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Improved Cognitive Content Endures for Two Years among Unstable Responders to Acute-phase Cognitive Therapy for Recurrent Major Depressive Disorder

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Abstract

Background—The cognitive model of depression suggests that cognitive therapy (CT) improves major depressive disorder (MDD) in part by changing depressive cognitive content (e.g., dysfunctional attitudes, hopelessness). The current analyses clarified (1) the durability of improvements in cognitive content made by acute-phase CT responders; (2) whether continuation phase CT (C-CT) or fluoxetine (FLX) further improves cognitive content; and (3) the extent to which cognitive content mediates continuation treatments' effects on depressive symptoms and major depressive relapse/recurrence.

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Conflict of Interest Statement

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Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation, including the American Psychological Association, and with the Helsinki Declaration of 1975, as revised in 2008.

Methods—Outpatients with recurrent MDD who responded to acute-phase CT ($N = 241$) were randomized to 8 months of C-CT, FLX, or pill placebo (PBO) and followed 24 additional months (Jarrett & Thase, 2010). Cognitive content was assessed approximately every 4 months using five standard patient-report measures.

Results—Large improvements in cognitive content made during acute-phase CT were maintained for 32 months, with 78-90% of patients scoring in normal ranges, on average. Cognitive content varied little between C-CT, FLX, and PBO arms, overall. Small, transient improvements in cognitive content among C-CT or FLX compared to PBO patients did not clearly mediate the treatments' effects on depressive symptoms or on major depressive relapse/recurrence.

Conclusions—Outpatients with recurrent MDD who respond to acute-phase CT show durable improvements in cognitive content. Continuation CT or FLX may not continue to improve patient-reported cognitive content substantively, and thus may treat recurrent MDD by other paths.

Keywords

cognitive therapy; fluoxetine; continuation; major depressive disorder; cognitive content

Introduction

The cognitive model of depression posits that cognitive therapy (CT) reduces depressive symptoms and prevents relapse partly by changing depressive cognition (Clark et al. 1999). Arguably, more is known about cognitive content during *acute-phase* CT, which aims to teach CT skills to currently depressed patients to reduce depressive symptoms, produce remission, and prevent relapse (Beck et al., 1979). We examined changes in cognitive content during *continuation-phase* treatment aimed at reducing residual symptoms, preventing relapse/recurrence among CT responders, and generalizing compensatory skills (Jarrett et al., 1998; Jarrett et al., 2008). Specifically, 241 CT responders with recurrent major depressive disorder (MDD) were randomized to 8 months of continuation cognitive therapy (C-CT), fluoxetine (FLX), or pill placebo (PBO) and followed 24 additional months (Jarrett & Thase, 2010). The current analyses clarified whether improvements in cognitive content during acute-phase CT are durable, and whether C-CT or FLX further improves cognitive content as a means to reduce residual symptoms and prevent relapse/recurrence.

In the cognitive model of depression, perceptions of external and internal stimuli are linked to negative affect (e.g., sadness, fear, anger; Clark et al., 1999). Internal, relatively stable cognitive structures, such as schema (e.g., assumptions such as “I must always be liked” and core beliefs such as “I am worthless”) and modes (groups of inter-related schema that handle demands; e.g., interpersonal loss or isolation) facilitate interpretation of stimuli. Cognitive structures activated by matching stimuli (e.g., interpersonal rejection activating the assumption “I must always be liked”) govern subsequent information processing. Activated cognitive structures then produce commensurate behaviors, thoughts, and emotions (e.g., thinking “I am unlovable and always will be” and avoiding social contact) including depression (Clark et al., 1999). As an efficacious treatment of depression, CT may reduce negative schema activation directly and/or strengthen top-down (effortful, reflective)

processing to correct biased information processing via observable neurophysiological mechanisms (Clark & Beck, 2010).

