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Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators

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Summary

Cognitive behavioral therapy (CBT) has been found superior to control conditions and as least as efficacious as other psychotherapies and antidepressant medication (ADM) in the acute treatment of depression. When adequately implemented, CBT can be as efficacious as ADM for patients with more severe depressions. CBT may also be of use as an adjunct to medications in the treatment of bipolar disorder, although the evidence there is not so clear or extensive. CBT reduces relapse/recurrence rates, with a magnitude of effect that might be comparable to keeping patients on medications, which is particularly noteworthy in a chronic recurrent disorder. Patients who are married or show low levels of pretreatment dysfunctional attitudes seem to be more likely to respond to CBT than patients who are unmarried or show high levels of dysfunctional attitudes. Unemployment, more antecedent life events and previous ADM exposures, and the absence of Axis II comorbidity are prescriptive factors associated with better response to CBT compared with medications. CBT seems to work through concrete CT-specific strategies and may be mediated by changes in cognition as specified by theory, although it remains unclear whether it is necessary to deal directly with cognition to produce those changes.

Introduction

Clinical depression is one of the most common and debilitating of the psychiatric disorders (Murray & Lopez, 1997). Lifetime prevalence has been estimated at 16.2% and rates of comorbidity and risk for suicide are high (Kessler et al., 2003). Up to one-third of all patients have episodes that last longer than 2 years, and more than three-quarters of all patients who recover from one episode go on to have at least one more (Keller, 2001). Although there are efficacious treatments for depression, many patients do not receive adequate treatment, and still more are refractory to available interventions (Rush et al., 2004).

Depression can be defined as a syndrome and a disorder. As a syndrome it involves episodes of sadness, loss of interest, pessimism, negative beliefs about the self, decreased motivation, behavioral passivity, suicidal thoughts and impulses, and changes in sleep, appetite, and sexual interest. As a disorder it comes in 2 forms. The unipolar type, which affects approximately 10% of men and 20% of women, includes only episodes of depression. Heritability estimates for unipolar depression have ranged from approximately 25% in less severe samples up to 50% in more severe samples (DeRubeis, Young, & Dahlsgaard, 1998). In the bipolar form, which is commonly known as manic depression, patients also (or exclusively) experience episodes of mania or hypomania that are in many ways the opposite of depression. Manic episodes are marked by euphoria or irritability, sleeplessness, grandiosity, recklessness, and uncontrollable impulses that can lead to buying sprees and sexual promiscuity (American Psychiatric Association [APA], 2000a).

Cognitive behavioral therapy (CBT) refers to a family of interventions that are among the best-known empirically supported treatments for depression. There are several different specific interventions that vary in their constituent components, with cognitive therapy (CT) being the most widely practiced, but all these interventions are closely related and the terms CBT and CT are used interchangeably in this article. CBT is based on the premise that inaccurate beliefs and maladaptive information processing (forming the bases for repetitive negative thinking) have a causal role in the cause and maintenance of depression. This cognitive model posits that when maladaptive thinking is corrected, acute distress and the risk for subsequent symptom return are reduced (Beck, Rush, Shaw, & Emery, 1979). This article focuses on the efficacy of individual CBT in the treatment of acute phase depression and the prevention of subsequent symptom return in adult populations, with an emphasis on the moderation and mediation of response.

The efficacy of CBT in the acute phase of depression

Meta-analytic findings

CBT has a medium effect size (d = 0.67) relative to a variety of control conditions ranging from the absence of treatment to nonspecific controls (Cuijpers et al., 2012). Translated into numbers needed to treat (NNT), this effect size corresponds to an NNT

of 2.75; this means that for just less than every 3 patients treated with CBT, one will get better solely because of having come into therapy. By way of comparison, medication treatment of severe hypertension produces an NNT of 15 and taking aspirin alone for myocardial infarction produces an NNT of 40 relative to no treatment (see NNT readings at http://www.evidence-based-medicine.co.uk). Effect sizes tend to be larger when CBT is compared with wait-list controls (d = 0.88) than when CBT is compared with care-as-usual (d = 0.38) or nonspecific controls (d = 0.38; Cuijpers et al., 2012). These findings suggest that CBT is more efficacious than its absence and somewhat more efficacious than the mobilization of hope and therapist contact. Effect sizes tend to be lower in high-quality studies or when corrected for publication bias (Cuijpers et al., 2012). It has been reported that the efficacy of CBT when delivered individually did not differ from the efficacy of a group format (d = 0.15, nonsignificant [ns]), but the quality of the relevant studies is low, limiting our confidence in this conclusion (Cuijpers, van Straten, & Warmerdam, 2001).

Gloaguen, Cottrauxa, Cucherata, and Blackburn (1998) found CBT superior to an assortment of other psychotherapies, but this estimate was likely inflated by the inclusion of nonbona fide therapies intended only to control for nonspecific factors (Wampold, Minami, Baskin, & Callen Tierney, 2002). This is in line with Cuijpers et al. (2012), who found no significant differences when comparing CBT with other psychotherapies. Gloaguen et al. (1998) also found CBT moderately superior to antidepressant medication (ADM); however, this estimate was likely to be inflated by the inclusion of early studies that did a questionable job of implementing pharmacotherapy (Butler, Chapman, Forman, & Beck, 2006). For example, Rush, Beck, Kovacs, and Hollon (1977) found CBT superior to the ADM imipramine in the treatment of depressed outpatients, but started medication withdrawal 2 weeks before the end of treatment, and Blackburn, Bishop, Glen, Whalley, and Christie (1981) found CBT superior to either amitriptyline or clomipramine in a general practice sample, but had such a poor response to ADM (14%) as to raise questions about the adequacy of the pharmacotherapy as implemented by the general practitioners. Subsequent studies that implemented pharmacotherapy more adequately typically found comparable outcomes between CBT and ADM (Murphy, Simons, Wetzel, & Lustman, 1984; Hollon et al., 1992). This result is in line with findings of a more recent meta-analysis by Cuijpers et al. (2012) that suggests that CBT and ADM are equally efficacious in the treatment of major depression.

