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Prevention of Recurrence After Recovery From a Major Depressive Episode With Antidepressant Medication Alone or in Combination With Cognitive Behavioral Therapy
Phase 2 of a 2-Phase Randomized Clinical Trial

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IMPORTANCE Antidepressant medication (ADM) maintenance treatment is associated with the prevention of depressive recurrence in patients with major depressive disorder (MDD), but whether cognitive behavioral therapy (CBT) treatment is associated with recurrence prevention remains unclear.

OBJECTIVE To determine the effects of combining CBT with ADM on the prevention of depressive recurrence when ADMs are withdrawn or maintained after recovery in patients with MDD.

DESIGN, SETTING, AND PARTICIPANTS A total of 292 adult outpatients with chronic or recurrent MDD who participated in the second phase of a 2-phase trial. Participants had recovered in the first phase of the trial receiving ADM, either alone or in combination with CBT. The trial was conducted in research clinics in 3 university medical centers in the United States. Patients in phase 2 were randomized to receive maintenance of or withdrawal from ADM and were followed up for 3 years. The first and last patients entered phase 2 in August 2003 and October 2009, respectively. The last patient completed phase 2 in August 2012. Data were analyzed from December 2013 to December 2018.

INTERVENTIONS Maintenance of or withdrawal from treatment with ADM.

MAIN OUTCOMES AND MEASURES Recurrence of an MDD episode using longitudinal interval follow-up evaluations; sustained recovery across both phases.

RESULTS A total of 292 participants (171 women, 121 men; mean [SD] age 45.1 [12.9] years) were included in analyses of depressive recurrence. Maintenance ADM yielded lower rates of recurrence compared with ADM withdrawal regardless of whether patients had achieved recovery in phase 1 with ADM alone (48.5% vs 74.8%; $z = -3.16$; $P = .002$; number needed to treat [NNT], 2.8; 95% CI, 1.8-7.0) or ADM plus CBT (48.5% vs 76.7%; $z = -3.49$; $P < .001$; NNT, 2.7; 95% CI, 1.9-5.9). Sustained recovery rates differed as a function of phase 2 condition, with maintenance ADM superior to ADM withdrawal ($z = 2.90$; $P = .004$; OR, 2.54; 95% CI, 1.37-4.84; NNT, 2.3; 95% CI, 1.5-6.4). Phase 1 condition was not associated with differential rates of sustained recovery (ADM alone vs ADM plus CBT; $z = 0.22$; $P = .83$; OR, 1.08; 95% CI, 0.52-2.11; NNT, 26.0; 95% CI, number needed to harm 3.2 to NNT 2.8), nor was there a significant interaction of phase 1 condition and phase 2 condition ($z = 0.30$; $P = .77$; OR, 1.14; 95% CI, 0.49-2.88).

CONCLUSIONS AND RELEVANCE Maintenance ADM treatment, but not previous exposure to CBT, was associated with reduced rates of depressive recurrence. In previous studies, when CBT has been provided without ADM, CBT has shown a preventive effect on depressive relapse. Whether CBT also has a preventive effect on depressive recurrence, or if adding ADM interferes with any such preventive effect, remains unclear.

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Research has indicated that antidepressant medications and cognitive behavioral therapy (CBT) have similar efficacies on acute outcomes (response or remission) in the treatment of patients with major depressive disorder (MDD),[1] and the combination of treatment with antidepressant medications and CBT is associated with better acute outcomes than either treatment modality alone.[2-4] A substantial proportion of patients with MDD experience a chronic or recurring course; thus, a crucial feature of a treatment modality or a combination of modalities is the ability to protect patients from relapse or recurrence. Acute treatment with antidepressant medications has not been associated with the prevention of recurrence or relapse, but continuing or maintaining antidepressant medication regimens for patients has been associated with forestalling symptom return.[5,6] Cognitive behavioral therapy, when delivered alone, appears to be associated with relapse prevention[7] (ie, the return of symptoms associated with a treated episode), but less is known about the association between CBT treatment and recurrence prevention (ie, the onset of wholly new episodes), whether CBT treatment is provided alone or as part of combination therapy.

This article describes the long-term outcomes of a 2-phase study of treatments for patients with MDD. In phase 1, patients were randomized to treatment with antidepressant medication monotherapy or a combination therapy of antidepressant medication plus CBT, and treatment with the combination therapy was associated with a higher rate of recovery.[8] Phase 2 comprised a 3-year follow-up of patients who had achieved recovery in phase 1. Patients who achieved recovery with monotherapy treatment were randomized to receive either maintenance or withdrawal of treatment with antidepressant medications, as were patients who achieved recovery with combination therapy treatment. Our primary analyses compared rates of recurrence as a function of phase 2 assignment (medication maintained vs medication withdrawn) in 2 patient samples, one in which recovery was achieved with monotherapy treatment (monotherapy maintained vs monotherapy withdrawn) and the other in which recovery was achieved with combination therapy treatment (combination therapy maintained vs combination therapy withdrawn).