The best-studied measures of depressive cognitive content include patient-report questionnaires (Dunkley et al., 2010). For example, the Attributional Style Questionnaire (ASQ; Peterson et al., 1982; Dykema et al., 1996) and Beck Hopelessness Scale (BHS; Beck et al., 1974) assess outputs of activated schema, whereas the Dysfunctional Attitudes Scale (DAS; Weissmann, 1979) measures depressive semantic content. The Self-Control Schedule (SCS; Rosenbaum, 1980), in contrast, measures learned resourcefulness (e.g., positive coping) to address challenging internal and external events. Although depression diagnostic criteria (American Psychological Association, 2013) and symptom measures (e.g., Hamilton, 1960; Beck et al., 1961) include cognitive items (e.g., guilt, pessimism), “depression” is distinguished from “cognitive content” in theory (Clark et al., 1999; Clark & Beck, 2010) and measurement (Lorenzo-Luaces et al., 2014). For example, the validity of patient-report measures of cognitive content has been supported in currently and previously depressed patients, as well as normative samples, by differentiating these groups (Otto et al., 2007; Riso et al., 2003; Steer et al., 1994) and by predicting changes in health status among patients (major depressive treatment response, relapse, recovery; suicide; Brown et al., 2000; Burns et al., 1994; Vittengl et al. 2010). Researchers have used patient-report measures to clarify how much cognitive content improves during CT and mediates CT’s effects on depression.

Depressed patients’ self-reported cognitive content improves substantively during acute-phase CT (e.g., on the ASQ, BHS, DAS; Garratt et al., 2007; Webb et al., 2012). For example, Jarrett et al. (2007) found substantive improvement in averages (median $d = 0.79$) and proportions of patients scoring in “healthy” ranges (from median 39 to 70%) from pre- to post-acute-phase CT on the ASQ (failure and success composites), DAS, and Self-Efficacy Scale (SCS; Sherer et al., 1982). Similarly in the current dataset, patients’ average cognitive content scores improved considerably (median $d = 0.96$ on the ASQ stable and global failure composites, BHS, DAS, and SCS) and proportions of healthy patients increased notably (from median 45 to 82% on the BHS, DAS, and SCS) during acute-phase CT (Vittengl et al., 2014a).

A smaller literature suggests that most of the improvement in cognitive content occurs during acute phase treatment, and these improvements are maintained but not greatly extended during continuation treatment. For example, among acute-phase CT responders randomized to 8 months of C-CT or assessment-control and followed 16 additional months, cognitive content was generally stable through 24 months with few differences between groups (Jarrett et al., 2007). C-CT modestly improved ASQ-Failure scores relative to control from months 8-12, however. Similarly, among responders to acute-phase fluoxetine, patients randomized to continuation fluoxetine plus CT maintained gains in cognitive content made during acute-phase treatment, whereas patients in continuation fluoxetine-only showed deteriorating cognitive content over 6 months (Petersen et al., 2004). This finding supports the hypothesis that CT has a unique, specific effect on improving cognitive content. The current analyses expanded the literature on longitudinal changes in depressed patients’ cognitive content during and after continuation treatments.

The potential causal role of cognitive content in CT's effects on depression is unclear (Kazdin, 2007; Longmore & Worrell, 2007). Moderately strong correlations between concurrent changes in cognitive content and depressive symptoms (e.g., from pre- to post-acute-phase CT; Jarrett et al., 2007; Vittengl et al., 2014a) suggested a causal link. However, depressive symptoms improved more, and more quickly, than cognitive content in acute-phase CT (Furlong & Oei, 2002; Jarrett et al., 2007). Further, change in cognitive content only partly accounted for change in depressive symptoms pre- to post-treatment (Christopher et al., 2009; Jarrett et al., 2007).

Causation also requires temporal precedence—earlier improvements in cognitive content should account for subsequent changes in depressive symptoms, according to the cognitive model. That is, cognitive content is expected to *mediate* CT's effects on depressive symptoms (Kazdin, 2009). At least three assessment periods (e.g., pre-, mid-, and post-CT) are needed to disentangle earlier from later changes. During acute-phase CT, earlier changes in cognitive content have sometimes (DeRubeis et al., 1990), but not always (Jarrett et al., 2007), predicted subsequent changes in depressive symptoms. In the current dataset, evidence that changes in cognitive content drove subsequent changes in depressive symptoms during acute-phase CT was limited (median $r = .06$; Vittengl et al., 2014a).

In randomized clinical trials, potential mediators can be evaluated more rigorously as variables that (1) are changed by treatment (i.e., mediators assessed after treatment begins differ between treatment groups); and (2) predict later outcomes as main effects or interactions with treatment group (Kraemer et al., 2002). Figure 1 depicts possible mediation of continuation treatments effects' on residual symptoms and relapse (path A) by cognitive content (paths B1, B2) and other variables beyond the current analyses (paths C1, C2). Previous analyses of the current dataset showed that C-CT or FLX decreased relapse (by nearly half; Jarrett et al., 2013a) and residual symptoms (by about 0.2 *SD*; Vittengl et al., 2014b) compared to PBO during the 8-month experimental phase (path A).

