modify therapy to permit couples sessions, interim telephone sessions, or a greater focus on interpersonal issues to try to enhance outcomes for the patients not responding rapidly to CBT. However, none of these potentially useful interventions was permitted in our study.

Although the advantage of pharmacotherapy over CBT was apparent in the overall analyses, several post hoc analyses suggested a larger difference among patients with chronic depressive disorders, which comprised nearly 50% of the study group. This proportion of patients with chronic depression is somewhat larger than that enrolled by Elkin et al.[4] and may also help to explain differences observed across studies. The favorable outcome of the chronically depressed men treated with pharmacotherapy again illustrates that chronicity per se is not synonymous with treatment resistance. Rather, most of these chronically depressed men had never before received a single adequate treatment trial.

Several groups in addition to our own have observed an association between chronicity and poorer response to CBT.[45–48] Recently, Dunner et al.[47] found trends favoring fluoxetine over CBT in a small pilot study of dysthymic disorder. Ravindran et al.[48] similarly found that sertraline, but not group CBT, was effective in a large, placebo-controlled study of dysthymia.

Such poorer responses to CBT in chronic depression may seem paradoxical because such patients often manifest high levels of dysfunctional attitudes, a negative attributional style, a decreased sense of self-efficacy, and more passive or avoidant coping behaviors, i.e., characteristics that may be viewed as highly appropriate "targets" for cognitive and behavioral interventions.[49,50] Nevertheless, high levels of negative cognitions are among the best-replicated predictors of poorer CBT response.[50–53] It may be that dysfunctional cognitive patterns become so incorporated within the chronically depressed person's

sense of self that therapeutic efforts to directly address such "ingrained" patterns via Socratic questioning or rational rebuttal strategies are less potent than previously appreciated.[50] Of note, several groups have reported more promising results in pilot studies of dysthymic disorder using more interpersonally focused psychotherapies.[54,55]

This report has a number of methodological shortcomings that limit interpretation of the results, including the use of sequential patient cohorts (rather than randomized, parallel groups), unblinded clinical evaluators, and the lack of a placebo-control group. As noted earlier, several prospective randomized clinical trials comparing CBT and SSRIs are underway, and results from these more methodologically rigorous studies will be available in about 3 years. In the meantime, the validity of our findings is supported by several factors: the protocols were conducted by a stable research team; ongoing quality assurance measures were used to ensure the reliability of assessments and the fidelity of treatments; the sociodemographic, clinical, and neurophysiologic characteristics of the 2 patient groups were quite similar; and results were similar on self-report and evaluator-administered outcome measures. Perhaps even more importantly, the study was conducted by a research team with a well-established professional allegiance to CBT. In fact, this was our Cognitive Therapy Clinic's first research experience using antidepressant medications. Demand characteristics and potential allegiance effects, if operative, should have favored the CBT condition.[56] Unfortunately, we did not collect data on patients' treatment preferences or their satisfaction with the treatment they received, which might have revealed differences in expectations between the 2 patient groups.

In summary, a comparison of sequential cohorts of depressed men treated with either CBT or newer generation antidepressants revealed a number of statistically and clinically significant advantages in favor of pharmacotherapy. Although these provocative results surely require prospective verification, our findings suggest that sample composition, the choice of antidepressant comparator, or an interaction of these factors may have had a significant impact on the results of earlier studies comparing CBT and tricyclic antidepressants.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), sertraline (Zoloft).

REFERENCES

1. Rush AJ, Beck AT, Kovacs M, et al. Comparative efficacy of cognitive therapy and pharmacotherapy in the treatment of depressed outpatients. Cog Ther Res 1977;1:17–37
2. Blackburn IM, Bishop S, Glen AIM, et al. The efficacy of cognitive therapy in depression: a treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination. Br J Psychiatry 1981;139: 181–189
3. Murphy GE, Simons AD, Wetzel RD, et al. Cognitive therapy and pharmacotherapy, singly and together in the treatment of depression. Arch Gen Psychiatry 1984;4:33–41
4. Elkin I, Shea MT, Watkins JT, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. Arch Gen Psychiatry 1989;46:971–982
5. Hollon SD, DeRubeis RJ, Evans MD, et al. Cognitive-therapy and pharmacotherapy for depression: singly and in combination. Arch Gen Psychiatry 1992;49:774–781
6. McKnight DL, Nelson-Gray RO, Barnhill J. Dexamethasone suppression test and response to cognitive therapy and antidepressant medication. Behav Ther 1992;1:99–111
7. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in outpatients with recurrent depression. Br J Psychiatry 1997;171:328–334
8. Meterissian BG, Bradwejn J. Comparative studies on the efficacy of psychotherapy, pharmacotherapy, and their combination in depression: was adequate pharmacotherapy provided? J Clin Psychopharmacol 1989;9: 334–339
9. Klein DF. Preventing hung juries about therapy studies. J Consult Clin Psychol 1996;64:81–87
10. Jacobson NS, Hollon SD. Cognitive-behavior therapy versus pharmacotherapy: now that the jury's returned its verdict, it's time to present the rest of the evidence. J Consult Clin Psychol 1996;64:74–80
11. Kocsis JH. Practice guidelines and professional challenges: what psychotherapists need to do. Arch Gen Psychiatry 1996;53:303–304
12. Thase ME. After the fall: cognitive behavior therapy of depression in the "post-collaborative" era. Behav Ther 1994;17:48–52
13. Thase ME, Kupfer DJ. Recent developments in the pharmacotherapy of mood disorders. J Cons Clin Psychol 1996;64:1–13
14. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
15. Song F, Freemantle N, Shelton TA. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. BMJ 1993;306:683–687
16. Montgomery SA, Henry J, McDonald G, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. Int Clin Psychopharmacol 1994;9:47–53
17. Quitkin FM, Stewart JW, McGrath PJ, et al. Columbia atypical depression: a subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. Br J Psychiatry 1993;163:30–34
18. Thase ME, Carpenter L, Kupfer DJ, et al. Clinical significance of reversed vegetative subtypes of current major depression. Psychopharmacol Bull 1991;27:17–22
19. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995;12:185–219
20. Stewart JW, Garfinkel R, Nunes EV, et al. Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Clin Psychopharmacol 1998;18: 429–434
21. Nofzinger EA, Thase ME, Reynolds CF III, et al. Sexual function in depressed men: assessment by self-report, behavioral, and nocturnal penile tumescence measures before and after treatment with cognitive behavior therapy. Arch Gen Psychiatry 1993;50:24–30
22. Nofzinger EA, Reynolds CF III, Thase ME, et al. REM sleep enhancement by bupropion in depressed men. Am J Psychiatry 1995;152:274–276
23. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for the Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1979;35:837–844
24. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 1978;35:773–782
25. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
26. Beck AT, Rush AJ, Shaw FB, et al. Cognitive Therapy of Depression: A Treatment Manual. New York, NY: Guilford Press; 1979
27. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 1995;56(suppl 6):12–21
28. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993;54:459–465
29. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
30. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring

depression. Arch Gen Psychiatry 1961;4:561–571
31. Thase ME, Simons AD, Reynolds CF III. Abnormal electroencephalographic sleep profiles in major depression: association with response to cognitive behavior therapy. Arch Gen Psychiatry 1996;53:99–108
32. Thase ME, Reynolds CF III, Frank E, et al. Do depressed men and women respond similarly to cognitive behavior therapy? Am J Psychiatry 1994; 151:500–505
33. Frank E, Prien RF, Jarrett DB, et al. Conceptualization and rationale to consensus definitions of terms in major depressive disorder: response, remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48: 851–855
34. Hollon SD, Kendall PC. Cognitive self-statements in depression: development of an Automatic Thoughts Questionnaire. Cog Ther Res 1980;4: 383–395
35. Weisman A, Beck AT. Development and validation of the Dysfunctional Attitudes Scale. Presented at the annual meeting of the Association for the Advancement of Behavior Therapy; 1978; Chicago, Ill
36. Derogatis LR. Affects Balance Scale. Baltimore, Md: Clinical Psychometric Research; 1975
37. Cox DR, Oakes D. Analysis of Survival Data. London, England: Chapman and Hall; 1984
38. Thase ME, Reynolds CF III, Frank E, et al. Response to cognitive-behavioral therapy in chronic depression. J Psychother Pract Res 1994;3: 204–214
39. Klein DF, Ross DC. Reanalysis of the National Institute of Mental Health Treatment of Depression Collaborative Research Program general effectiveness report. Neuropsychopharmacology 1993;8:241–251
40. Elkin I, Gibbons RD, Shea MT, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1995; 63:841–847
41. Reimherr FW, Woods DR, Byerley B, et al. Characteristics of responders to fluoxetine. Psychopharmacol Bull 1984;20:70–72
42. Goodnick PJ, Extein IL. Bupropion and fluoxetine in depressive subtypes. Ann Clin Psychiatry 1989;1:119–122
43. Thase ME, Frank E, Mallinger AG, et al. Treatment of imipramine-resistant recurrent depression, III: efficacy of monoamine oxidase inhibitors. J Clin Psychiatry 1992;53:5–11
44. Thase ME, Frank E, Kornstein S, et al. Gender differences in response to treatments of depression. In: Frank E, ed. Gender and Its Effects on Psychopathology. Washington, DC: American Psychiatric Press; 2000: 103–129
45. Hoberman HM, Lewinsohn PM, Tilson M. Group treatment of depression: individual predictors of outcome. J Consult Clin Psychol 1988;56: 393–398
46. Sotsky SM, Glass DR, Shea MT, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry 1991;53: 283–290
47. Dunner DL, Schmaling KB, Hendrickson H, et al. Cognitive therapy versus fluoxetine in the treatment of dysthymic disorder. Depression 1996;4: 34–41
48. Ravindran AV, Anisman H, Merali Z, et al. Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments. Am J Psychiatry 1999;156:1608–1617
49. Scott J. Chronic depression: can cognitive therapy succeed when other treatments fail? Behav Psychother 1992;20:25–36
50. Thase ME, Howland R. Refractory depression: relevance of psychosocial factors and therapies. Psychiatr Ann 1994;24:232–240
51. Keller KE. Dysfunctional attitudes and the cognitive therapy for depression. Cog Ther Res 1983;7:437–444
52. Stewart JW, Mercier MA, Quitkin FM, et al. Demoralization predicts nonresponse to cognitive therapy in depressed outpatients. J Cog Psychother 1993;7:105–116
53. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. Am J Psychiatry 1992;149:1046–1052
54. Mason BJ, Markowitz JC, Klerman GL. Interpersonal psychotherapy for dysthymic disorders. In: Klerman GL, Weissman MM, eds. New Applications of Interpersonal Psychotherapy. Washington, DC: American Psychiatric Press; 1993:225–264
55. McCullough JP. Psychotherapy for dysthymia: a naturalistic study of ten patients. J Nerv Ment Dis 1991;179:734–740
56. Luborsky L, Diguer L, Seligman DA, et al. The researcher's own therapy allegiances: a "wild card" in comparisons of treatment efficacy. Clin Psychol: Sci Pract 1999;6:95–106