ORIGINAL ARTICLE

Cognitive Reactivity to Sad Mood Provocation and the Prediction of Depressive Relapse

Zindel V. Segal, PhD; Sidney Kennedy, MD; Michael Gemar, PhD; Karyn Hood, MA; Rebecca Pedersen, MA; Tom Buis, MA

Context: Episode remission in unipolar major depression, while distinguished by minimal symptom burden, can also be a period of marked sensitivity to emotional stress as well as an increased risk of relapse.

Objective: To examine whether mood-linked changes in dysfunctional thinking predict relapse in recovered patients who were depressed.

Design: In phase 1 of this study, patients with major depressive disorder were randomly assigned to receive either antidepressant medication or cognitive behavior therapy. In phase 2, patients who achieved clinical remission underwent sad mood provocation and were then observed with regular clinical assessments for 18 months.

Setting: Outpatient psychiatric clinics at the Centre for Addiction and Mental Health, Toronto, Ontario.

Participants: A total of 301 outpatients with major depressive disorder, aged 18 to 65 years, participated in phase 1 of this study and 99 outpatients with major depressive disorder in remission, aged 18 to 65 years, participated in phase 2.

Main Outcome Measure: Occurrence of a relapse meeting *DSM-IV* criteria for a major depressive episode as as-sessed by the longitudinal interval follow-up evaluation and a Hamilton Depression Rating Scale score of 16 or greater.

Results: Patients who recovered through antidepressant medication showed greater cognitive reactivity following the mood provocation than those who received cognitive behavior therapy. Regardless of type of prior treatment, the magnitude of mood-linked cognitive reactivity was a significant predictor of relapse over the subsequent 18 months. Patients whose mood-linked endorsement of dysfunctional attitudes increased by a minimum of 8 points had a significantly shorter time to relapse than those whose scores were not as elevated.

Conclusion: The vulnerability of remitted depressed patients for illness relapse may be related to the (re) activation of depressive thinking styles triggered by temporary dysphoric states. This is the first study to link such differences to prognosis following successful treatment for depression. Further understanding of factors predisposing to relapse/recurrence in recovered patients may help to shorten the potentially lifelong course of depression.

Arch Gen Psychiatry. 2006;63:1-7

Author Affiliations:
Department of Psychiatry, University of Toronto (Drs Segal and Kennedy, and Ms Hood), Centre for Addiction and Mental Health (Dr Segal, Ms Pedersen, Ms Hood, and Mr Buis), University Health Network (Dr Kennedy), Smartrisk Foundation (Dr Gemar), and Department of Psychology, York University (Ms Pedersen and Mr Buis), Toronto, Ontario.

RELAPSE AND RECURRENCE following recovery from major depressive disorder are common and debilitating outcomes that carry enormous social costs.[1-3] Since routine clinical management of depressed patients targets symptom reduction within the acute episode as its primary goal, little attention has been paid to strategies for reducing the risk of recurrence postrecovery or toward measures capable of signaling that risk in recovered patients.

Cognitive accounts of depression vulnerability have addressed this problem by positing a residual form of psychological reactivity in remitted depressed patients.[4,5] This formulation involves the operation of multiple cognitive processes, some of which dominate during the acute episode of depression (eg, accessible automatic thinking), and others that endure well into recovery (eg, ingrained explanatory styles or pervasive assumptions about self-worth) and that can be re-accessed given the proper context.

Initial empirical studies of this model yielded mixed findings. Patients successfully treated for depression sometimes did[6] and often did not[7,8] show residual dysfunctional thinking or differ from never-depressed controls in endorsing these views. A problem encountered in many of these studies was the failure to operationalize the dynamic nature of the relationship between a patient's vulnerability and the conditions required to activate this vulnerability. Guided in part by Teasdale's differential activation hypothesis,[9] along with the rationale underlying experimental in-

vestigations of cognitive priming,[10] subsequent studies incorporated strategies intended to make negative modes of thinking more accessible before their assessment. This work tested the notion that it is not the persistence of dysfunctional thinking styles postrecovery per se, but the ease with which they can be brought back to mind, that characterizes the diathesis of remitted depressed patients. The results from these studies suggest that when tested under conditions designed to provoke their vulnerability, remitted depressed patients revert to a depressive information processing style.

For example, Ingram et al[11] used a dichotic listening task and experimentally manipulated participants' moods to measure the degree of attentional bias for negative material. Formerly depressed patients were more attentive to depressive adjectives when they were mildly sad but did not show this bias when tested under normal mood conditions. In contrast, never-depressed control subjects allocated their attention equally across both mood states regardless of the type of material presented. More recently, Timbremont and Braet[12] had never-depressed, currently depressed, and recovered depressed adolescents undergo a sad mood provocation before completing an adjective-rating task. The currently depressed and recovered depressed patients rated more negative words as being self-descriptive than the never-depressed controls. Demonstrating mood-related changes in cognitive processing among formerly depressed patients is an important first step but it is not definitive. It still leaves unanswered the question of whether such changes in processing style are predictive of later relapse risk and the question of what effects treatment has on altering this processing style.