Combining CBT with ADM results in higher effect sizes than medication alone (d = 0.27, P<.05; NNT = 6.58; Cuijpers et al., 2012). This finding means that the combination produces a modest increment compared with medication monotherapy; combining CBT with ADM improves acute response for 1 out of nearly every 6 patients. Combined treatment produces only a small nonsignificant effect relative to CBT alone (d = 0.15; ns; NNT = 11.9), an effect about half the magnitude of adding CBT to medications (Cuijpers et al., 2012). However, these estimates are based on controlled treatment trials that often provide greater training and supervision than is the case in practice. Whether most patients have access to comparably trained CBT therapists is a matter

of conjecture. Combining medications with CBT as typically practiced in applied settings may enhance treatment response.

CBT has been found to work better than its absence and may work for specific reasons. CBT seems to be at least as efficacious as other active treatments, including medications. Adding CBT to ADM has resulted in a modest improvement of efficacy. The benefits of adding medication to CBT relative to CBT alone have been less apparent, although these effects might be larger in applied clinical practice than in the controlled setting of a treatment trial.

CBT for severe depression

The National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP) was the first major trial comparing CBT with a pill-placebo control and the results were not supportive of CBT. Although there were no differences across the full sample (Elkin et al., 1989), CBT was no more efficacious than pill-placebo and less efficacious than either the ADM imipramine or interpersonal psychotherapy (IPT) among patients with more severe depressions (Elkin et al., 1995). The results of the TDRCP had a major effect on the field, because of the size of the sample and the rigor of the design. It led many to conclude that CBT was not efficacious with more severe depressions, and subsequent guidelines strongly suggested that such patients should not be treated with psychotherapy alone (APA, 2000b).

Despite the rigor of its design, questions have been raised about the adequacy of the implementation of CBT in the TDCRP (Jacobson & Hollon, 1996a). Outcomes for CBT varied considerably across the 3 study sites, with CBT performing no better than pill-placebo at the 2 sites with less experienced therapists and as well as ADM at the remaining site, where the cognitive therapists had previous experience with the approach (Jacobson & Hollon, 1996b). Subsequent placebo-controlled trials that have implemented CBT more successfully have shown it to be comparable with ADM and each superior to pill-placebo controls. For example, Jarrett et al. (1999) found CT as efficacious as phenelzine (a monoamine oxidase inhibitor [MAOI]) for the treatment of atypical depression. This group has worked closely with the Beck Institute in Philadelphia to ensure that their cognitive therapists were well trained and had session tapes rated for competence by an off-site consultant expert in the approach. Similarly, MAOIs are the medications of choice for atypical depression and were prescribed at dosage levels that were appropriate.

DeRubeis et al. (2005) attempted a direct replication of the TDCRP with respect to the comparison between CBT and ADM among more severely depressed patients. Patients who met the TDCRP criterion for moderate to severe depression (scores of 20 or above for 2 consecutive weeks on the Hamilton Depression Rating Scale [HDRS]) were randomly assigned to 16 weeks of either CBT or paroxetine pharmacotherapy or 8 weeks of pill-placebo (a sufficient length of time to establish drug-placebo differences). Paroxetine is generally considered the best of the selective serotonin reuptake inhibitors for dealing with patients with more severe depressions. In addition, patients in the ADM condition who were not fully responsive by the end of 8

weeks of treatment were augmented with either lithium or desipramine through the end of the 16-week trial. This is a more aggressive pharmacotherapy regime than is typically used in short-term treatment trials. The study was conducted at 2 sites, one of which was the original home of CT (University of Pennsylvania), whereas the other had less experienced cognitive therapists (Vanderbilt University). Ratings conducted by experts at the Beck Institute suggested that the less experienced cognitive therapists at Vanderbilt were not performing at the same level of competence as the more experienced cognitive therapists at Penn. Therefore, the Vanderbilt therapists were provided with additional training through the extramural training program at the Beck Institute during the early years of the trail.

CBT and paroxetine pharmacotherapy were superior to pill-placebo across the first 8 weeks of the trial and virtually identical to one another by the end of the full 16-week acute treatment period. There were differences between the sites, with CBT showing a nonsignificant advantage relative to ADM at Penn and ADM performing significantly better than CBT at Vanderbilt. Differences between the sites were more pronounced in the beginning of the trial, with the less experienced cognitive therapists at Vanderbilt catching up with their more experienced colleagues at Penn across time with respect to competence ratings and patient outcomes. There also were indications that patients with comorbid Axis II disorders did better on ADM than they did in CBT, whereas the opposite was true for patients without Axis II disorders (Fournier et al., 2008). Patients with Axis II disorders constituted a larger portion of the sample at Vanderbilt and differences in patient composition and therapist experience largely explained the differences between the sites. These findings suggest that CBT can be as efficacious as ADM with more severely depressed patients if provided by experienced cognitive therapists who are competent to implement that modality.