The current analyses tested (1) the durability of improvements in cognitive content made by acute-phase CT responders, including the proportions of patients with cognitive content in "healthy" ranges; (2) whether C-CT or FLX further improved cognitive content relative to PBO (Figure 1, path B1); and (3) whether cognitive content mediated continuation treatments' effects on depressive symptoms and relapse/recurrence (Figure 1, path B2). To our knowledge, the current analyses were the first to test cognitive mediators of C-CT's effects in a randomized clinical trial.

Method

Participants

Data were drawn from a two-site randomized clinical trial described in detail by Jarrett and Thase (2010) and Jarrett et al. (2013a). Participants were outpatients who (a) provided written informed consent; (b) met criteria for recurrent MDD (American Psychiatric Association, 2000) on the Structured Clinical Interview (First et al., 1996); (c) had history of remission between depressive episodes, 1 depressive episode with complete inter-episode recovery, or antecedent dysthymic disorder; (d) scored ≥ 14 on the 17-item Hamilton Rating

Scale for Depression (HRSD; Hamilton, 1960)¹; and (e) were 18-70 years old. Exclusion criteria were (a) severe or poorly controlled concurrent medical disorders that could cause depression; (b) psychotic or organic mental disorders, bipolar disorder, active substance dependence, or primary obsessive-compulsive or eating disorders; (c) inability to complete questionnaires in English; (d) active suicide risk; (e) <18 or >70 years old; (f) history of non-response to 8 weeks of CT or 6 weeks of fluoxetine; and (g) pregnancy current or planned within 11 months post-intake. Participants ($N = 523$) were $M = 42.4$ ($SD = 12.1$) years old with $M = 15.1$ ($SD = 2.9$) years of education; 67.5% women; 80.9% white, 10.3% black, and 8.8% other races/ethnicities. Participants' age of MDD onset was $M = 21.2$ ($SD = 10.8$) years and their current depressive episode had lasted $M = 25.0$ (median = 10.0, $SD = 45.1$) months.

Acute phase

Patients taking psychotropic medications were withdrawn individually by their prescribing physicians or by a study physician before, and were not prescribed medications during, the acute phase. The 16 cognitive therapists had completed 1 year of CT training, submitted session videotapes for review, participated in group supervision/feedback sessions weekly, and demonstrated competence by maintaining Cognitive Therapy Scale (Young & Beck, 1980) scores ≥ 40 . The acute-phase CT protocol was 12 weeks, with 2 additional weeks allowed for rescheduling. Patients received twice-weekly CT sessions for 4 weeks. Then patients with $\geq 40\%$ reduction in HRSD scores received 8 weekly sessions (16 total sessions), whereas patients with less improvement in HRSD scores received 8 twice-weekly sessions before 4 weekly sessions (20 total sessions).² Patients with less early improvement received more CT sessions to increase their chance of response and eligibility for the continuation phase. Among 523 consenting, 292 patients responded to acute phase CT (no major depressive episode and final HRSD ≤ 12 ; a liberal response threshold was used because the trial design focused on relapse prevention; Jarrett & Thase, 2010).

Continuation Phase

Among 292 acute-phase CT responders, 241 with higher risk for relapse based on *a priori* criteria (≥ 1 of the last 7 acute-phase HRSD scores ≥ 7 ; Jarrett & Thase, 2010) consented to randomization to 8 months of continuation-phase CT (C-CT; $n = 86$), fluoxetine with clinical management (FLX; $n = 86$), or pill placebo with clinical management (PBO; $n = 69$).³

The C-CT protocol included 4 biweekly then 6 monthly (10 total) sessions, each approximately 60 minutes (Jarrett et al., 1989; Jarrett et al., 2008). C-CT patients were taught to apply compensatory skills to residual and emergent depressive symptoms; to generalize CT skills across situations, problems, and time; and to cope preemptively with

¹Due to a scoring error, 2 patients erroneously entered CT with HRSD = 13 at one of two diagnostic visits. During CT, one of these patients responded and one dropped out. As recommended by the Data Safety and Monitoring Board (DSMB), the two patients are analyzed here as they were treated during data collection.

²Four (1 early and 3 late) responders were misclassified as late and early responders, respectively. As recommended by the DSMB, they are analyzed here as they were treated during data collection.