The recurrence rates in the combination of phase 1 and phase 2 treatment conditions could be compared with each other, but valid causal inferences regarding the prevention of recurrence achieved by combination therapy treatment compared with monotherapy treatment could not be drawn from these comparisons. This study was unable to establish causal inferences because the populations in the monotherapy and combination therapy groups differed, as was evident from the differential recovery rates observed in phase 1.[8] However, a sustained recovery system of measurement,[9,10] which combines outcomes across the 2 phases, could be applied and compared across the 4 combinations of treatment conditions (monotherapy maintained, monotherapy withdrawn, combination therapy maintained, and combination therapy withdrawn). Such a measure reflects the ability of a treatment regimen to get patients well and keep them well.

Key Points

Question What are the effects of combining cognitive behavioral therapy with antidepressant medications on the prevention of depressive recurrence when antidepressant medications are withdrawn or maintained after recovery in patients with major depressive disorder?

Findings In this phase 2 randomized clinical trial of 292 adult patients with major depressive disorder who recovered from a chronic or recurrent major depressive episode, withdrawal of antidepressant medication treatment was associated with higher rates of recurrence compared with maintenance of antidepressant medication treatment regardless of whether patients achieved recovery with or without acute cognitive behavioral therapy treatment.

Meaning Maintenance of antidepressant medication treatment was associated with a reduced risk of depressive recurrence, but previous treatment with cognitive behavioral therapy was not; whether cognitive behavioral therapy has a similar protective effect or whether adding antidepressant medications to cognitive behavioral therapy treatment interferes with any such protective effect remains unclear.

Methods

Patients

For the primary analyses of phase 2 data, the sample comprised a subset of patients diagnosed with either chronic (episode duration ≥2 years) or recurrent (an episode in the past 3 years even if only a second episode) MDD using the *DSM-IV*; these patients were previously randomized in phase 1 of the clinical trial, which compared patients who received monotherapy treatment (n = 225) with patients who received combination therapy treatment (n = 227).[8] Other inclusion and exclusion criteria were described in the phase 1 report.[8] The characteristics of patients who participated in phase 2 are reported in **Table 1.** Data were analyzed from December 2013 to December 2018.

The study was conducted at outpatient research clinics at the University of Pennsylvania in Philadelphia, Rush Medical Center in Chicago, Illinois, and Vanderbilt University in Nashville, Tennessee. The clinical trial protocol is available in Supplement 1. The institutional review boards at the respective institutions approved the clinical trial protocol, and the study implementation was monitored by an independent data safety monitoring board. Written informed consent was received before any research activity began and was again obtained at the second randomization. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Procedures

Figure 1 depicts the study design and patient flow. The procedures used in phase 1 of the clinical trial were described in a previous article.[8] A total of 318 of 452 participants (70%) from phase 1 were eligible to participate in phase 2 because they met the criteria for recovery before the maximum allowable time