Dimidjian et al. (2006) found a pattern of results in a subsequent placebo-controlled trial that was reminiscent of the one found in the TDCRP, but that might still be consistent with the notion that competence matters with respect to CBT for more severely depressed patients. In that trial, patients with major depression representing a full range of severity were randomly assigned to 16 weeks of CBT, behavioral activation (BA), paroxetine pharmacotherapy (without augmentation), or pill-placebo (8 weeks only). As in the TDCRP, there were no differences between any of the treatment conditions among less severely depressed patients. Among the more severely depressed patients (those with HDRS scores of 20 or greater), ADM and BA were found to be superior to either pill-placebo (at week 8) or CBT (at week 8 and week 16). The advantage of BA compared with CBT was largely a consequence of a subset of patients who showed an extremely poor response to CBT (Coffman, Martell, Dimidjian, Gallop, & Hollon, 2007). These patients were severely depressed, functionally impaired, and had problems with their primary support group; most also described themselves as having lifelong depressions. Although Dimidjian et al. (2006) did not assess the full array of personality disorders (PDs), these patients were similar in many respects to the Axis II patients who did poorly in CBT in the Penn/Vandy trial (Fournier et al., 2008). There were as many such patients in that earlier study and although they did not do well in CBT, they did not show the extreme nonresponse that

they showed in the study by Dimidjian et al. (2006). The cognitive therapists started the Dimidjian et al. (2006) study with about the same level of experience as the less experienced cognitive therapists at the Vanderbilt site in the DeRubeis et al. (2005) study, but did not have the advantage of the additional training through the Beck Institute during the study proper.

CBT seems to be as efficacious as ADM in the treatment of depression. Two studies found that CBT performed less well than either ADM or an other psychotherapy among more severely depressed patients (Elkin et al., 1995; Dimidjian et al., 2006). It is not clear that the cognitive therapists were experienced with the approach in those 2 trials and CBT has performed as well as ADM in other placebo-controlled trials when therapist experience was not an issue (Jarrett et al., 1999; DeRubeis et al., 2005). Thus, CBT seems to work as well as ADM for more severely depressed patients, if conducted by well-trained therapists.

It is not clear how much experience and training is necessary to ensure therapist competence but it does seem that much of the variation in the CBT literature is related to the skill with which the modality is implemented. We have emphasized the role played by such variability in determining outcomes in the handful of placebo-controlled trials precisely because they are the most influential studies found in the literature and (one would hope) the most carefully conducted. The bulk of these trials were efficacy studies and it is likely that variability is even greater (and competence less likely to be assured) in the effectiveness literature. Those studies that found the best outcomes for CBT typically selected experienced cognitive therapists (as at the University of Pennsylvania) or provided extended training coordinated with the Beck Institute in Philadelphia (as at the Vanderbilt site in that same study or in the study of atypical depression); studies that depended on more limited training and off-site supervision typically produced less impressive findings relative to alternative interventions (especially medications). These differences were most apparent with severe and complicated patients and it is likely that therapist competence is more an issue with such patients because that is where treatment differences are usually found. How much training and supervision are required and whether it varies as a function of patient difficulty are issues that deserve further exploration.

Cognitive behavioral analysis system of psychotherapy for chronic depression

The cognitive behavioral analysis system of psychotherapy (CBASP) was developed specifically for the treatment of chronic depression and combines techniques from cognitive, behavioral, psychodynamic and interpersonal psychotherapies. It shares with CBT its structured approach, the use of homework assignments, and the systematic focus on assessing and changing behaviors or interpretations of a situation. It differs from CBT, however, by its primary focus on interpersonal interaction. Keller et al. (2000) compared the efficacy of CBASP with that of nefazodone, and with the combination of CBASP and nefazodone, and found that after 12 weeks of acute treatment CBASP and nefazodone resulted in equal response rates (both 48%), whereas combined treatment significantly outperformed both monotreatments (response rate 73%). However, these analyses were based on a modified intention-to-

treat in which patients who either did not start treatment or who could not achieve a minimum dose of 300 mg of nefazodone per day by week 3 were dropped from the analyses; it would have been better if the analyses had been conducted on the full intention-to-treat sample.

CBT to prevent relapse and recurrence

Depression is a chronically recurrent disorder. Although up to two-thirds of all patients respond to acute treatment with ADM (about half of whom fully remit), a sizable number experience a return of symptoms after treatment is over (Hollon, Thase, & Markowitz, 2002). According to conventions developed in the pharmacotherapy literature, symptom return during the first 6 to 12 months among remitted patients is assumed to represent a return of the treated episode (relapse) and treatment provided during that interval is called continuation treatment. Patients who go more than 12 months without relapse following remission are said to be recovered; symptom return following that interval among recovered patients is said to represent the onset of a wholly new episode (recurrence), and treatment provided after the end of that interval is called maintenance treatment (Frank et al., 1991). Although ADM can suppress the expression of symptoms (a purely palliative effect), there is no evidence that it can shorten the duration of the underlying episode or reduce subsequent risk for recurrence (Hollon et al., 2002), and current medical practice calls for keeping patients with a history of recurrent or chronic depression on medication indefinitely (APA, 2000b). On the other hand, if CBT has an enduring effect it can be said to be more than purely palliative (Hollon, Stewart, & Strunk, 2006). Whether it is truly curative depends on how long this enduring effect can be said to last and how and to what extent it prevents subsequent episodes.

