The Efficacy of Cognitive-Behavioral Therapy in Bipolar Disorder: A Quantitative Meta-Analysis

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Objective: The goal of the current study was to conduct a quantitative meta-analysis investigating the role of cognitive-behavioral therapy (CBT) as adjunctive treatment to medication for patients diagnosed with bipolar disorder.

Data Sources: Studies included in the sample were identified through a computer search of articles in English in the MEDLINE database from January 1980 to March 2008. Key terms entered were *cognitive and bipolar disorder*, *cognitive therapy and bipolar disorder*, *cognitive behavioral therapy and bipolar disorder*, *psychotherapy and bipolar disorder*, and *psychosocial and bipolar disorder*.

Study Selection: Inclusion criteria were (1) randomized clinical trial investigating the role of adjunctive CBT in patients diagnosed with bipolar disorder, (2) clearly defined CBT intervention, (3) the inclusion of a control group, and (4) sufficient data reported to allow calculation of effect sizes. Twelve randomized clinical trials were selected for analysis on the basis of these criteria.

Data Extraction: Effect sizes (Cohen *d*) were calculated according to published procedures.

Data Synthesis: We found a low to medium overall effect size of CBT at posttreatment ($d = -0.42$, $P < .05$) and follow-up ($d = -0.27$, $P < .05$), and we found a positive impact of CBT on clinical symptoms (posttreatment $d = -0.44$, $P < .05$), cognitive-behavioral etiopathogenetic mechanisms (posttreatment $d = -0.49$, $P < .05$), treatment adherence (posttreatment $d = -0.53$, $P < .05$), and quality of life (posttreatment $d = -0.36$, $P < .05$). The impact was less evident in the case of relapse and/or recurrence (posttreatment $d = -0.28$). These effects on outcome categories were more evident at posttreatment compared to follow-up.

Conclusions: Cognitive-behavioral therapy can be used as an adjunctive treatment to medication for patients with bipolar disorder, but new CBT strategies are needed to increase and enrich the impact of CBT at posttreatment and to maintain its benefits during follow-up.

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Bipolar disorder is a severe, recurrent mood disorder, with prevalence rates of 1%–1.5%, featuring 1 or more episodes of mania/hypomania or mixed episodes of mania/hypomania and depression.[1] The median age at onset of the disorder is in the mid-20s, and it runs a natural course of high frequency of relapses and serious suicide risk.[2] The impact of bipolar disorder on the everyday lives of patients and their families can be devastating. Although many patients manage to complete education and develop a career, they often lose employment due to repeated relapses. Interpersonal relationships are also highly affected by the alternation between manic/hypomanic and depressive moods and by behaviors during manic episodes. Indeed, data show that, 1 year after the episode, only 30% of the individuals have returned to their previous level of social and professional functioning.[3]

Psychosocial Treatments for Bipolar Disorder

The standard treatment for bipolar disorder over the last decades has been, and currently remains, pharmacotherapy.[3,4] However, efficacy (ie, how it works in clinical trials) and effectiveness (ie, how it works in real-life clinical settings) studies show that, even under optimal clinical conditions, medication protects fewer than 50% of individuals with bipolar disorder against further episodes.[3,4] Moreover, about 30%–50% of patients do not adhere to prescribed prophylactic treatments and/or continue having significant residual symptoms.[3,4] Given this situation, the necessity of developing and testing specific psychotherapy interventions for bipolar disorder is evident. These psychosocial interventions are usually focused on issues remaining unaddressed by medication such as residual symptoms, medication adherence, awareness and understanding of the disorder, early identification of prodromal symptoms, and coping skills.[5] Several psychosocial strategies have been employed in bipolar disorder,[4,6] such as psychoeducation, family-focused therapy, interpersonal and social rhythm therapy, and cognitive-behavioral therapy (CBT).

Interest in a CBT approach to bipolar disorder has been growing among clinicians and researchers during the past 2 decades and so have the available data from open and randomized clinical trials. In fact, CBT is among the most well-researched manualized psychological approaches, and studies conducted so far[3] show that it is a promising approach for improving functioning in bipolar disorder. Typically, CBT employs cognitive (eg, cognitive restructuring

of dysfunctional and irrational beliefs) and behavioral (eg, modification of maladaptive behaviors) techniques to help bipolar patients (1) understand the disorder and have a better monitoring and self-regulation of the disorder and a better adherence to the treatment (education phase), (2) identify residual symptoms and/or prodromal symptoms and use coping mechanisms to control them in order to prevent relapse (skill-training phase), and (3) approach very specific interpersonal and personal problems resulting from the disorder (core beliefs restructuring and behavioral modification phase). For details, see reference 7.