Relevant data are reported in a study of a small group of formerly depressed patients who completed a measure of depressive thinking styles under both normal and induced sad moods.[13] Those patients showing the greatest increase in negative thinking when they were mildly dysphoric were most likely to relapse over a 30-month interval. Although promising for their implications, confidence in these findings is limited by poor methodology. The assessment of relapse status was entirely retrospective and was based on a single end-point interview rather than frequent prospective contact. In addition, previous treatment was not constrained and patients may have already been at differing risk thresholds before the mood provocation and follow-up occurred.

The present study is designed to address these limitations by (1) treating patients to remission within the framework of the study rather than recruiting formerly depressed patients, (2) randomly assigning patients to receive either antidepressant medication (ADM) or cognitive behavior therapy (CBT) for depression, (3) using an 18-month prospective follow-up of clinical status, and (4) evaluating whether this mood-based assessment improves the prediction of relapse compared with defining risk solely by the number of past depressive episodes. We hypothesize that cognitive reactivity will significantly predict depressive relapse in remitted patients. Because we consider cognitive reactivity to be a marker of a processing style that is residual to effective treatment, we also predict that the strength of the relationship between cognitive reactivity and relapse will not be affected by the type of treatment received.

METHODS

The study protocol was approved by the institutional review board at the Centre for Addiction and Mental Health, Toronto, Ontario. All participants provided written consent prior to any research activity. Subjects were recruited through clinical referrals from the Mood and Anxiety Disorders Program at the Centre for Addiction and Mental Health or from media announcements. Diagnostic eligibility for the study was determined using the Structured Clinical Interview for *DSM-IV* diagnoses.[14] Inclusion criteria were diagnosis of major depressive disorder according to *DSM-IV* criteria, aged between 18 and 65 years, minimum eighth-grade education, and ability to read English and to provide informed consent. Exclusion criteria were (1) a current diagnosis of bipolar disorder, substance abuse disorder, schizophrenia, or borderline personality disorder (2) a trial of electroconvulsive therapy within the past 6 months (3) a score of less than 12 on the Hamilton Depression Rating Scale.[15] In our final sample, 127 patients achieved clinical remission and 99 underwent mood provocation and entered an 18-month clinical follow-up.

TREATMENT PROCEDURES

The goal of treatment was to maximize the number of patients achieving clinical remission because this would then render them eligible for the mood challenge. Patients in the ADM condition were treated with 1 of 3 first-line antidepressant medications (Zoloft, 50-200 mg; Paxil, 20-50 mg; or Effexor, 75-225 mg) for a period of 6 months. There were 4 study psychiatrists (3 male/1 female) with considerable expertise (8-25 years) in the pharmacological treatment of major depressive disorder. Choice of medication was naturalistic and based on the treating psychiatrist's clinical judgment. Patients who failed to respond to their first ADM were allowed to discontinue and start on a second. If they failed both trials, they were then removed from the study and offered alternative care in the Depression Clinic at the Centre for Addiction and Mental Health. Pharmacotherapy sessions were 20 minutes in duration and followed the recommendations for clinical management developed by Fawcett et al.[16] They emphasized both medication management (education, dosage adjustment, dosage scheduling, and side effects) and clinical management (discussion of functionality, support, and limited advice). Psychotherapeutic strategies, especially CBT techniques, were prohibited. Patients attended approximately 10 to 13 sessions with their study psychiatrist over a 26-week period and were continued on ADM over that time.

Patients in the CBT condition received a course of 20 individual weekly sessions of CBT, according to the protocol developed by Beck et al,[17] which with tapering of the final 2 sessions, spanned between 22 to 24 weeks. Sessions were 50 minutes in length. Treatment was provided by 1 (male) licensed clinical psychologist (a member of the Academy of Cognitive Therapy) and 7 master's level staff (2 male/5 female, supervised by Mark Lau, PhD) with extensive experience conducting CBT (5-15 years). Treatment fidelity was assessed using the Cognitive Therapy Scale[18] ratings of 18 audiotapes (early, middle, and late sessions) from 6 randomly chosen patients. The mean rating for each of the 2 raters across all tapes was 46.94 and 47.35, and the level of inter-rater agreement was 0.826 (intraclass coefficient).