Enduring effects of CBT

There is evidence that CBT has an enduring effect that lasts beyond the end of treatment. Among patients who respond to acute treatment, relapse rates are lower following treatment termination after acute CBT than after acute ADM and also lower for patients treated with combined treatment than for patients treated with ADM alone (Vittengl, Clark, Dunn, & Jarrett, 2007). This finding suggests that it is not so much the withdrawal of medication that provokes relapse in remitted patients as that previous exposure to CBT prevents it. It remains unclear whether this effect is specific to CBT, because other psychotherapies have rarely been tested against medication withdrawal.

A pair of recent studies found that the magnitude of the enduring effect of CBT was at least as large as keeping patients on continuation ADM (Hollon et al., 2005; Dobson et al., 2008). In both these studies patients who responded to CBT were essentially withdrawn from that treatment and compared with ADM responders randomized to either ADM continuation or withdrawal onto pill-placebo. CBT responders were significantly less likely to relapse following treatment termination than ADM

responders withdrawn from ADM and no more likely to relapse than ADM responders kept on continued medication. Both studies found previous CBT superior to medication withdrawal even after patients were continued on ADM for up to a year after initial response.

Although these results suggest that previous exposure to acute CBT prevents subsequent symptom return, it is possible that these findings may be an artifact of differential mortality. As described by Klein (1996) acute treatment may act as a differential sieve if high-risk patients are more likely to respond to one treatment than another. Although there is no evidence that this was the case in either study, the fact that only about half of the patients initially randomized completed and responded to treatment leaves open the possibility that what seems to be an enduring effect might be nothing more than the differential retention of high-risk patients. Therefore, although the existing evidence is consistent with the notion that CBT has an enduring effect, it is less than wholly conclusive.

Studies that provide CBT following the end of acute treatment are not subject to the possible biasing effects of differential mortality as long as all patients receive the same acute phase treatment. Fava, Rafanelli, Grandi, Conti, and Belluardo (1998) found that adding a version of CBT including well-being therapy and lifestyle modification resulted in lower subsequent recurrence rates following medication discontinuation among patients with recurrent depression who were first treated to recovery with ADM, with enduring effects evident up to 6 years later (Fava et al., 2004). Similarly, Paykel et al. (1999) found that adding CBT reduced rates of relapse and subsequent recurrence relative to ADM alone in patients with residual depressive symptoms following initial medication treatment, with enduring effects found up to 3.5 years after the completion of CBT (Paykel et al., 2005). Bockting et al. (2005) found that among patients in remission after various types of treatment adding CBT resulted in significantly lower rates of relapse/recurrence than treatment-as-usual (TAU) alone for patients with a history of 5 or more depressive episodes; no such differences were evident for patients with fewer than 5 previous episodes. In a pair of studies (Teasedale et al., 2000; Ma & Teasdale, 2004), Teasdale and colleagues found that adding mindfulness-based CT (MBCT) reduced subsequent rates of relapse/recurrence relative to TAU in a 1-year period for patients with 3 or more previous episodes of depression; no such differences were evident for patients with 2 or fewer previous episodes. MBCT is a group intervention that combines CBT with meditation techniques aimed at teaching patients to relate to depressive thoughts and feelings as mental events, rather than as accurate reflections of reality, to prevent relapse as a result of dysphoric mood. Only Perlis et al. (2002) failed to find an advantage for adding CBT, but did so in the context of providing ongoing ADM with dose increase for all patients that should have reduced rates of relapse and recurrence regardless of whether CBT was added. These studies suggest that CBT has an enduring effect that is robust to the biasing effects of differential mortality.

CBT as a continuation and maintenance treatment

In addition to the enduring effects of acute CBT treatment, research has focused on the efficacy of keeping patients in CBT after they first respond to that treatment. Jarrett et al. (2001) focused on whether extending the duration of CBT adds to the efficacy of acute treatment by comparing CBT with and without a continuation phase for CBT responders with a history of recurrent depression. During the ensuing 8 months significantly fewer patients relapsed when CBT was continued than when it was not. Patient characteristics moderated the effects of extending CBT for the full 24-month follow-up period such that patients with an earlier age of depression onset or who showed an unstable pattern of remission were less likely to relapse or recur if provided with continuation/maintenance treatment than if not, whereas extending CBT treatment did not matter for patients with a later age of depression onset or who showed a stable pattern of remission. These findings suggest that extending CBT might be necessary only for patients at higher risk for relapse. Jarrett et al. (2000) also examined the efficacy of CBT as continuation treatment after acute treatment of patients with atypical depression, but sample sizes were so small that no meaningful conclusions could be drawn.

Klein et al. (2004) examined the efficacy of CBASP as a maintenance treatment of chronic depression. Treatment responders to 12 weeks of acute and 16 weeks of continuation CBASP treatment in their earlier trial were randomly assigned to CBASP maintenance treatment versus an assessment-only control. Over 52 weeks, CBASP maintenance treatment resulted in lower recurrence rates. Moreover, patients in the CBASP condition experienced a small reduction in depressive symptoms, whereas depressive symptoms increased somewhat for patients in the control condition. This sample consists solely of patients who showed a sustained response to CBASP (all chronically depressed). For this group of patients CBASP maintenance treatment after 28 weeks of acute and continuation phase treatment seems more efficacious than its absence.