³Three acute phase CT non-responders and one lower risk responder were randomized in error but are included here in intent-to-treat analyses (Jarrett et al., 2013).

cognitive and behavioral risks identified previously. With few exceptions (e.g., due to a therapist's maternity leave), patients' C-CT and acute-phase therapists were the same.

The FLX and PBO clinical-management protocol (Fawcett et al., 1987) was double-blinded, provided by experienced pharmacotherapists, and included 10 sessions on the same schedule as C-CT. Pharmacotherapists met with patients 30-45 minutes for the first, and 15-30 minutes for subsequent, sessions. Pharmacotherapists provided supportive contact focusing on signs and symptoms of depression, effects of medication, and information about depression but were prohibited from using specific C-CT methods. Research pharmacies dispensed active fluoxetine or identical placebo capsules for double-blinded administration. Patients received 10 mg/day for the first 2 weeks, 20 mg/day for 2 additional weeks, and 40 mg/day thereafter. Pharmacotherapists could decrease doses to reduce side effects. Patients intolerant to 10mg/day were withdrawn from medication and received only clinical management. Most patients (73%) achieved 40mg/day (Jarrett et al., 2013a).

Follow-up Phase

After the continuation phase, patients entered a 24-month follow-up. Blinded evaluators assessed patients every 4 months. Patients were encouraged to contact study staff for interim evaluation if they experienced depressive symptoms. Patients were referred out for treatment if they met criteria for MDD.

Cognitive Content Measures

Dysfunctional Attitudes Scale (DAS)—Patients completed the 40-item DAS (Form A; Weissman, 1979), rating statements about their self-concept, happiness, perfectionism, and depression-relevant thoughts and feelings on 7-point scales. Higher total scores indicate stronger and more pervasive dysfunctional attitudes. In support of its validity, the DAS differentiated persons diagnosed with depression from non-depressed controls (Otto et al., 2007; Nelson et al., 1992). Pooling data across assessments, the DAS showed high internal consistency (.95) in the current sample.

Attributional Style Questionnaire: Stable (ASQ-S) and Global (ASQ-G) Failure Attributions—Patients completed the revised ASQ (Dykema et al., 1996) by generating causes for 12 hypothetical negative events and rating the extent to which the events' causes were stable (vs. unstable) and global (vs. specific) on 7-point scales. Higher total scores reflect more stable and global failure attributions. Higher ASQ scores predicted acute and chronic depression (Riso et al., 2003), and poorer rehabilitation in cardiac patients (Bennett & Elliott, 2005), in support of the measure's validity. The ASQ stable (.88) and global (.85) scales showed moderate internal consistency in the current sample.

Beck Hopelessness Scale (BHS)—Patients completed the BHS, answering true/false to 20 items reflecting negative expectancies about the future (Beck & Steer, 1988; Beck et al., 1974). Higher total scores indicate greater hopelessness. BHS scores correlated positively with greater depression severity (Beck et al., 1975) and suicidality (Beck et al., 1985), in support of the measure's validity. The BHS showed high internal consistency (.92) in the current sample.

Self-Control Schedule (SCS)—On the SCS, patients rated 36 items tapping cognitive strategies, problem-solving strategies, delay of gratification, and belief in one's ability to regulate internal events on a 6-point scale. Higher total scores reflect learned resourcefulness and use of self-control methods to solve behavioral problems (Rosenbaum, 1980). In support the measure's validity, SCS scores correlated positively with confidence (Akgun, 2004) and response to CT (Burns, Rude, Simons, Bates, & Thase, 1994), and negatively with depressive symptoms (Slessareva & Muraven, 2004). The SCS showed moderate internal consistency (.89) in the current sample.

Depression Measures

Depressive symptom severity—Patients completed the 21-item Beck Depression Inventory (Beck et al., 1961) and 30-item Inventory for Depressive Symptomatology (Rush et al., 1986), and clinicians administered the 17-item HRSD. These measures are well-validated and marked the same symptom construct, both cross-sectionally and longitudinally, during treatment of MDD (Vittengl et al., 2005; Vittengl et al., 2013). Consequently, we standardized the three symptom measures based on their distributions at acute-phase intake and averaged them to form a robust symptom index. Higher scores indicated greater symptomatology. The symptom composite showed high internal consistency reliability (.95) in the current sample.