Table 1. Baseline Characteristics of Phase 2 Participants

Variable	Patients, No. (%)							
		Site			Acute			
					Combination Therapy		Monotherapy	
	Total (N = 292)	Penn (n = 92)	Vand (n = 97)	Rush (n = 103)	Maintained (n = 85)	Withdrawn (n = 70)	Maintained (n = 68)	Withdrawn (n = 69)
HRSD score, mean (SD)[a]	5.6 (4.1)	4.6 (3.8)	5.7 (3.6)	6.6 (4.3)	5.8 (4.0)	5.4 (3.9)	5.4 (4.0)	6.0 (4.4)
Male[b]	121 (41)	52 (57)	38 (39)	31 (30)	37 (44)	29 (41)	29 (43)	26 (38)
Age, mean (SD), y[b]	45.1 (12.9)	47.5 (14.2)	45.9 (11.8)	42.0 (12.2)	45.6 (13.0)	43.9 (11.8)	45.3 (12.6)	45.6 (14.3)
White race[b]	256 (88)	81 (88)	91 (94)	84 (82)	72 (85)	60 (86)	63 (93)	61 (90)
Hispanic ethnicity[b]	16 (5)	4 (4)	3 (3)	9 (9)	7 (8)	5 (7)	1 (1)	3 (4)
College graduate[b]	176 (60)	64 (70)	51 (53)	61 (59)	53 (62)	48 (69)	38 (56)	37 (54)
Income <$40 000/y[b]	168 (58)	49 (53)	63 (65)	56 (54)	54 (64)	42 (60)	35 (51)	37 (54)
Married or cohabitating[b]	113 (39)	32 (55)	39 (40)	42 (41)	32 (38)	27 (39)	27 (40)	27 (40)
MDD[b]								
Chronic	109 (37)	34 (37)	57 (59)	18 (17)	30 (35)	22 (31)	34 (50)	23 (34)
Recurrent	249 (85)	77 (84)	85 (88)	87 (84)	71 (84)	62 (89)	56 (82)	60 (88)
Age at onset, mean (SD), y[b]	24.6 (13.4)	23.3 (14.5)	24.5 (13.7)	26.1 (11.8)	23.8 (12.9)	27.2 (14.4)	23.9 (11.4)	23.8 (14.6)
Previous episodes, No., mean (SD)[b]	8.8 (19.3)	8.1 (14.2)	3.9 (7.4)	14.5 (28.7)	9.2 (20.0)	4.8 (5.2)	11.8 (26.1)	9.1 (19.5)
Melancholic[b]	114 (39)	23 (25)	47 (48)	44 (43)	34 (40)	27 (39)	21 (31)	32 (47)
Atypical[b]	63 (22)	18 (20)	27 (28)	18 (17)	16 (19)	18 (26)	13 (19)	16 (24)
Comorbid disorder[c]								
Axis I	131 (45)	29 (32)	51 (53)	51 (50)	40 (47)	28 (40)	33 (49)	30 (44)
Axis II[b]	137 (47)	25 (27)	55 (57)	57 (55)	37 (44)	36 (51)	32 (47)	32 (47)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; MDD, major depressive disorder; Penn, University of Pennsylvania; Rush, Rush University; Vand, Vanderbilt University.

[a] Measured at time of reassignment to phase 2 treatment condition.

[b] Measured at intake before assignment to phase 1 treatment condition.

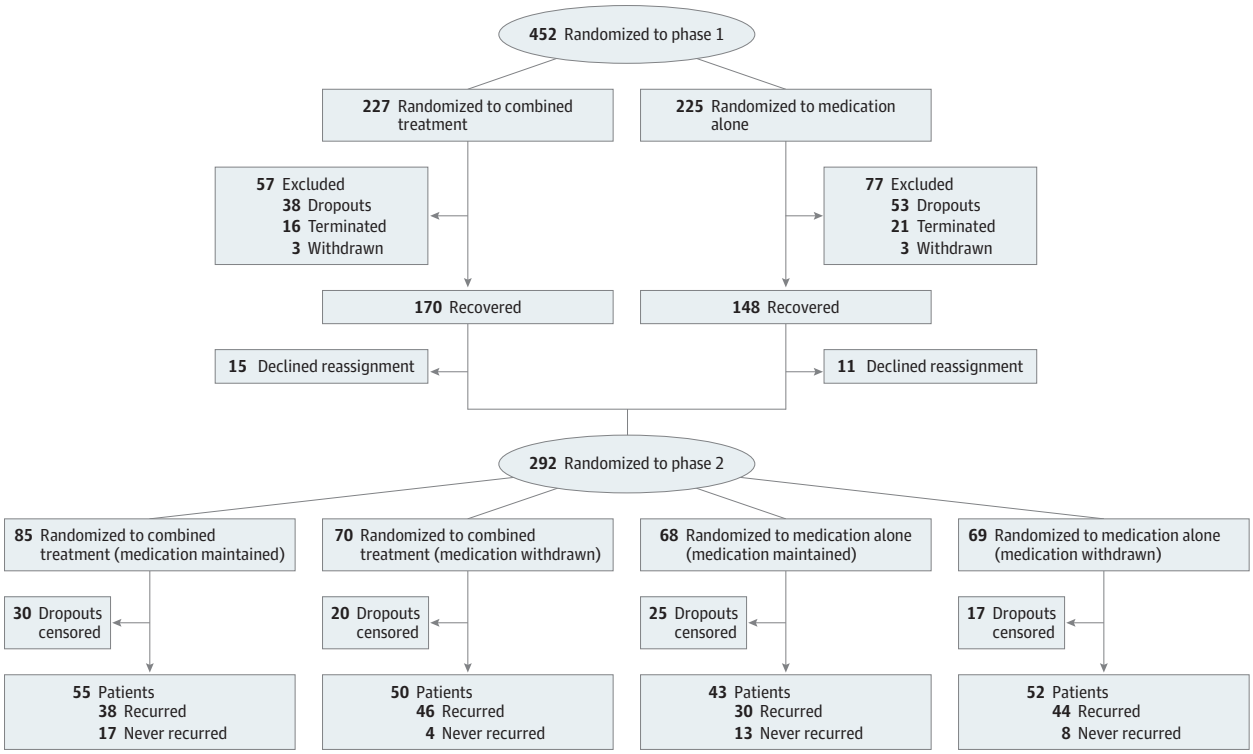
[c] Identified using the *DSM-IV*.