DETERMINATION OF CLINICAL REMISSION AND RELAPSE STATUS

Posttreatment evaluations were based on *DSM-IV* criteria derived from the Longitudinal Interval Follow-Up Evaluation (LIFE)[19] interview and the 17-item Hamilton Depression Rating Scale (HDRS-17). Following the consensus recommendations,[20] remission was defined as the patient reporting minimal symptoms for a minimum of 12 weeks, no longer meeting diagnostic criteria for major depressive episode (MDE), and a HDRS-17 score of less than or equal to 10. These criteria were used to determine which patients would be eligible to participate in the mood provocation phase of the study. Following the mood provocation, we implemented a multilevel assessment plan using both self-report inventories and structured interviews to observe patients over the subsequent 18 months. We conducted brief, symptom-focused evaluations on a bimonthly basis, supplemented with monthly mailings of the Beck Depression Inventory II (BDI II)[21] and phone calls reminders. Any patient scoring 15 or greater on the BDI II or 16 or greater on the HDRS-17 was reinterviewed in 1 week. If their scores remained in the same range, they were assessed with the LIFE[19] to determine whether their level of symptomatology met criteria for MDE. Patients were judged to have relapsed if they were given a diagnosis of MDE at any time during the follow-up. All evaluations were audio-recorded and a subset of these tapes (n=17) were rerated by an independent research psychiatrist. The κ coefficient for agreement for presence or absence of MDE between the evaluator and the psychiatrist was .60. Interrater agreement at the item level, using the intraclass coefficient computed as a 2-way mixed model treating rater as a fixed factor, was 0.80.

MEASURES

Visual Analogue Scale

Patients rated current mood on a visual analogue scale (VAS) measuring 76 mm from center to each of 2 end points. The descriptor "sad" was located to the left of center and "happy" was located on the right side with arrows indicating increasing strength of mood associated with greater distance from center.[22]

DYSFUNCTIONAL ATTITUDES SCALE

The Dysfunctional Attitudes Scale[23] was used to assess endorsement of dysfunctional beliefs that are theorized to guide a person's self-evaluation. These beliefs are important in accounts of cognitive vulnerability because they are presumed to be more enduring than the characteristic negative automatic thinking associated with the depressive episode itself.[4] Good internal consistency (α values ranging from .89-.93) and the availability of psychometrically sound equivalent forms of the DAS are also important features of this instrument. In the present study, the 40-item Forms A and B of the DAS were administered.

MOOD PROVOCATION

Patients were asked to listen to a piece of music presented on a CD player and to try and recall a time in their lives when they felt sad. The music came from previous work by Clark and Teasdale[24] and was the orchestral introduction by Prokofiev entitled "Russia under the Mongolian Yoke" from the film Alexander Nevsky. The taped segment played to patients was remastered at half speed and presented through earphones. This type of provocation (combining elements of music associated with sad mood and autobiographical recall) has been found to be effective in bringing on transient dysphoric mood states.[25]

Patients provided demographic information about themselves and completed the verbal subscale of the Hartford-Shipley,[26] a test of verbal IQ. The experimenter then administered the HDRS and the BDI. Following these tests, participants completed a mood VAS rating and were presented with 1 of the 2 equivalent forms of the DAS (Form A or B). The order of presentation of either form was counterbalanced across participants. Next, participants listened to the music for 10 minutes and tried to recall a time in their lives when they felt sad. Immediately following, they filled out the DAS a second time (Form A or B) and provided a mood VAS rating.

STATISTICAL ANALYSES

Segal et al,[13] reported that the pre-post mood provocation difference in DAS scores yielded an effect size of 0.59 standard deviation units. Using this as an estimate of the effect size for the 1-way analysis of variance (ANOVA) for treatment group, a sample of 28 patients per cell would be required to achieve a power of 0.8 to detect a difference with .05 α using a 2-tailed test. Similarly, using the predictor means and event rates reported in logistic regression by Segal et al[13] as an estimate for the prediction of relapse from reactivity scores, a total sample size of 50 would yield 0.8 power to detect a significant effect with .05 α using a 2-tailed test.

Changes in DAS scores obtained during euthymic and (provoked) sad moods served as the main dependent variable. Because variability among initial scores is a problem common to many pre-post comparisons, we constructed residualized DAS change scores using a simple linear regression model in which post-DAS scores were predicted by pre-DAS scores. The standardized residuals (Zres-DAS) for each case were saved from this model. In this way, the variability among residuals can be considered independent (ie, partialed) from the pre-DAS scores.[27] All analyses, except where indicated, were conducted using Zres-DAS scores but are reported in raw score equivalents.

To examine differences in cognitive reactivity as a function of prior treatment, we used a 1-way ANOVA for patients who underwent both mood provocations. We then used Zres-DAS as a continuous predictor in a Cox proportional hazards regression[28] and as a categorical predictor in a Kaplan-Meier survival analysis[29] to gauge the impact of different levels of cognitive reactivity on survival and to examine relapse rates for certain prognostic variables. Patients lost to follow-up were treated as censored observations up to their last assessment occasion.