The goal of the present study was to estimate the impact of adjunctive CBT in the treatment of patients diagnosed with bipolar disorder. Most reviews conducted so far[4,5,7–11] have focused on psychosocial treatments as a whole or were qualitative meta-analyses (reviews) of specific treatments (eg, CBT). To our knowledge, this is the first quantitative meta-analysis dedicated to CBT alone. Although individual clinical studies (eg, Williams et al[12]) have suggested that CBT is effective for controlling symptoms and improving the course of the disorder (eg, treatment adherence, number of episodes, relapse rates), no quantitative meta-analyses have been conducted so far to confirm the benefits of CBT and to estimate its effect size in bipolar disorder. Until a few years ago, this state of things was understandable considering the paucity of randomized clinical trials investigating CBT in bipolar disorder. Although rigorous studies are still very much needed and are quite few compared to other disorders (eg, major depressive disorder), during recent years, research in this field has reached a level that justifies a quantitative analysis of the effectiveness of CBT in bipolar disorder. Randomized clinical trials have been described as the gold standard for research on clinical interventions,[13] and they are fundamental for evaluating the internal validity of the theory that CBT is useful in treating bipolar patients as the first necessary step before exploring the generalizability and effectiveness of this theory (ie, the usefulness of CBT in treating bipolar patients in real-life clinical settings).

The objective of this study was to undertake such an analysis for the first time, to our knowledge. Specifically, we provide (1) a quantitative estimate of the overall effect size of adjunctive CBT across outcome domains and methods of administration and (2) a comparison of effect sizes by outcome domains.

METHOD

Studies included in the sample were identified through a computer search of articles in English in the MEDLINE database from January 1980 to March 2008. The key terms entered were *cognitive and bipolar disorder*, *cognitive therapy and bipolar disorder*, *cognitive behavioral therapy and bipolar disorder*, *psychotherapy and bipolar disorder*, and *psychosocial and bipolar disorder*. The initial search resulted in 1,360 articles. Initial inclusion criteria were (1) a randomized clinical trial investigating the role of adjunctive CBT (defined as such by the authors of each study) in patients diagnosed with bipolar disorder, (2) a clearly defined CBT intervention, (3) the inclusion of a control group, and (4) sufficient data reported (eg, means, standard deviations, inferential statistics) to allow calculation of effect sizes; if these data were not available for only some of the measures, the study was still included, and the analyses were conducted on the measures for which we had enough data.

On the basis of these standardized methods, we identified 12 studies (10 reported posttreatment measures and the other 2 reported only follow-up measures; Table 1). In all studies, CBT was adjunctive to standard care (ie, medication and clinical management) and was compared to standard care (medication plus clinical management). One study[23] was discussed in a review of the literature regarding psychosocial interventions in bipolar disorder[11] as being a study of CBT intervention, but the authors of the study did not describe it as such; therefore, it was not included in our analysis. Another study[24] compared adjunctive integrated group CBT intervention with group drug counseling for patients with bipolar disorder and current substance dependence; however, during the intervention, 74% of patients were also in various forms of individual psychotherapy. Because we were focused on randomized clinical trials, aiming to increase the internal validity of the relation between CBT and its effects in patients with bipolar disorder, this study was also excluded.

The clinical status of patients included in the trials was different across studies, ranging from subjects "not in episode"[17,18] to patients satisfying criteria for various types of episodes (eg, manic, depressive, hypomanic).[21] However, even in the cases of heterogeneous patient groups, results were typically reported for the group as a whole.

Intervention outcomes were measured at various points in the trials; the studies were very heterogeneous from this point of view. Follow-up measures were also conducted and reported in quite different manners. Most studies reported follow-up at certain intervals from the beginning of the trial (eg, 6 months, 12 months, 18 months). We chose to keep this manner of reporting (from the beginning of the trial), particularly as there were several cases when therapy was not delivered over a fixed period of time (eg, therapy sessions extended over 6 months, with some subjects completing it earlier than others) and because doing so was consistent with how the authors of the study defined the follow-up. Thus, in order to compare the studies, we classified them into 4 categories (see Table 1) (2 experts in clinical psychology, randomized clinical trials, and affective disorders grouped outcomes into these categories, and final agreement between them was 100%): (1) posttreatment (usually ranging from 6 weeks to 9 months), (2) from posttreatment to 6-month follow-up, (3) >6 months to 12-month follow-up, and (4) >12-month follow-up. Thus, we have 1 posttreatment assessment point and 3 follow-up assessment points. The reason we chose these 3 follow-up points is related to the naturalistic

Table 1. Study Characteristics and Mean Effect Sizes (Cohen *d*[a]) by Publication Date