(3.5 years). Of those, 292 patients provided consent to be randomized to either maintain treatment with antidepressant medications or to be slowly withdrawn from medications. Of the 170 patients who met recovery criteria in the combination therapy group, 155 (91%) provided consent to participate in phase 2; 85 patients were assigned to the maintenance group (combination therapy maintained) and 70 to the withdrawal group (combination therapy withdrawn). Of the 148 patients who met recovery criteria in the monotherapy group, 137 (93%) consented to participate in phase 2; 68 patients were assigned to the maintenance group (monotherapy maintained) and 69 to the withdrawal group (monotherapy withdrawn). Thus, 160 patients (72 in combination therapy and 88 in monotherapy) who were assigned to phase 1 treatment conditions did not receive assignments to phase 2 treatment conditions because they either did not achieve recovery or achieved recovery but did not consent to phase 2 assignment.

Random assignment to treatment was implemented using an adaptive (urn) randomization procedure, which can accommodate a larger number of factors than stratified randomization.[11] The factors included in the adaptive randomization algorithm for phase 2 assignment were current medication (serotonin norepinephrine reuptake inhibitor vs selective serotonin reuptake inhibitor), sex (male vs female), number of episodes (≤2 vs ≥3), personality disorder (absent vs present), and recovery status (complete vs partial). After the last patient was randomized, the balance of each structure was assessed across intervention assignment, indicating balance was achieved for each. The project coordinator at each site was able to access a patient's assignment only after the patient met recovery criteria and provided informed consent. Intake for phase 1 occurred from September 13, 2002, through February 22, 2006. The first patient entered phase 2 on August 13, 2003, and the last patient entered phase 2 on October 19, 2009. The last patient completed phase 2 on August 19, 2012. Data were analyzed from December 2013 to December 2018.

Patients who had received combination therapy treatment during phase 1 ended their course of CBT treatment when phase 2 began. The mean (SD) number of CBT sessions received by patients in the combination therapy group during phase 1 was 33.3 (22.8). The mean (SD) length of time patients received combination therapy or monotherapy treatment before reassignment to phase 2 was 80.3 (40.0) weeks. Patients assigned to receive medication maintenance (monotherapy maintained or combination therapy maintained) met with their pharmacotherapist every 12 weeks; adjustment or augmentation of the medication regimen was permitted. A detailed account of the medications used will be reported separately. Patients assigned to medication withdrawal (monotherapy withdrawn or combination therapy withdrawn) were tapered from their regimen over a 4-week period, or longer if clinically indicated. Because medication withdrawal was not ac-

Figure 1. CONSORT Diagram



companied by the use of placebo, phase 1 assignments were not blinded for patients or pharmacotherapists.

Outcome Assessment

Interviewers who were blinded to the patients' treatment conditions assessed patient status using the Longitudinal Interval Follow-up Evaluation (LIFE) every 4 weeks for the first 12 weeks of phase 2 and every 12 weeks thereafter. The LIFE tool provides weekly retrospective assessments of each patient's psychiatric status rating on a scale of 1 to 6, with scores of 5 or 6 indicating the patient met the *DSM-IV* symptom criteria for MDD that week. Recurrence was defined as LIFE ratings of 5 or 6 for 2 consecutive weeks at any time after the first 8 weeks of phase 2. To ensure we did not misconstrue the symptoms of medication discontinuation as a recurrence, 3 consecutive weeks with a LIFE rating of 5 or 6 were required for a classification of recurrence during the first 8 weeks. The LIFE interviews were conducted until a patient withdrew from the study, experienced a documented recurrence, or completed 3 years without recurrence. Serious adverse events were reported to the respective institutional review boards and the data safety monitoring board as they occurred.