Three studies focused on the efficacy of CBT continuation treatment compared with ADM continuation. First, Blackburn, Eunson, and Bishop (1986) compared 6 months of continuation treatment with CBT or ADM or their combination for patients who had responded to acute phase treatment in those same modalities. No differences were found across the 6 months of continuation treatment, suggesting a continuation effect of CBT comparable with medication. Across a 2-year follow-up (the last 18 months of which was treatment free) the number of patients who relapsed or recurred was significantly higher following withdrawal from medication alone than for previous CBT with or without medication, suggesting an enduring effect of CBT. However, given that patients were randomized to different treatments during the acute phase, it is possible that acute treatment could have served as a differential sieve that systematically unbalanced the groups of treatment responders and thereby produced a spurious enduring effect that accounted for the results observed. Second, Blackburn and Moore (1997) examined the relative efficacy of CBT and ADM maintenance treatments. Patients were randomly assigned to acute ADM followed by maintenance ADM, acute ADM followed by maintenance CBT, and acute CBT followed by maintenance CBT.

There were no differences in the reduction of acute phase symptoms and no significant differences between maintenance CBT and maintenance ADM, regardless of whether maintenance CBT followed acute treatment with CBT or with ADM. These results suggest that maintenance CBT can have prophylactic effects similar to maintenance ADM, although it is always treacherous to draw causal inferences from null findings in a small sample, and medication doses were reduced during the maintenance phase. Although maintenance CBT may be as efficacious as maintenance ADM, these studies do little to contribute to our confidence, for the reasons cited.

Kuyken et al. (2008) compared MBCT plus ADM discontinuation with ADM maintenance treatment in patients with a history of multiple depressive episodes who were fully or partially remitted after initial treatment with ADM. No significant differences in relapse/recurrence rate were found over a 15-month period. Only about three-quarters of the MBCT patients discontinued medications, but that group contained most of the high-risk patients, and comparisons between those in the MBCT group who did discontinue and patients in the ADM maintenance group who were fully compliant also found no differences. Although MBCT might be as efficacious as keeping patients on continuation ADM, methodological problems limit the interpretation of similar findings with regard to CBT.

CBT to prevent relapse in bipolar disorder

Whereas the distinction between relapse and recurrence is relevant to unipolar depression (patients are either in episode and thus at risk for relapse when asymptomatic or not in episode and thus at risk for recurrence), bipolar disorder is thought of as a chronic disorder that never goes away and is marked by periodic symptomatic relapses into mania and depression. Although stabilization on medications is the cornerstone of treatment of bipolar disorder, there has been considerable interest in recent years in using CBT to treat existing symptoms (particularly depression) and to prevent subsequent relapse when euthymic. In addition to such general features as examining the accuracy of dysfunctional beliefs and improving communication and problem-solving skills, CBT also focuses on teaching skills to cope with prodromes (periods when symptoms first emerge but have not yet reached maximum severity) and disruption of routines (especially sleep) that contribute to the onset of an episode in bipolar disorder. These are features that it shares with other promising adjunctive psychosocial interventions like interpersonal social rhythm therapy and family-focused therapy (Miklowitz et al., 2007). In a pilot study, Lam et al., (2000) found that adding CBT reduced the frequency of bipolar episodes across the following year relative to TAU alone in euthymic bipolar I patients who continued to have relapses despite the use of mood stabilizers, but were not currently facing an acute bipolar episode. These investigators subsequently replicated this finding in a larger sample across the course of a 1-year (Lam et al., 2003) and 2-year follow-up, although the differential relapse prevention effects occurred mainly in the first year after treatment (Lam, Hayward, Watkins, Wright, & Sham, 2005). CBT

patients also reported fewer days in episode and better mood ratings, social functioning, and coping with bipolar prodromes. Subsequent studies typically found benefits for CBT compared with TAU in medicated patients, either at the level of a nonsignificant trend (Ball et al., 2006) or in terms of days free from depression and reductions in medication use (Zaretzky, Lancee, Miller, Harris, & Parikh, 2008).

A recent multicenter trial by Scott et al. (2006) largely failed to replicate these effects. These investigators studied a more heterogeneous sample, including patients who were currently in episode, and found that the addition of CBT did not result in lower relapse rates or symptom levels for the full sample. Post hoc analyses did suggest an interaction with previous episodes (moderation), such that adding CBT was significantly more effective for patients with fewer than 12 previous episodes, but less efficacious for those with 12 or more previous episodes. This finding led the investigators to conclude that CBT might be helpful for only the minority of bipolar patients with relatively fewer previous episodes, and the investigators of a recent meta-analysis to conclude that CBT was of little use for bipolar patients (Lynch, Laws, & McKenna, 2010). However, Lam (2006) has criticized this study for including a mixed patient sample; almost one-third of the patients were currently in episode and the focus on acute symptom reduction rather than relapse prevention might have undercut any possible relapse prevention effect. It should be possible to reanalyze the data for only those patients not in episode at the start of the trial to see whether that subsample replicated the effects found in the Lam studies, but that has not yet been done. It also would have been helpful to know whether medication dosing varied between the 2 conditions in the Scott study, because such confounds sometimes obscure the effects of added treatments (Zaretzky et al., 2008).