RESULTS

PATIENT FLOW AND DROPOUT

A total of 484 patients were evaluated for the study, 57 of whom did not meet diagnostic criteria for MDE. Another 126 patients met the following exclusion criteria: (1) another *DSM-IV* Axis I disorder judged to require preferential treatment to depression (n=68), (2) *DSM-IV* Axis II diagnosis of borderline, antisocial, or schizotypal personality disorder (n=16), (3) major depressive disorder secondary to a medical condition (n=5), (4) already on medication or failure on at least 2 trials of ADM in the past 2 years (n=6), (5) participating in another study or scheduling difficulties (n=31).

A total of 301 patients met study entry criteria and were randomly assigned to either ADM (n=149) or CBT (n=152). Of these patients, 144 completed treatment. Sixty-nine patients (50 [72%] in ADM and 19 [28%] in CBT)

Table 1. Demographic and Clinical Data for Intitial Sample, Treatment Completers, and Dropouts*

	Pretreatment		Treatment Completers		Treatment Dropouts	
	ADM (n = 152)	CBT (n = 149)	ADM (n = 56)	CBT (n = 88)	ADM (n = 96)	CBT (n = 93)
Mean age ± SD, y	36.84 ± 11.59	37.89 ± 11.25	39.70 ± 12.43	38.09 ± 10.92	35.17 ± 10.80	34.82 ± 10.8
Sex (M/F)	67/85	66/83	25/31	33/55	42/54	39/54
Duration ± SD, wk†	33.25 ± 21.44	33.69 ± 25.04	34.73 ± 22.21	34.33 ± 22.33	30.55 ± 20.89	29.79 ± 20.16
Single/recurrent‡	26/125	22/126	9/47	12/76	17/78	16/76
Previous episodes of depression, No. ± SD	1.38 ± 0.49	1.35 ± 0.48	1.32 ± 0.47	1.27 ± .45	1.41 ± .49	1.40 ± .49
Prior ADM, %§	42.95	41.73	43.63	38.24	42.55	41.76
Mean BDI score ± SD	32.18 ± 9.34	31.79 ± 9.07	9.96 ± 10.25	10.29 ± 10.19	31.38 ± 9.35	31.48 ± 9.18
Mean HDRS score ± SD	19.36 ± 3.91	19.57 ± 3.50	6.00 ± 4.83	5.84 ± 4.67	20.21 ± 3.55	19.70 ± 3.53
Mean DAS score ± SD	158.65 ± 30.72	153.80 ± 35.45	131.73 ± 28.10	132.27 ± 28.18	154.46 ± 36.74	154.56 ± 31.84

Abbreviations: ADM, antidepressant medication; BDI, Beck Depression Inventory; CBT, cognitive behavior therapy; DAS, Dysfunctional Attitudes Scale; HDRS, Hamilton Depression Rating Scale.
*None of the mean values differed between any pair of ADM/CBT treatment groups within treatment stages.
†Reported duration of depressive symptoms during the past 2 years.
‡Number of patients reporting single episode vs chronic/recurrent depression.
§Percentage of sample using antidepressant medication.

Table 2. Demographic and Clinical Data for Mood Provocation Samples by Treatment Group and Completers*

	Mood Induction		Completed 18-mo Follow-up, ADM and CBT (n = 78)
	ADM (n = 40)	CBT (n = 59)	
Mean age ± SD, y	39.65 ± 11.49	38.17 ± 10.95	38.95 ± 11.23
Sex (M/F)	17/23	23/36	30/48
Duration ± SD, wk†	33.61 ± 22.19	34.29 ± 22.48	33.25 ± 22.95
Single/recurrent‡	14/26	13/46	18/60
Previous episodes of depression, No. ± SD	1.65 ± .48	1.71 ± .46	1.27 ± .45
Prior ADM, %¶	38.5	38.6	40.9
Mean BDI score ± SD	6.20 ± 4.90	7.76 ± 5.74	7.45 ± 5.65
Mean HDRS score ± SD	5.23 ± 2.77	5.29 ± 2.80	5.59 ± 2.72
Mean preprovocation DAS score ± SD	134.73 ± 28.09	128.17 ± 30.04	131.08 ± 30.30

Abbreviations: ADM, antidepressant medication; BDI, Beck Depression Inventory; CBT, cognitive behavior therapy; DAS, Dysfunctional Attitudes Scale; HDRS, Hamilton Depression Rating Scale.
*None of the mean values differed for any demographic or clinical variable.
†Reported duration of depressive symptoms during the past 2 years.
‡Number of patients reporting single episode vs chronic/recurrent depression.
§Percentage of sample using antidepressant medication.

did not attend their first treatment session and a further 51 patients (29 [57%] in ADM and 22 [43%] in CBT) dropped out of the study within the first 4 treatment sessions. Thirty-seven patients (17 [46%] in ADM and 20 [54%] in CBT) discontinued treatment during remaining sessions. Refusal of randomization or disappointment with treatment assignment was the most frequent explanation given for study attrition. As indicated in **Table 1**, the demographic characteristics and clinical history of patients who completed treatment did not differ from those who never started or dropped out of the study.