Statistical Analyses

Recurrence

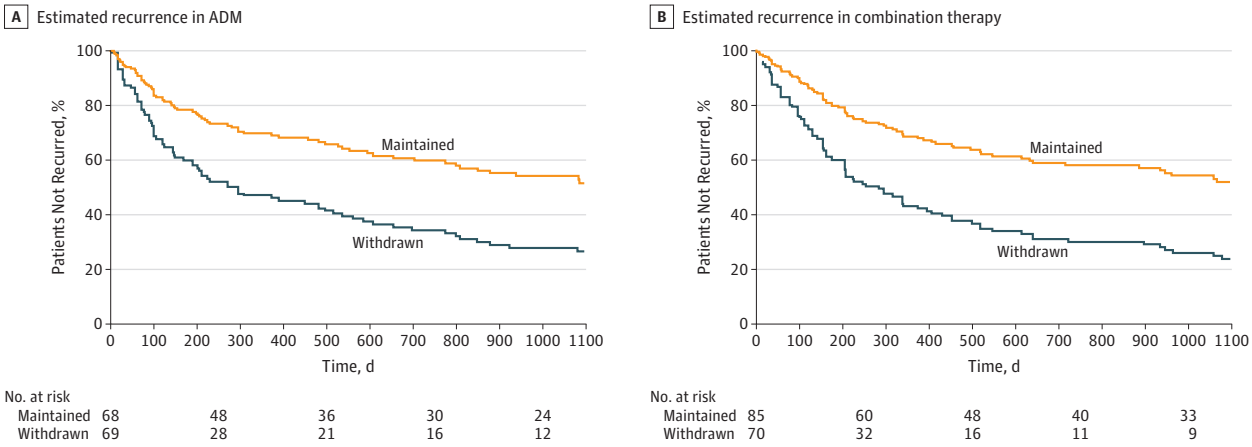
The fact that only patients who met recovery criteria in phase 1 were eligible to participate in phase 2 created the possibility that the proportions of patients entering phase 2 would differ between the combination therapy and monotherapy treatment conditions, which they did (75.2% of the combination therapy group vs 65.6% of the monotherapy group entered phase 2).[8] Even if the proportions had not differed, the phase 1 treatment conditions could have acted as a differential sieve that reflected differential risk if the 2 samples entering phase 2 differed on characteristics that are associated with recurrence risk.[12]

Therefore, analyses of recurrence rate as a function of phase 2 assignment (maintained vs withdrawn) were conducted separately for the monotherapy maintained vs monotherapy withdrawn groups and for the combination therapy maintained vs combination therapy withdrawn groups. Cox proportional hazards regression models were used to test for differences in recurrence rates and to provide estimates of the likelihood of recurrence over the 3-year follow-up. The main effects of the phase 2 treatment condition, site, and condition-by-site interaction were modeled, with the interaction term retained in the final models only when significant. Estimates of recurrence were calculated using the averages-of-survival-curves approach.[13] To characterize the clinical significance of the findings, we computed the number needed to treat. All statistical analyses were performed with R software, version 3.3.3 (GNU Project) using the survival package.[14]

Sustained Recovery

Because both recovery and recurrence are important for long-term outcomes, we calculated estimates of sustained recovery for the monotherapy maintained, monotherapy withdrawn, combination therapy maintained, and combination

Figure 2. Estimated Recurrence Following Phase 1 Conditions: ADM Monotherapy or Combination Therapy



The x-axis represents time, in days, from random assignment to be maintained on or withdrawn from medications. The y-axis represents the estimated recurrence rates across the 3-year maintenance period. ADM, antidepressant medication.

therapy withdrawn groups by prorating the estimates of nonrecurrence by the respective rates of recovery in phase 1. A patient was considered to have experienced sustained recovery if he or she recovered in phase 1 and completed phase 2 (3 years of follow-up) without a recurrence.

To account for all 452 patients initially assigned to treatment in phase 1 and to include them in the sustained recovery analysis, we needed to include the 160 patients who did not receive a phase 2 assignment. We estimated sustained recovery rates in each of the 4 treatment condition combinations as if these patients, within each phase 1 treatment condition, were assigned equally to the phase 2 treatment conditions. Because none of these patients provided data during phase 2, the assignment of specific patients to the phase 2 treatment conditions was not a factor in the sustained recovery estimates. Patients who did not recover were represented only in the respective denominators, whereas those who recovered but were not assigned to a phase 2 treatment condition were prorated with respect to sustained recovery estimates.

Estimates of the number of patients who achieved sustained recovery in each of the phase 1 and phase 2 treatment combinations were calculated for the initially randomized 452 patients by rounding the product of the sustained recovery rate and the total overall assignment to each treatment condition (actual assignments plus imputed assignments). The use of these values, in which sustained recovery for each observation was either a 0 or a 1, allowed for estimates of the main effects of phase 1 assignment, phase 2 assignment, and their interaction using logistic regression analysis.