More research is needed to determine whether CBT truly has an adjunctive role to play in the treatment or prevention of bipolar disorder and, if so, whether those beneficial effects of CBT (if any) are because of its specific content or because of nonspecific treatment factors like therapist contact and the mobilization of hope and expectation.

Predictors of CBT efficacy

Because different patients respond differently to different treatments, it is important to know who responds best to what with particular reference to CBT. Two types of information are relevant to this question: prognostic information in which you hold treatment constant and allow patient characteristics to vary, and prescriptive information in which you hold patient characteristics constant and allow treatment to vary (Fournier et al., 2009). Prognostic factors predict outcome to a given treatment (or to treatment in general) and can be used to determine which patients are more likely to respond to CBT relative to other patients. However, although it is useful to know what to expect when starting treatment, prognostic factors are of little use in deciding what treatment to select. On the other hand, prescriptive information (also known as moderators) can detect different patterns of outcomes between different

treatments for different types of patients and provide a basis for choosing the best treatment of a given patient (Kraemer, Wilson, Fairburn, & Agras, 2002).

Demographic factors

Little research has focused on age, gender, education and other demographic predictors of response to CBT for depression adequately controlling for pretreatment severity (Hamilton & Dobson, 2002). A notable exception is a study by Fournier et al. (2009) that found that older age and lower intelligence each predicted relatively poor response to CBT and ADM and were therefore purely prognostic factors, whereas being unemployed and having more antecedent life events predicted superior response to CBT relative to ADM and were therefore potentially prescriptive. For whatever reason, married patients seem to do better in CBT than unmarried patients (Burns & Spangler, 2000; Jarrett, Eaves, Granneman, & Rush, 1991; Sotksy et al., 1991; Thase, Simons, Cahalane, McGeary, & Harden, 1991). This finding is an example of prognostic information that allows a prediction of likely outcome but does not (on its own) provide a basis for choosing CBT rather than other treatments for such patients. However, Barber and Muenz (1996) reanalyzed data from the TDCRP and found that married patients did better in CBT than they did in IPT, whereas unmarried patients showed the opposite pattern. Similarly, Fournier et al. (2009) found that patients who were married or cohabiting did better in CT than they did in ADM. Both sets of findings are potentially prescriptive and could be used to select CBT rather than either IPT or ADM if replicated. Thus, marital status seems to be prognostic (married patients do better than unmarried patients in CBT) and prescriptive (married patients do better in CBT than they do in at least some other treatments) with respect to CBT efficacy. In addition, more antecedent life events and unemployment are potentially prescriptive factors, associated with better response to CBT relative to ADM.

Illness Characteristics

Chronic depression was found to be prognostic of poor response to either CBT or ADM in one study (Fournier et al., 2009) and brief duration of the current depressive episode, a later age of depression onset, absence of a family history of affective disorder, and a history of more previous episodes of depression predictive of good response to CBT in another (Sotksy et al., 1991). All these indices were purely prognostic and should not be used as a basis for treatment selection. Leykin et al. (2007) found that the more previous medication exposures that patients had the less well they did in ADM; no such relationship was evident for CBT. Although the investigators did not report tests for treatment differences as a function of number of previous exposures, they did report an effect size favoring CBT rather than ADM for patients with 2 or more previous exposures of sufficient magnitude (d = 0.46) to suggest that the difference would have been significant if tested. There is little evidence to support the long-standing belief that patients with melancholic depression would be less responsive to CBT than to ADM (Hollon, Jarrett, et al., 2005). It is also widely assumed that ADM is to be preferred to CBT in the treatment of patients with more severe depressions (APA, 2000b). In their review, Hamilton and Dobson (2002)

conclude that depression severity is associated with poor response to CBT (prognostic), but that there is no reason to conclude that alternative treatments such as ADM are any more efficacious than CBT for severely depressed patients (prescriptive). When CBT has failed relative to ADM it has been with patients with more severe depressions (Elkin et al., 1995; Dimidjian et al., 2006), but as discussed earlier, questions can be raised about the quality of the CBT in those studies. When CT has been adequately implemented, it seems to be about as efficacious as ADM with such patients (Jarrett et al., 1999; DeRubeis et al., 2005). In sum, chronicity and severity seem to be prognostic only and melancholia does not seem to be prescriptive, although patients with more previous medication exposures may do better in CBT than on ADM.

Personality characteristics/disorders

The presence of a comorbid PD might be relevant from a prognostic and prescriptive perspective. Fournier et al. (2008) found that depressed patients with Axis II PDs (excluding antisocial, schizotypal, and borderline) were less responsive to CBT than to paroxetine ADM (44% vs 66% response), whereas patients without comorbid Axis II PDs showed the opposite pattern (70% vs 49%). Moreover, only patients with PDs showed a medication discontinuation effect (they were more likely to relapse if withdrawn onto pill-placebo than if continued on active medications); patients without PDs showed no such effect. Patients with PDs who did respond to CT were no more likely to relapse following treatment termination than patients without PDs, suggesting that the patients with PDs who did respond to CT tended to sustain their response. Treatment guidelines published by the American Psychiatric Association (2000b) suggest that CBT is superior to ADM in the treatment of patients with PDs, but that claim was based on a misreading of findings from the TDCRP that Axis II disorder was predictive of poor response within ADM or IPT but not in CBT. In point of fact, patients with PDs did not do better in CBT than they did in other treatments, but patients without PDs did worse in CBT (Shea et al., 1990). Hardy et al. (1995) similarly found that cluster C PDs predicted differential response within an interpersonal intervention but not within CBT (prognostic). However, the treatment by PD interaction was nonsignificant and the investigators did not conduct the kinds of direct treatment comparisons within patient subgroups required to establish moderation. Barber and Muenz (1996) found CBT superior to IPT for patients with avoidant personality traits and IPT superior to CBT for patients with obsessive personality traits. Similarly, McBride, Atkinson, Quilty, and Bagby (2006) found that patients with high levels of attachment avoidance (a reluctance to initiate intimate contact and a tendency to withdraw when facing an attachment threat) had better outcomes to CBT than to IPT and Joyce et al. (2007) found that avoidant and schizoid symptoms predicted poorer response to IPT but not to CBT. Despite the differences in study design and the measures used, these studies approach a conceptual replication of the Barber and Muenz (1996) findings with regard to avoidant personality, although Joyce and colleagues (2007) did not replicate the finding that IPT might be more efficacious than CBT for patients with obsessive-compulsive traits. In sum, there are consistent