The overall response rates for patients who completed treatment (n=127) were 80% for ADM and 72% for CBT. Remission rates were 71% for ADM and 61% for CBT. Of the 127 patients who were eligible for the mood provocation phase of the study, 99 patients underwent both mood provocations and entered the clinical follow-up where they were contacted bimonthly during the next 18 months. Reasons for attrition at this point

in the study included elevated HDRS scores at time of testing (>10, n=6) and declining to participate in the mood induction (n=15) and/or the clinical follow-up (n=7). Seventy-eight patients completed the full 18 months of follow-up. As presented in **Table 2**, the demographic characteristics and clinical history of patients who underwent the mood provocation at posttreatment did not differ from those who completed the 18-month follow-up. Eighty-six percent (36/42) of patients in the ADM condition were on continuation medication when they participated in the mood provocation. The percentage of patients relapsing over the follow-up period did not differ according to the type of prior treatment received (ADM, 47.5% [19/40] and CBT, 39% [23/59]; $P = .40$).

EFFECTS OF SAD MOOD PROVOCATION

The mood provocation protocol produced significant changes in VAS self-rated sadness across patients in both

treatment groups. Mean change in mood was –25.48 for patients who received CBT and –21.29 for patients who received ADM, which indicates that while both groups became more sad, they did not differ in the level of dysphoria they experienced (P=.37). We also compared mood ratings for patients who did and did not relapse during the follow-up. The VAS means for these 2 groups were –19.39 and –25.51, respectively, which indicates that there were increases in sadness following the provocation but no difference in magnitude between these 2 groups (P=.23).

COGNITIVE REACTIVITY
FOLLOWING ADM OR CBT

Changes in dysfunctional thinking following sad mood provocation differed significantly according to whether patients achieved remission through either ADM or CBT ($F_{1,97}$=4.56, P=.035; Cohen d=0.42). According to the marginal means (in DAS raw-score equivalent units), patients receiving ADM showed increases in cognitive reactivity (+4.06), whereas patients remitted through CBT showed decreases (–2.76), although there was noticeable within-group variance (**Figure 1**).

COGNITIVE REACTIVITY, 18-MONTH SURVIVAL,
AND PAST DEPRESSIVE EPISODES

To examine the relationship between cognitive reactivity assessed at posttreatment and prospective survival time during 18 months, we used Cox proportional hazard regression with Zres-DAS as the predictor. This model proved to be significant (Wald χ_1^2=7.12, P=.008, hazard ratio=1.54) indicating that patients in remission who showed cognitive reactivity were at increased risk for clinical relapse. The rate of relapse did not differ significantly between the ADM and CBT treatment conditions cumulatively across the 18 months (Wald χ_1^2=0.256). The proportion of patients who remained well at the end of the first 3 months was 0.68 for ADM and 0.75 for CBT. At the end of 9, 12, and 18 months, 0.55, 0.53, and 0.53, respectively, of the patients treated with ADM and 0.75, 0.63, and 0.61, respectively, of the patients treated with CBT had not yet relapsed.

Next, we sought to determine whether cognitive reactivity would be incrementally predictive of time to relapse after controlling for the effects of past depressive episodes and prior treatment. We used a sequential Cox regression model with the number of past episodes entered in the first step followed in a second step by type of treatment and Zres-DAS. This model treated the number of past episodes as an initial nontreatment covariate and Zres-DAS and prior treatment as experimental predictors.

In the first step, we found that the number of previous depressive episodes was associated with an increased risk of relapse (Wald χ_1^2=7.48, P=.006, hazard ratio=2.54). Patients' levels of cognitive reactivity remained a significant predictor in the second step, (Wald χ_1^2=4.64, P=.031, hazard ratio=1.42). The treatment and Zres-DAS by treatment interaction did not add significantly to the model. This analysis demonstrates that after taking a patient's history of depression into account, cognitive reactivity continues to make a meaningful contribution to the prediction of relapse irrespective of previous treatment modality. Based on
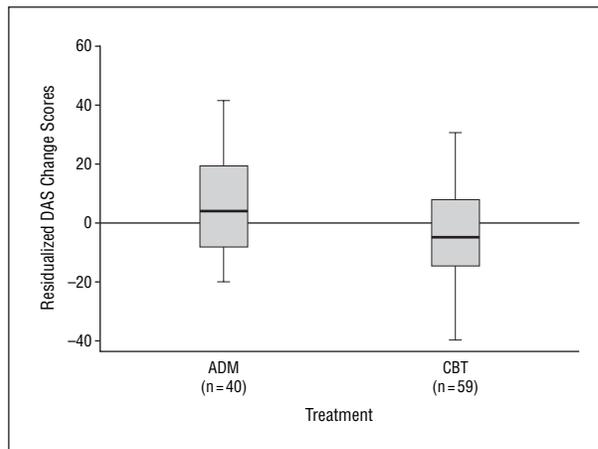