To detect an advantage of 20% in sustained recovery in the combination therapy vs monotherapy group comparison (relative to a 25% rate), we had approximately 0.99 power using a 2-tailed analysis with a significance of $\alpha = .05$. The smallest advantage that could be detected (relative to a 25% rate) with a power of 0.80 was 12.2%. For the comparison of greatest interest (combination therapy withdrawn vs monotherapy withdrawn), the power to detect a 20% advantage (relative to a 15% rate) was 0.94. The smallest advantage that could be detected (relative to a 15% rate) with a power of 0.80 was 15.5%.

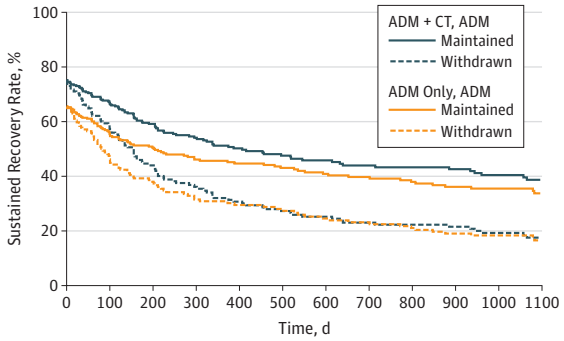
In phase 1 of the clinical trial, the higher recovery rate observed in the combination therapy compared with the monotherapy group was moderated by chronicity; patients with nonchronic MDD had a higher rate of recovery with combination therapy treatment vs monotherapy treatment (80.1% vs 61.9%, respectively), but this higher rate was not observed in patients with chronic MDD (72.1% vs 66.3%, respectively). Further, the advantage of combination therapy compared with monotherapy treatment within the nonchronic group was moderated by severity such that the patients with severe nonchronic MDD experienced an even greater benefit from receiving combination therapy compared with monotherapy treatment. We therefore conducted exploratory analyses to test whether severity and chronicity also moderated sustained recovery.

Results

Recurrence

The outcomes of 292 adult outpatients (171 women and 121 men; mean [SD] age, 45.1 [12.9] years) were included in the analyses of depressive recurrence. Among patients who had achieved recovery in the monotherapy group (n = 137), recurrence rates were lower in those randomized to the monotherapy maintained compared with the monotherapy withdrawn group (48.5% vs 74.8%, respectively; $z = -3.16$; $P = .002$; hazard ratio [HR], 0.47; 95% CI, 0.29-0.75; number needed to treat [NNT], 2.8; 95% CI, 1.8-7.0). Among patients who had achieved recovery in the combination therapy group (n = 155), recurrence rates were similar, with lower rates in the combination therapy maintained compared with the combination therapy withdrawn group (48.5% vs 76.7%, respectively; $z = -3.49$; $P < .001$; HR, 0.46; 95% CI, 0.30-0.71; NNT, 2.7; 95% CI, 1.9-5.9).

Figure 3. Estimated Sustained Recovery as a Function of Phase 1 and Phase 2 Condition



The x-axis represents time, in days, from random assignment to be maintained on or withdrawn from medications. The y-axis represents the estimated sustained recovery rates across the 3-year maintenance period. The beginning points for the CT and ADM conditions from phase 1 reflect the percentage of patients with these conditions who met recovery criteria during phase 1. Sustained recovery was estimated as a function of phase 1 and phase 2 treatment conditions. ADM + CT, combination antidepressant medication and cognitive behavior therapy during phase 1; ADM Only, antidepressant medication alone during phase 1.

Figure 2 shows the 2 pairs of survival curves corresponding to these analyses. Condition-by-site interactions were not observed in either model, so only the main effect of site was included as a covariate.

Sustained Recovery

Sustained recovery curves (**Figure 3**) were produced by prorating the values in the survival curves of the monotherapy maintained, monotherapy withdrawn, combination therapy maintained, and combination therapy withdrawn groups by recovery rates in the respective phase 1 treatment conditions (monotherapy or combination therapy). Note that the curves start at the level determined by the respective recovery rates at the end of phase 1. Estimates of sustained recovery at the end of phase 2 are shown in **Table 2** along with the values used to calculate the estimates.

The outcomes of 266 women and 186 men (mean [SD] age, 43.2 [13.1] years) were included in the analyses of sustained recovery, which considered the differential rates of recovery observed in phase 1. After inclusion of all patients assigned to phase 1 treatment conditions, the main effect of the phase 2 treatment condition (maintained vs withdrawn) on sustained recovery was significant (z = 2.90; P = .004; odds ratio [OR], 2.54; 95% CI, 1.37-4.84; NNT, 2.3; 95% CI, 1.5-6.4), which echoed the advantage of medication maintained compared with medication withdrawn in each of the analyses of recurrence rates. The main effect of the phase 1 treatment condition (monotherapy vs combination therapy) was not significant (z = 0.22; P = .83; OR, 1.08; 95% CI, 0.52-2.11; NNT, 26.0; 95% CI, number needed to harm 3.2[15] to NNT 2.8), nor was the interaction between the phase 1 and phase 2 treatment conditions (z = 0.30; P = .77; OR, 1.14; 95% CI, 0.49-2.88).