indications that presence of PD dimensions may be prescriptive, although the exact nature of that prediction may depend on the specific comparison (CBT may be superior to IPT on some and inferior to ADM on others).

Treatment preference

Two studies have examined the role of a patient's preference as a moderator of treatment efficacy. Leykin, DeRubeis et al. (2007) found no differences in symptom reduction or likelihood of attrition between patients who received their preferred treatment versus those who did not (CBT vs ADM). On the other hand, Kocsis et al. (2009) found that patients who preferred either CBT alone or ADM alone had higher rates of remission and fewer depressive symptoms if they received what they preferred than if they received combined treatment. Thus, patient preferences in that study appeared to be driven more by a disaffection for a specific monotherapy than a preference for the other.

Dysfunctional attitudes

Several studies have reported that high levels of pretreatment dysfunctional attitudes predict poorer response to CBT (prognostic; Keller, 1983; Jarrett et al, 1991; Sotsky et al., 1991; Thase et al., 1991). Furthermore, Sotsky et al. (1991) found that patients with lower dysfunctional attitudes did better in CBT (or ADM) than in pill-placebo. Thus, lower levels of dysfunctional attitudes was prescriptive relative to pill-placebo (but not to ADM) in that study. It is unclear whether levels of dysfunctional attitudes are prescriptive relative to other alternative treatments (Hamilton & Dobson, 2002).

Mediators of CBT efficacy

Although CBT has been found to be efficacious in the treatment and prevention of depression, questions remain about precisely how it works (mediation). Such questions are relevant to the identification of the active ingredients in the treatment process and the mechanisms of change within the patient. Cognitive theory posits that negative automatic thoughts and maladaptive information-processing proclivities play a causal role in the cause and maintenance of depression (Beck et al., 1979). According to this theory, CBT works by virtue of implementing efforts (process) to correct these errors in thinking (mechanism). To the extent that this is true, efforts to help patients learn how to examine the accuracy of their own beliefs should help ameliorate the level of existing distress and reduce risk for future episodes. Others factors that also are believed to mediate the efficacy of psychotherapy are the quality of the therapeutic relationship and facilitative conditions, such as therapist warmth and empathy. If cognitive theory is correct, then adherence to the specific components of CBT should drive symptom change and subsequent freedom from relapse over and above whatever contribution is made by nonspecific factors common to other therapies.

Treatment process

Several studies have shown that nonspecific factors are correlated with change across the course of CT (Burns & Nolen-Hoeksema, 1992; Castonguay, Goldfried, Wiser, Raue, & Hayes, 1996; Krupnick et al., 1996). Conversely, several studies have found that homework compliance (assessed retrospectively at the end of treatment) was associated with better response to CBT (Burns & Nolen-Hoeksema, 1991, 1992; Burns & Spangler, 2000). However, these studies did not adequately control for reverse causality (that it was symptom change that drove treatment process rather than the other way around); doing so would have required controlling for symptom change up until the point at which homework compliance was measured. Shaw et al. (1999) found only limited support for the role of therapist competence (it was the ability to structure treatment rather than CBT skills that best predicted outcome), but also did not examine the pattern of temporal relations over time (doing so would have required controlling for previous symptom change at the point at which competence was measured). DeRubeis and Feeley (1990, Feeley, DeRubeis, & Gelfand, 1999) revisited these issues in a pair of studies that controlled for symptom change before the assessment of treatment process and then monitored the effects of treatment process on subsequent symptom change. What these investigators found was that after controlling for previous symptom change, the extent to which therapists used concrete symptom-focused CBT methods in an early session predicted subsequent change in depression, whereas nonspecific processes like the helping alliance and facilitative conditions did not. Moreover, ratings of the helping alliance in subsequent sessions were predicted by previous depression change. This finding suggests that concrete symptom-focused techniques may play a causal role in the alleviation of depressive symptoms in CBT, whereas the quality of the therapeutic relationship may be more a consequence than a cause of change. Neither study ruled out possible third variable causality (that some unmeasured patient characteristic facilitated concrete symptom-focused techniques and led to subsequent symptom change with no direct causal link between the two), but they did suggest that specific CBT techniques were predictive of (and possibly causal to) subsequent symptom change in a manner that nonspecific processes were not.