Figure 1. Residualized change (by treatment differences) in the Dysfunctional Attitudes Scale associated with provoked sadness.

the hazard ratio derived from this model, each single unit increase in Zres-DAS (equalling a raw score increase of 16 points on the DAS) following the provocation of transient sadness increases the risk of relapse by 42%.

EFFECTS OF MARKED AND MINIMAL
COGNITIVE REACTIVITY ON
18-MONTH SURVIVAL

As a next step, we were interested in studying the effects of marked and minimal levels of reactivity to gauge whether these categories would be clinically informative of relapse vulnerability. Our approach to operationalizing reactivity levels involved 2 steps. We compared the mean DAS residual change scores between relapsers and nonrelapsers and found that they differed significantly ($F_{1,76}$=5.174, P=.026, Cohen d=0.52). We then used the absolute magnitude of the range in DAS residualized change scores to define the separation between relapsers (3.68) and nonrelapsers (–4.30 using raw score equivalents) and for constructing our categories. This yielded a score of 7.98 (rounded to 8.00) and allowed us to construct the following 3 categories of cognitive reactivity: (1) marked increases for patients whose scores increased by 8 or more, (2) minimal change for patients whose scores changed within the range of 7 to –7, and (3) marked decreases for patients whose scores decreased by 8 or more.

As illustrated in **Figure 2**, this classification produced curves that showed significant differences in survival according to the level of cognitive reactivity exhibited (χ_2^2=12.18, P=.002). Log-rank tests revealed that patients with marked increases in cognitive reactivity had significantly higher relapse rates (69%) than patients showing either minimal cognitive reactivity (30%) (χ_1^2=7.85, P=.005) or marked decreases associated with mood provocation (32%) (χ_1^2=8.56, P=.003).

Repeating these analyses within ADM or CBT alone, this classification yielded significant differences in survival rates for patients treated with CBT (χ_2^2=6.04, P=.049) and marginally significant differences for patients treated with ADM (χ_2^2=5.70, P=.058). Similar to the previous analysis, marked increases in cognitive reactivity were associated with the highest rates of relapse in each treatment condition.
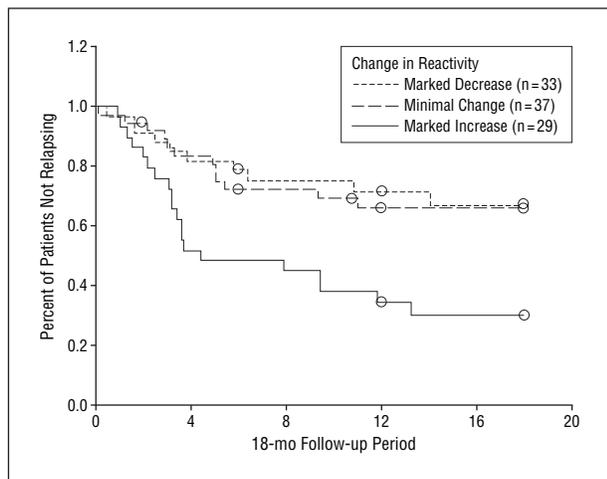
Figure 2. Cumulative proportion of survival in recovered patients across 3 levels of cognitive reactivity.

RELATIONSHIP BETWEEN COGNITIVE REACTIVITY AND ONGOING TREATMENT

Given the protection afforded patients by continuing treatment past the point of remission,[27] there is the possibility that the relapses we observed during the follow-up period were merely a function of patients discontinuing such treatment. Of the 40 relapsers in our sample, 12 were in treatment at the time of relapse and 28 were not. When we compared the mean Zres-DAS scores between these 2 groups, we found that their reactivity scores did not differ (raw DAS change score equivalent for relapsers in treatment = 3.89 and for relapsers not in treatment = 4.18; $P = .48$).