In the nonchronic subgroup, sustained recovery differed as a function of the phase 2 treatment condition, with medication maintained indicating better results than medication withdrawn (z = 3.00; P = .003; OR, 3.49; 95% CI, 1.58-8.15; NNT, 1.8). Neither the phase 1 treatment condition (combination therapy vs monotherapy; z = 0.75; P = .45; OR, 1.40; 95% CI, 0.58-3.44; NNT, 6.0) nor the interaction of the phase 1 and phase 2 treatment conditions was significant (z = 0.27; P = .79; OR, 0.85; 95% CI, 0.29-2.62). In the severe nonchronic subgroup, sustained recovery differed as a function of the phase 2 treatment condition (z = 2.03; P = .04; OR, 3.18; 95% CI, 1.07-10.31; NNT, 1.9). Neither the effects of the phase 1 treatment condition (combination therapy vs monotherapy; z = 0.41; P = .68; OR, 1.30; 95% CI, 0.37-4.58; NNT, 7.7) nor the interaction of the phase 1 and phase 2 treatment conditions (z = 0.09; P = .91; OR, 1.09; 95% CI, 0.23-5.28) was significant.

No statistically significant differences were observed in the number of serious adverse events across the 4 treatment conditions (17 events for monotherapy maintained, 20 for monotherapy withdrawn, 19 for combination therapy maintained, and 16 for combination therapy withdrawn; F_{3288} = 0.605; P = .61).

Discussion

Among patients with chronic or recurrent MDD who achieved recovery with antidepressant medication treatment or a combination of CBT and medication treatments, recurrence rates were substantially lower in patients who were maintained on medication treatment compared with those who were withdrawn from medication treatment. This finding is in line with a large body of previous evidence.[5,6] Further, the difference was observed regardless of whether recovery was achieved with antidepressant monotherapy or combination therapy treatment. No evidence was found that the provision of CBT during acute/continuation treatment provided protection against subsequent recurrence. An analysis of sustained recovery rates, which integrated outcomes from both the acute/continuation and maintenance phases of the study, also did not reveal that a significant advantage was provided by the addition of CBT treatment in the acute/continuation phase. If anything, the initial advantage of the combination therapy treatment that was observed in phase 1 appeared to decrease during the phase 2 follow-up period. Even in the subgroup of patients with severe nonchronic MDD, who were observed to have benefitted from the addition of CBT treatment in phase 1, the added value of CBT treatment did not appear to be sustained across the 3-year follow-up period.

The fact that we did not detect an association between CBT treatment and recurrence prevention in this study might appear to be at odds with data from 2 previous clinical trials in which patients who received previous CBT treatment experienced enduring recurrence prevention compared with recovered patients who were withdrawn from monotherapy treatment.[9,16] Neither of these clinical trials, however, combined treatment with CBT and medication therapies during the acute or continuation phases. When CBT treatment has been delivered in the context of combination therapy, findings

Table 2. Recurrence, Survival, and Sustained Recovery Rates in Phase 2 Treatment Conditions[a]

Treatment Condition	Phase 2 (N = 292)		
	Recurrence Rate, %[b]	Survival Rate, %[c]	Sustained Recovery Rate, % (95% CI)[d]
Monotherapy			
Monotherapy maintained (n = 68)	48.5	51.5	33.8 (25.1-42.5)
Monotherapy withdrawn (n = 69)	74.8	25.2	16.6 (9.7-23.5)
Combination therapy			
Combination therapy maintained (n = 85)	48.5	51.5	38.7 (29.7-47.7)
Combination therapy withdrawn (n = 70)	76.7	23.3	17.6 (10.6-24.6)

[a] Patients who met recovery criteria in phase 1 were eligible to participate in phase 2. Of the 452 patients eligible for phase 2, 155 of 227 (75.2%) from the combination therapy group and 137 of 225 (65.6%) from the monotherapy group provided consent to enter phase 2.[8]

[b] Recurrence rates were estimated using Cox proportional hazards regression models. Estimates were calculated from survival analyses; therefore, numerator values were not available.

[c] Survival rates reflect 1 recurrence. Estimates were calculated from survival analyses; therefore, numerator values were not available.