Cognitive mechanisms

In a similar fashion, early studies assessing whether cognitive change mediated the effects of CBT typically reported that ADM produced as much change in cognition as CBT (Imber et al., 1990; Simons, Garfield, & Murphy, 1984), leading investigators to conclude that cognitive change was more of a nonspecific consequence of change in depression rather than a cause (Simons, Garfield, & Murphy, 1984). However, as in the treatment process literature, these early studies did not assess the temporal pattern of change between cognition and subsequent depression and therefore were unable to address the possibility that cognitive change mediated change in depression in one treatment but was a consequence of change in depression in another Hollon, DeRubeis, & Evans, 1987). DeRubeis et al. (1990) found that early change in cognition was predictive of subsequent change in depression in CBT but not in ADM despite the

fact that both produced comparable change in cognition across the course of treatment, a pattern that is consistent with differential mediation in CBT but not in ADM. Recent studies have extended this line of inquiry by examining the relation between cognitive change and subsequent relapse. Strunk, DeRubeis, Chiu, and Alvarez (2007) found that among treatment responders, patient competence in CBT coping skills and their independent implementation predicted the risk of relapse in the year following treatment termination. Among partially remitted patients, Teasdale et al. (2001) found that CBT reduced the tendency to use an absolutist, dichotomous thinking style, and that this change (rather than simply becoming more positive) reduced the likelihood of subsequent relapse. Moreover, there is evidence that CBT reduces the extent to which patients think negatively with increased dysphoria (cognitive reactivity; Beevers & Miller, 2005) and that this reduction in cognitive reactivity predicts subsequent risk for relapse (Segal et al., 2006). Collectively, these studies support the notion of cognitive mediation in CBT by ruling out reverse causality (that cognitive change is caused by change in depression), although as for the process studies they do not rule out third variability causality (that some unmeasured patient factor caused change in cognition and change in depression with no causal link between the two). Thus, some ambiguity still remains as to whether CBT works by virtue of changing cognitions, although the existing evidence is consistent with that notion.

Sudden gains

Tang and DeRubeis (1999) described a pattern of substantial stable decreases in depressive symptoms in CBT with implications for treatment process and the mechanisms of change that they termed sudden gains. Several studies have since replicated the presence of sudden gains during CBT (Hardy et al., 2005; Tang, DeRubeis, Beberman, & Pham, 2005; Tang, DeRubeis, Hollon, Amsterdam, & Shelton, 2007). Sudden gains seem to appear in 30% to 50% of patients, accounting for 50% to 60% of the total improvement in these patients. They generally have a magnitude of 10 or more points on the Beck Depression Inventory and appear in the first half of treatment (between sessions 4 and 8). Although the presence of sudden gains during CBT has been consistently associated with better end-of-treatment outcomes, nearly as many patients respond to treatment who show a more gradual course of change (Hardy et al., 2005; Tang & DeRubeis, 1999; Tang et al., 2005; Tang et al., 2007). Most striking is the finding that sudden gains predict freedom from relapse among treatment responders (Tang et al., 2007). Earlier studies had found an inconsistent relation between sudden gains and levels of depression following treatment termination, but had relied on cross-sectional assessments that did not take into account intercurrent relapses that could lead to subsequent treatment (Tang & DeRubeis, 1999; Hardy et al., 2005). Conversely, Vittengl, Clark, and Jarrett (2005) found little evidence that sudden gains predicted differential relapse following successful treatment, but used a different definition that allowed modest gains to pass the threshold. Using the original more stringent definition, Tang et al. (2007) found that sudden gains predicted freedom from subsequent relapse among treatment

responders even when controlling for end-of-treatment depression scores, and that that effect disappeared when they applied the less stringent definition used by Vittengl et al. (2005). What makes these findings relevant to mediation (and possible process) is that Tang and DeRubeis (1999) found more cognitive change in the session preceding the sudden gains than in control sessions from the same patients (with no differences found for other therapeutic factors), and replicated this in a subsequent study Tang et al., 2005). This finding suggests that sudden gains might be triggered by cognitive change, which in turn is likely related to CBT-specific processes on the part of the therapist, as posited by cognitive theory. However, given the correlational nature of this finding, third variable causality cannot be ruled out, and sudden gains also have been found in other types of treatments that are less likely to be mediated by cognitive change (Hardy et al., 2005; Vittengl et al., 2005).

Cognitive change versus BA

The studies described here all relied on correlational analyses to identify the causal mechanisms of change in CBT. Jacobson et al. (1996) used a more experimental approach to dismantle CBT in an effort to identify its active ingredients and came up with a different answer. In that study, the investigators compared the efficacy of 3 different CBT components by comparing (1) BA only, (2) BA plus the activation and modification of dysfunctional thoughts (AT), and (3) BA plus AT plus the identification and modification of core schemes (CT), and found no differences in efficacy between these different components. This finding was surprising because cognitive theory posits that direct efforts to change beliefs are necessary to maximize change in depression and the BA condition did not address those beliefs directly. Moreover, no differences were found on purported mediators hypothesized to be differentially affected by the respective components (pleasant events, automatic thoughts, and attributional style) and early change in cognition was associated with subsequent change in BA (but not in CT) and early change in pleasant events was associated with subsequent change in CT (but not in BA). This study suggests that specific efforts to change beliefs may not be necessary to produce cognitive change, yet at the same time leaving open the possibility that cognitive change (no matter how it is produced) may still play a meditational role in the subsequent reduction of distress. More research is needed in this regard.

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