Relapse/recurrence—Independent evaluators completed the Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987) every 4 months post-acute-phase CT, at study exit, and when patients, therapists, or follow-up evaluators suspected major depressive relapse or recurrence. This semi-structured retrospective interview included weekly psychiatric status ratings of *DSM-IV* MDD. Ratings of 1 (no symptoms) or 2 (one or two mild symptoms) for 35 continuous weeks defined recovery, whereas ratings of 5 (meets MDD criteria) or 6 (meets MDD criteria with severe impairment and/or psychosis) for 2 weeks defined relapse and recurrence before and after recovery, respectively (Jarrett & Thase, 2010).

Non-protocol Treatment

The LIFE included weekly ratings (present or absent) of use of potentially mood-altering treatment outside the experimental protocol. Because non-protocol treatment was uncommon (Jarrett et al., 2013a), and to match the frequency of cognitive-content assessments, weekly ratings were collapsed into 4-month intervals, each scored as present or absent for non-protocol treatment.

Identification of Participants with Healthy Cognitive Content

We estimated proportions of patients with “healthy” scores on the BHS, DAS, and SCS using available norms. Following established cutoffs (Jarrett et al., 2007; Vittengl et al., 2014a), we identified patients within 1.28 *SD* of the normative mean in the pathological direction as “healthy” (i.e., about 90% of the normative population would be “healthy” and 10% “unhealthy”). Although more conservative than a cutoff of 2 *SD* from the mean, which would identify about 98% of the normative population as healthy, the 1.28 *SD* cutoff is consistent with the higher prevalence of MDD (Kessler et al., 2005). We used pooled adult

norms for the DAS ($M = 115.0$, $SD = 26.7$) and BHS ($M = 3.06$, $SD = 3.11$) from Dozois et al. (2003) and for the SCS ($M = 26.04$, $SD = 22.29$) from Vittengl et al. (2014a). We did not compute health estimates for the revised ASQ because few normative data were available.

Statistical Analyses

Appendix 1 shows descriptive statistics for the randomized sample on the current measures. To estimate means and proportions, and to test differences among treatments, we computed repeated-measures multilevel models using PROC GLIMMIX in SAS 9.3 software (SAS Institute, Inc.). Continuous outcomes (e.g., raw BHS scores) were modeled assuming a normal distribution and identity link function, whereas dichotomous outcomes (e.g., “healthy” vs. “unhealthy” BHS scores) were modeled assuming a binary distribution and logit link function. Models included fixed effects of continuation treatment and assessment time, the continuation treatment $\times$ time interaction, and receipt of non-protocol treatment as a covariate. The models’ error structures were compound symmetric. We computed effect size d and z scores with least-squares means estimated from these models and the SD of patients at acute-phase intake. To predict time to relapse/recurrence, we computed Cox regression analyses using PROC PHREG. Cox regression models excluded the non-protocol treatment covariate because patients were referred out for treatment if they relapsed/recurred during the follow-up phase.

Results

Levels of Depressive Cognitive Content

We predicted continuous scores on the five cognitive-content measures (BHS, DAS, SCS, ASQ-Stable, ASQ-Global) from assessment time (acute-phase CT intake, randomization, and approximately every 4 months after randomization through 32 months), continuation-phase treatment (C-CT, FLX, PBO), and the treatment-by-time interaction, controlling non-protocol treatment. Table 1 shows the main effects and interactions from multilevel models. The non-protocol treatment covariate was not significant, whereas the main effect of time was significant, in all models. Cognitive content was improved at all assessments throughout the experimental and follow-up phases relative to acute-phase intake (all pairwise contrasts $p < .01$) among acute-phase CT responders, with large effect sizes (mean d) for the BHS (1.38), DAS (1.28), SCS (1.21), ASQ-Stable (1.04), and ASQ-Global (1.06) (see Figure 2).

The main effect of continuation-phase treatment was significant only on the ASQ-Stable, with FLX patients (mean = 0.14) showing lower average scores than the C-CT (mean = 0.42, $d = 0.32$, $p = .02$) and PBO (mean = 0.49, $d = 0.39$, $p = .01$) groups, which did not differ ($p = .63$). However, the treatment-by-time interaction was not significant (see Table 1), indicating that differences between groups on the ASQ-Stable were relatively consistent and not clearly changed by starting or ending continuation treatments. Similarly, treatment-by-time interactions were not significant for the BHS, DAS, SCS, or ASQ-Global.