[d] Estimates of sustained recovery for the monotherapy maintained, monotherapy withdrawn, combination therapy maintained, and combination therapy withdrawn groups were calculated by prorating the estimates of nonrecurrence by the respective rates of recovery in phase 1.

regarding the prevention of relapse or recurrence have been mixed. One clinical trial reported an enduring effect of previous CBT treatment,[17] a second was inconclusive,[18] and a third found no enduring effect.[19] Although the failure to find an effect in this study does not preclude the possibility that an effect could be found in future clinical trials, the addition of the present findings does cast further doubt on the ability of acute CBT treatment to produce an enduring effect when delivered in the context of combination therapy.

A similar pattern has been observed in the treatment of patients with anxiety such that the combination of certain anxiolytic medications with CBT during the acute treatment phase attenuates the long-term positive effects of CBT treatment.[20,21] In a study by Barlow et al,[22] patients with panic disorder who achieved remission with imipramine treatment were twice as likely to relapse after treatment termination than patients who achieved remission with CBT treatment; patients who achieved remission with a combination of CBT and imipramine treatments had the same elevated risk of relapse as those who received imipramine treatment alone, whereas patients who achieved remission with CBT treatment and placebo were no more likely to relapse after treatment termination than patients who achieved remission with CBT treatment alone. In effect, the receipt of antidepressant medication interfered with the enduring effect of CBT treatment, whereas simply believing that one was receiving a medication did not. In the current study, we did not include a CBT-alone or a CBT-plus-placebo treatment condition. Had we done so, we would have been able to address directly the question of whether adding monotherapy treatment interferes with any enduring effect that CBT treatment may have with respect to recurrence and, if so, whether this enduring effect is due to psychological or pharmacological reasons. In the Barlow et al[22] clinical trial, the enduring effect was clearly for pharmacological reasons.

Other researchers have found recurrence-prevention benefits of psychotherapy that is received after initial recovery with antidepressant monotherapy treatment.[23-25] However, those studies differed from the present study in the following ways: (1) the psychotherapy provided was focused on the prevention of future depressive relapse or recurrence, (2) the psychotherapy was provided after initial confirmed recovery with acute antidepressant medication treatment, and (3) the patients were all discontinued from antidepressant medication treatment after recovery. Thus, with the exception of a normal tapering window, patients did not receive a combination therapy regimen of antidepressant medication and psychotherapy treatments over an extended period.

Limitations

Our overall study design lacked a CBT-alone treatment condition in phase 1, which limited the ability to compare our findings with studies in which patients receiving CBT treatment alone experienced a relapse or recurrence prevention effect. Our findings can, at most, be generalized to populations of patients with chronic or recurrent MDD and not to patients experiencing a first depressive episode, for whom the prevention of recurrence would be of great interest.

The sample sizes for the primary comparisons of sustained recovery rates had sufficient power to detect differences between treatments of approximately 10% to 15%, but the study did not have sufficient power to detect smaller differences.

Participants were randomized to their phase 2 treatment condition only after recovering in phase 1 and consenting to participate in phase 2. One reason we opted for a sequential randomization procedure was to avoid making an assignment that could be implemented as many as 180 weeks after the initial assignment. However, this procedure could have resulted in differences among the phase 2 samples that may have affected estimates of sustained recovery.[26]

Conclusions

The combination of psychotherapy and antidepressant medication treatments is an evidence-based recommendation for optimizing efficacy in the acute treatment of patients with MDD.[2-4] Findings from phase 1 of the present clinical trial are in line with this recommendation, as treatment with a combination of CBT and antidepressant

medications was associated with a higher rate of recovery than treatment with antidepressant medications alone, an advantage that was especially evident in the subset of patients with nonchronic but more severe MDD. However, the findings from the 3-year follow-up reported herein raise questions about whether adding antidepressant medication therapy during acute and continuation treatment interferes with the enduring effect of CBT treatment. Patients with chronic and recurrent MDD who achieved recovery with antidepressant medication treatment benefited from medication maintenance, although only an estimated one-third of patients achieved sustained recovery, and indications exist to suggest that combining monotherapy with CBT may interfere with any enduring effect CBT treatment may have.

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Additional Information: Drs DeRubeis, Fawcett, and Hollon were the principal investigators; Drs Amsterdam, Zajecka, and Shelton were the coprincipal investigators. Drs DeRubeis, Hollon, and Young oversaw the implementation of computed tomography at the University of Pennsylvania, Vanderbilt University, and Rush University, respectively. Dr Fawcett oversaw the implementation of pharmacotherapy across the study; Drs Amsterdam, Zajecka, and Shelton supervised the implementation of pharmacotherapy at the respective sites.

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