COMMENT

Remitted depressed patients who endorsed greater dysfunctional cognitions as mood worsened were at significantly greater risk of relapse during the subsequent 18 months. While patients may have achieved remission through either psychological or pharmacological treatment, the relapse risk indexed by cognitive reactivity was not differentially modified by either CBT or ADM. Patients showing marked increases in cognitive reactivity had significantly lower survival rates than those whose thinking styles showed a minimal change or a marked decrease. Furthermore, cognitive reactivity contributed additionally to the prediction of relapse, even after controlling for patients' past number of depressive episodes, which is the most robust clinical predictor of relapse to date.

Previous studies of cognitive reactivity have relied primarily on cross-sectional designs for reporting differences between patients high and low in relapse risk.[30] This is the first study to link such differences to prognosis. While the exact nature of the vulnerability indexed via cognitive reactivity is not fully known, part of the answer may lie in understanding how mild dysphoria effects the endorsement of dysfunctional attitudes. One view holds that these attitudes are embedded within an elaborative cognitive structure, or schema, that though formed through previous experience with depression, is largely inaccessible in the remitted state.[6] Sad mood serves to activate the depression-related content in this schema, with the increased endorsement of dysfunctional attitudes being a by-product. Studies of cognitive priming and mood-dependent memory support this view.[7,24] Alternatively, the ironic process theory suggests that dysfunctional attitudes are difficult to detect in remitted depressed patients, not because they are inactive but because their influence is masked through ongoing mental control, such as thought suppression. In this case, mild dysphoria disrupts these processes of mental control by placing an additional load on the cognitive resources necessary to maintain them. The effects of degraded mental control are seen in elevated DAS scores as these attitudes become more intrusive.[31,32] Further research is needed to test these 2 competing accounts.

A recent report by Kendler et al[33,34] suggests that sensitivity to mild life stress, another form of cognitive reactivity, predicted MDE in patients with a functional variant in the serotonin transporter *5-HTT* gene. What is not known is the pathway through which the psychological effects of mild stress eventuate in depression. Our description of dysphoria-linked changes in cognitive processing is positioned halfway between the cell and the environment, and may characterize the proximal cognitive-affective processes through which this increased sensitivity is expressed. Given that both cognitive reactivity and stress sensitivity increase the risk for major depression, it might be that these constructs describe a similar phenomenon of dysregulation but at different levels of analysis. Studies in which assessments of both cognitive reactivity and genetic status are conducted would be an important next step to advancing knowledge in this area.

Our findings suggest that effective relapse prevention might be achieved through approaches that target cognitive reactivity directly. The attempt here would be to uncouple the mood-dependent accessibility of these beliefs and attitudes, perhaps through the teaching of metacognitive skills that serve to render this type of automatic processing more accessible to effortful reflection. Such treatments may include components that first help patients deliberately monitor and observe their thinking patterns when they feel sad, and then help patients respond to these thoughts and feelings in a way that allows them to inhibit the cognitive elaboration of their content.[35] Data from one approach that specifically trains recovered depressed patients in how to disengage from dysphoria-linked thinking styles suggest a significant prophylactic advantage compared with treatment as usual.[36,37]

LIMITATIONS

There are a number of limitations to this work that need to be acknowledged. From a measurement viewpoint, the use of DAS Forms A and B can be improved on because they are not psychometrically identical and thus could have introduced additional error variance into the DAS change scores. Although we did not find that the variable of the DAS form was a significant predictor when it was entered into the Cox Regression, future studies might want to consider the split-half version of the DAS published by Power et al.[38] Similarly, the ecological validity of inducing sad mood through music enhanced autobio-

graphical recall may differ from methods that rely on viewing sad films or being rejected by a social partner.

While the tendency of patients treated with CBT as a group is to show reduced reactivity compared with ADM, the results suggest that reactivity may have been modified by treatment; this would be difficult to conclude in the absence of a pretreatment assessment of reactivity. The group difference may be owing to the fact that exposure to the DAS itself differed across the 2 treatment conditions. Patients in the CBT group would have worked on the types of attitudes and thinking styles captured by this scale at some point in their treatment. There was no such focus for patients in the ADM group who only completed the DAS at pretreatment and posttreatment intervals. It is not clear what effect such prior exposure may have had on patients completing the DAS at the mood provocation session. One possibility is that CBT patients' lower DAS scores both before and after induced sadness reflected demand characteristics that were reinforced in their therapy. Alternatively, lower scores might be owing to effortful, compensatory strategies used by patients to moderate the intrusion of dysfunctional thoughts. If patients treated with CBT were responding solely on the basis of demand, then we might expect more of them to show marked decreases in reactivity compared with ADM. We did not find this to be the case (30% of patients had decreased scores by 8 or more for ADM and 36% had decreased scores for CBT).

SIGNIFICANCE

Our study indicates that even a mild negative mood, when experienced by someone with a history of depression, can re-instate some of the cognitive features observed in depression itself. The presence of such reactivity in recovered patients signals a residual but heightened risk for episode relapse that has not been fully addressed by treatment.