Patients with “Healthy” Cognitive Content

We predicted the proportion of patients with healthy-range cognitive content on the BHS, DAS, and SCS (see Table 1). The non-protocol treatment covariate was non-significant,

whereas the main effect of assessment time was significant, for all measures. The proportions of acute-phase CT responders scoring in the healthy range during the experimental and follow-up phases on the BHS (mean 78.2, range 72.6-83.2%), DAS (mean 90.1, range 86.4-93.1%), and SCS (mean 85.5, range 79.5-89.8%) were higher than at acute-phase intake, all pairwise contrasts $p < .01$ (see Figure 3). In addition, the main effect of treatment and the treatment-by-time interaction were not significant (see Table 1). Relative to large improvements from acute-phase intake to month 0 (randomization), proportions of healthy patients from months 0-32 fluctuated little.

Contrasts among Continuation Groups

Because the clinical trial was designed to test relapse prevention during the continuation phase, and durability of continuation treatments' effects during follow-up (Jarrett & Thase, 2010), we computed *a priori* contrasts of C-CT, FLX, and active treatment (C-CT or FLX) vs. PBO at months 4, 8, 20, and 32 (middle and end of the experimental phase, plus follow-up years 1 and 2) in the multilevel models of continuous scores. Only 4 of 60 contrasts were significant at $p < .05$, two-tailed: At month 4, FLX patients (mean = 0.08) had lower ASQ-Stable scores than did PBO patients (mean = 0.45), $d = 0.42$, $p = .04$. At month 8, C-CT (mean = 26.01), $d = 0.36$, $p = .0495$, and active treatment (C-CT or FLX; mean = 25.64), $d = 0.35$, $p = .03$, patients had higher SCS scores than PBO patients (mean = 16.70). Finally, at month 20, FLX patients (mean = 0.08) again had lower ASQ-Stable scores than did PBO patients (mean = 0.56), $d = 0.54$, $p = .02$. Thus, C-CT and/or FLX produced only small, transient improvements in cognitive content relative to PBO.

Mediation Tests

Lower ASQ-Stable scores among FLX patients at month 4, and higher SCS scores among C-CT and active treatment (C-CT or FLX) patients at month 8, compared to PBO, suggest possible mediation of the 8-month continuation treatments' effects, albeit by a subset of measures during limited periods. We tested mediation in three multilevel models predicting subsequent depressive symptoms in relevant treatment groups (see Table 2). Two of the three models provided some evidence of mediation with significant main effects of cognitive content. First, ASQ-Stable scores at month 4 ($r = .28$) predicted subsequent depressive symptoms among FLX and PBO patients. In addition, SCS scores at month 8 ($r = -.22$) predicted subsequent depressive symptoms among C-CT and PBO patients. However, SCS scores at month 8 ($r = -.13$) did not significantly predict subsequent depressive symptoms among active treatment (C-CT or FLX) and PBO patients. Moreover, all mediators became non-significant ($ps > .34$) after adding depressive symptoms assessed concurrently with cognitive content to the models (i.e., so that the models predicted subsequent *changes* in depressive symptoms).

We also computed three Cox-regression models testing mediation of C-CT and FLX's effects on relapse/recurrence. Parallel to models in Table 2, we predicted relapse/recurrence after the cognitive-content assessment showing group differences. Model predictors were the cognitive-content measure, the relevant treatment-group contrast, and the cognitive content-by-treatment interaction. The potential mediators' main effects and interactions were non-significant in all models ($ps > .11$).

Discussion

The current analyses clarified the durability of improvements in cognitive content among responders to acute-phase CT, the effects of 8-month continuation-phase treatments (C-CT, FLX, or PBO) on cognitive content, and whether cognitive content mediated continuation-phase treatments' effects on depressive symptoms and relapse/recurrence. Consistent with past research, we found that large gains during acute-phase CT in five measures of cognitive content were largely maintained across 32 months (8-month continuation plus 24-month follow-up phases). Moreover, most acute-phase CT responders maintained scores in the healthy range on the BHS, DAS, and SCS for 32 months (means 78-90%). Thus, responders' improvements in cognitive content during acute-phase CT were clearly durable.

Previous analyses showed that C-CT and FLX each reduced relapse and residual symptoms compared to PBO, as long as treatments were active (Jarrett et al., 2013a; Vittengl et al., 2014b). However, in the current analyses, the continuation-phase arms produced few differences in cognitive content. Whether C-CT, FLX, and PBO helped to maintain gains in cognitive content similarly is unclear because the trial lacked an assessment-only control. However, a prior trial found similar durability in improvements in cognitive content made during acute-phase CT in both assessment-only and C-CT arms across 24 months, with few differences between arms (Jarrett et al., 2007). Consequently, we speculate that the current continuation conditions have little effect on cognitive content and most of the clinically significant change occurs earlier during acute phase CT.

We found a few, small differences in cognitive content among continuation-treatment groups, all in hypothesized directions. In particular, FLX patients had lower ASQ-Stable scores at months 4 and 20, and C-CT and active treatment (C-CT or FLX) patients had higher SCS scores at month 8, compared to PBO. The findings at months 4 and 8, when continuation treatments were active, suggested possible mediation (Kraemer et al., 2002). Supporting partial mediation, ASQ-Stable scores at months 4 predicted subsequent depressive symptoms among FLX and PBO patients, and SCS scores at month 8 predicted subsequent depressive symptoms among C-CT and PBO patients.

However, the mediators' effects on depressive symptoms were small, accounted for by residual depressive symptoms, and did not extend to relapse/recurrence. Limited evidence for cognitive mediation of C-CT's effects parallels limited evidence for cognitive mediation of acute-phase CT's effects in the current (Vittengl et al., 2014a) and other (e.g., Jarrett et al., 2007) analyses of self-report measures. Although self-reported cognitive content may not strongly mediate CT's effects, depressive cognitive content measured after acute-phase CT response predicts poorer longitudinal outcomes (e.g., Vittengl et al., 2010; Vittengl et al., 2015) and thus signals need for additional treatment or clinical monitoring.

Qualities of our methods and sample limit our conclusions. First, negative-mood induction before assessment may reveal additional depressive cognition (Dunkley, Blankstein, & Segal, 2010), but patients were not primed before assessment in the current analyses. Only unprimed (not primed) DAS scores predicted relapse in the current dataset (Jarrett et al., 2012), however. Similarly, non-verbal assessments of depression-related cognition (e.g.,

reaction time, imaging studies; Lim & Kim, 2005; Siegle et al., 2006) may better differentiate cognitive content from depressive symptom measures and diagnostic criteria than do the self-reports used here. Second, we assessed cognitive content about every 4 months. More frequent assessment might reveal more time-limited continuation-treatment-group differences and mediation processes (Forman et al., 2012). Third, our design did not include an assessment-only (no treatment) control, possibly limiting detection of changes in cognitive content relative to depression-specific (C-CT and FLX) and non-specific (PBO with clinical management) treatments. Fourth, our patient sample had carefully diagnosed recurrent MDD, responded to acute phase CT with higher risk for relapse, and was treated by proficient cognitive and pharmacological therapists in a research protocol. The extent to which our findings generalize to different patient populations (e.g., CT non-responders, chronically depressed), treatments (e.g., acute-phase medication, combined CT and medication), and routine clinical practice is unclear. For example, not working for pay, less frequent use of CT skills, poorer social functioning, and a history of fewer depressive episodes predicted non-response to acute-phase CT in the current dataset (Jarrett et al., 2013b). Other variables (e.g., biochemical, genetic) may also distinguish non-responders and limit the generalizability of our findings concerning acute-phase CT responders.

Meta-analyses show that C-CT for depression has preventive effects greater than treatment-as-usual and non-active controls, and equal to or greater than active medication (Biesheuvel-Leliefeld et al., 2015; Vittengl et al., 2007). Similarly, C-CT reduced residual symptoms and relapse compared to PBO in the current dataset (Jarrett et al., 2013a; Vittengl et al., 2014b). Although hypothesized in the cognitive model, the importance of cognition in CT's preventive effects is unclear (Lorenzo-Luaces et al., 2014). Our analyses extended the literature by showing that improvements in patient-reported cognitive content made during acute-phase CT are durable for 32 months. However, we also found that C-CT and FLX had only small effects on cognitive content relative to PBO, and cognitive content weakly mediated the continuation treatments' preventive effects. Further clarification of cognitive mediation may require methodological advancements, including measures of cognition more distinct from depressive symptoms, more frequent measurement during treatment, and patient populations with high variability in cognitive and outcome variables (Biesheuvel-Leliefeld et al., 2015). Nonetheless, monitoring cognitive content and residual depressive symptoms is important clinically to predict longitudinal outcomes and need for retreatment (Brown et al., 2000; Vittengl et al., 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The current analyses tested the extent to which continuation cognitive therapy or fluoxetine's effects on residual symptoms and relapse/recurrence (path A) are mediated by cognitive content. We tested whether continuation cognitive therapy or fluoxetine improved cognitive content relative to placebo (path B1), and the extent to which cognitive content accounted for subsequent outcomes (path B2). Other variables not analyzed here may also mediate the continuation treatments' effects (path C1, C2).