REFERENCES

1. Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Coryell W, Kunovac JL, Mueller TI, Rice JP, Keller MB. Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry*. 2000;57:375-380.
2. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry*. 2003;64:1465-1475.
3. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997;349:1436-1442.
4. Kovacs M, Beck AT. Maladpative cognitive structures in depression. *Am J Psychiatry*. 1978;135:525-533.
5. Hollon SD, Stewart MO, Strunk D. Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety. *Annu Rev Psychol*. 2006;57:285-315.
6. Eaves G, Rush AJ. Cognitive patterns in symptomatic and remitted unipolar major depression. *J Abnorm Psychol*. 1984;93:31-40.
7. Hamilton EW, Abramson LY. Cognitive patterns and major depressive disorder: a longitudinal study in a hospital setting. *J Abnorm Psychol*. 1983;92:173-184.
8. Silverman JS, Silverman JA, Eardley DA. Do maladaptive attitudes cause depression? *Arch Gen Psychiatry*. 1984;41:28-30.
9. Teasdale JD. Cognitive vulnerability to persistent depression. *Cogn Emot*. 1988;2:247-274.
10. Ingram RE, Miranda J, Segal ZV. *Cognitive Vulnerability to Depression.* New York, NY: Guilford Press; 1998.
11. Ingram RE, Bernet CZ, McLaughlin SC. Attention allocation processes in depressed individuals. *Cognit Ther Res*. 1994;18:317-332.
12. Timbremont B, Braet C. Cognitive vulnerability in remitted depressed children and adolescents. *Behav Res Ther*. 2004;42:423-437.
13. Segal ZV, Gemar M, Williams S. Differential cognitive response to a mood challenge following successful cognitive therapy or pharmacotherapy for unipolar depression. *J Abnorm Psychol*. 1999;108:3-10.
14. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).* Washington, DC: American Psychiatric Press Inc; 1996.
15. Hamilton M. Rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
16. Fawcett J, Epstein P, Fiester SJ, Elkin I, Autry JH. Clinical management: imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. *Psychopharmacol Bull*. 1987;23:309-324.
17. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression.* New York, NY: Guilford Press; 1979.
18. Vallis TM, Shaw BF, Dobson KS. The Cognitive Therapy Scale: psychometric properties. *J Consult Clin Psychol*. 1986;54:381-385.
19. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC. The longitudinal interval follow-up evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry*. 1987;44:540-548.
20. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Arch Gen Psychiatry*. 1991;48:851-855.
21. Beck AT, Steer RA, Brown GK. *The Beck Depression Inventory.* 2nd ed. San Antonio, Tex: Psychological Corporation; 1996.
22. Grossberg JM, Grant BF. Clinical psychophysics: applications of ratio scaling and signal detection methods to research on pain, fear, drugs, and medical decision making. *Psychol Bull*. 1978;85:1154-1176.
23. Weissman A. *The Dysfunctional Attitude Scale: A Validation Study* [dissertation]. Philadelphia, Pa: University of Pennsylvania; 1979.
24. Clark DM, Teasdale JD. Constraints of the effects of mood on memory. *J Pers Soc Psychol*. 1985;48:1595-1608.
25. Martin M. On the induction of mood. *Clin Psychol Rev*. 1990;10:669-697.
26. Shipley WC. A self-administering scale for measuring intellectual impairment and deterioration. *J Psychol*. 1940;9:371-377.
27. Cohen J, Cohen P. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1983:414-417.
28. Cox DR. Regression models and life tables. *J R Stat Soc Ser A Stat Soc*. 1972;34:187-220.
29. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
30. Taylor L, Ingram RE. Cognitive reactivity and depressotypic information processing in children of depressed mothers. *J Abnorm Psychol*. 1999;108:202-210.
31. Wegner DM. When the antidote is the poison: ironic mental control processes. *Psychol Sci*. 1997;8:148-150.
32. Wenzlaff RM, Bates DE. Unmasking a cognitive vulnerability to depression: how lapses in mental control reveal depressive thinking. *J Pers Soc Psychol*. 1998;75:1559-1571.
33. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301:386-389.
34. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry*. 2005;62:529-535.
35. Teasdale JD, Segal Z, Williams JMG. How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help? *Behav Res Ther*. 1995;33:25-39.
36. Teasdale JD, Segal ZV, Williams JMG, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol*. 2000;68:615-623.
37. Ma SH, Teasdale JD. Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. *J Consult Clin Psychol*. 2004;72:31-40.
38. Power MJ, Katz R, McGuffin . The Dysfunctional Attitudes Scale: comparison of form-A and form-B and proposals for a new subscaled version. *J Res Pers*. 1994;28:263-276.