Figure 2.

Patients with unstable response to acute-phase cognitive therapy ($N = 241$) showed large, relatively stable decreases in depressive cognitive content maintained through 8 months of continuation phase treatment (randomization at month 0 to cognitive therapy, fluoxetine, or pill placebo) and 24 months of follow-up. Self-control Schedule scores are reflected so that lower scores mark reductions in depressive cognitive content.

Figure 3.

Proportions of patients ($N = 241$) with normative cognitive content increased substantively during unstable response to acute-phase cognitive therapy and remained relatively stable through 8 months of continuation phase treatment (randomization at month 0 to cognitive therapy, fluoxetine, or pill placebo) and 24 months of follow-up.

Table 1
Prediction of Cognitive Content through Acute, Continuation, and Follow-up Phases

Measure	Non-protocol treatment covariate			Assessment time main effect			Continuation treatment main effect			Treatment × time interaction		
	df	F	p	df	F	p	df	F	p	df	F	p
Continuous Scores												
BHS	1, 1170	0.74	.391	9, 1170	102.91	<.001	2, 235	0.20	.821	18, 1170	1.48	.088
DAS	1, 1211	0.14	.713	9, 1211	95.21	<.001	2, 238	0.50	.609	18, 1211	0.84	.654
SCS	1, 1180	0.00	.999	9, 1180	72.07	<.001	2, 234	0.38	.682	18, 1180	1.27	.196
ASQ-Stable	1, 1165	2.90	.089	9, 1165	40.55	<.001	2, 234	4.04	.019	18, 1165	1.38	.133
ASQ-Global	1, 1166	0.38	.536	9, 1166	35.85	<.001	2, 234	1.93	.147	18, 1166	0.74	.769
Proportion Healthy												
BHS	1, 1172	0.21	.650	9, 1172	34.60	<.001	2, 235	0.71	.491	18, 1172	1.21	.244
DAS	1, 1212	3.09	.079	9, 1212	27.52	<.001	2, 238	0.30	.741	18, 1212	0.49	.964
SCS	1, 1180	0.61	.437	8, 1180	25.47	<.001	2, 234	0.21	.808	18, 1180	0.91	.567

Note. $N = 241$ patients who had unstable response to acute-phase cognitive therapy and were randomized to 8 months of continuation treatment (cognitive therapy, fluoxetine, or placebo) and followed up to 24 additional months. The 10 assessments occurred at intake to acute-phase cognitive therapy and approximately every 4 months thereafter. Tabled results are from repeated-measures multilevel models. BHS = Beck Hopelessness Scale. DAS = Dysfunctional Attitudes Scale. SCS = Self-control Schedule. ASQ = Attributional Style Questionnaire.

Table 2
Mediation Tests: Prediction of Subsequent Depressive Symptoms from Prior Cognitive Content

Effect	Model 1			Model 2			Model 3		
	df	F	p	df	F	p	df	F	p
Non-protocol treatment covariate	1, 419	8.36	.004	1, 340	0.01	.935	1, 533	0.69	.408
Assessment time main effect	6, 419	0.88	.509	5, 340	1.20	.308	5, 533	1.48	.194
Continuation treatment main effect	1, 92	0.56	.457	1, 82	0.32	.574	1, 128	0.04	.833
Time × treatment interaction	6, 419	1.12	.349	5, 340	1.29	.270	5, 533	0.78	.567
Mediator variable main effect	1, 92	7.99	.006	1, 82	3.98	.049	1, 128	2.13	.147
Time × mediator interaction	6, 419	0.93	.474	5, 340	0.60	.697	5, 533	0.41	.845
Treatment × mediator interaction	1, 92	0.89	.347	1, 82	1.07	.304	1, 128	0.09	.761
Time × treatment × mediator interaction	6, 419	1.19	.310	5, 340	0.54	.747	5, 533	0.23	.948

Note. Depressive symptoms (DEP) and cognitive content assessed at randomization and every 4 months during the 8-month experimental and 24-month follow-up phases. SCS = Self-control schedule. ASQ = Attributional Style Questionnaire. C-CT, FLX, and PBO = continuation phase cognitive therapy, fluoxetine, and pill placebo, respectively. Active = C-CT or FLX.