					Posttreatment			Posttreatment to 6-Month Follow-Up			>6 Months to 12-Month Follow-Up			>12-Month Follow-Up		
Study	Type of CBT	Subjects, N (based on ITT principle)	Treatment Group	Control Group[b]	*d*	No. of Effect Sizes Per Study	95% CI	*d*	No. of Effect Sizes Per Study	95% CI	*d*	No. of Effect Sizes Per Study	95% CI	*d*	No. of Effect Sizes Per Study	95% CI
Cochran (1984)[14]	Individual	28	Standard care + CBT	Standard care	−0.50*	8	−0.78 to −0.22	−0.39*	9	−0.62 to −0.15	…	…	…	…	…	…
Lam et al (2000)[2]	Individual	23	Standard care + CBT	Standard care	−0.58*	8	−0.96 to −0.21	…	…	…	−0.98*	11	−1.5 to −0.46	…	…	…
Scott et al (2001)[15]	Individual	42	Standard care + CBT	Standard care + waiting list	−0.55*	9	−0.69 to −0.42	…	…	…	…	…	…	…	…	…
Schmitz et al (2002)[16]	Individual	46	Standard care + CBT	Standard care	−0.47	6	−1.00 to 0.04	…	…	…	…	…	…	…	…	…
Lam et al (2003)[17]	Individual	103	Standard care + CBT	Standard care	−0.36*	8	−0.58 to −0.14	…	…	…	−0.38*	13	−0.63 to −0.11	…	…	…
Lam et al (2005)[18]	Individual	103	Standard care + CBT	Standard care	…	…	…	…	…	…	…	…	…	−0.41*	14	−0.56 to −0.27
Lam et al (2005)[19]	Individual	103	Standard care + CBT	Standard care	−0.10	4	−0.43 to 0.21	…	…	…	…	…	…	−0.005	4	−0.36 to 0.35
Ball et al (2006)[20]	Individual	52	Standard care + CBT	Standard care	−0.39*	16	−0.54 to −0.25	−0.19*	12	−0.30 to −0.08	−0.21*	21	−0.32 to −0.10	…	…	…
Scott et al (2006)[21]	Individual	253	Standard care + CBT	Standard care	0.06	3	−0.22 to 0.33	…	…	…	−0.04	3	−0.19 to 0.11	0.05	3	−0.09 to 0.19
Miklowitz et al (2007)[6]	Individual	152	Standard care + CBT	Collaborative care	−0.11	3	−0.37 to 0.15	…	…	…	…	…	…	…	…	…
Miklowitz et al (2007)[22]	Individual	293	Standard care + CBT	Collaborative care	…	…	…	…	…	…	−0.30	2	−1.8 to 1.22	…	…	…
Williams et al (2008)[12]	Group	14	Standard care + CBT	Standard care	−0.93	2	−4.6 to 2.7	…	…	…	…	…	…	…	…	…

[a]Definition of categories for *d*: no effect (0–0.2), low effect (0.2–0.5), medium effect (0.5–0.8), and high effect (> 0.8).
[b]Collaborative care is a more structured care (eg, involving a greater role of nonmedical specialists) in comparison to standard care.
*Significant at $P < .05$.
Abbreviations: CBT = cognitive-behavioral therapy, ITT = intent-to-treat.
Symbol: … = not applicable.

studies of the disorder. It has been shown that a typical bipolar disorder episode (eg, depressive) can be expected to last from 6 to 12 months, with an intermorbid period of 3 to 4 years before the onset of the next episode[25]; thus, by this classification, we can identify both the relapse (ie, the return of symptoms associated with a treated episode) and recurrence (ie, the onset of a whole new episode).

The selected studies report a considerable variety of outcomes—the studies were again very heterogeneous from this point of view. On the basis of our reviews of the literature, we have categorized outcomes as follows (Table 2): (1) clinical symptoms (eg, depressive symptoms, manic symptoms), taking into account duration (eg, number of days) and/or intensity (eg, the score on a specific scale); (2) cognitive-behavioral etiopathogenetic mechanisms (eg, dysfunctional cognitions, coping skills); (3) quality of life and life/social adjustment (eg, well-being, social adjustment); (4) relapse (eg, number of relapses) and/or recurrence (eg, time to recurrence); (5) treatment adherence (eg, self-reported compliance, lithium level); and (6) treatment costs. Again, 2 experts in clinical psychology, randomized clinical trials, and affective disorders grouped the outcomes into these categories, and final agreement between them was 100%. The list of all outcomes distributed in each category is available upon request from the first author. These categories make sense if one conceptualizes bipolar disorder comprehensively: certain etiopathogenetic mechanisms are responsible for a specific clinical condition, which impacts the quality of life and adjustment. With severe clinical conditions, such as bipolar disorder, adherence to treatment is fundamental, and relapse and/or recurrence is common. Also, because of the severity of the condition, long-term treatment is fundamental, and, thus, treatment cost is also relevant.

Effect sizes (Cohen *d*) were calculated according to published procedures.[26] More precisely, mean differences between CBT groups and control groups were calculated for each study and then divided by the standard deviation of the control group (a minus sign signifies an effect in favor of CBT). When data were not presented in this format, we used the odds ratio and its transformation into Cohen *d* to compute the effect sizes.[27] On the basis of Cohen estimations,[26] effect sizes have been categorized along a continuum of no effect (0–0.2), low effect (0.2–0.5), medium effect (0.5–0.8), and high effect (>0.8). In computing the effect sizes, the intent-to-treat principle was applied for determining sample size (intent to treat was used by most of the authors in the studies included in the meta-analysis). To estimate the overall effect of adjunctive CBT intervention (objective 1), the 95% confidence interval for the effect size of CBT compared to control was calculated and then compared to zero. If the 95% confidence interval included zero, there would be no significant effect of CBT. Next (for objective 2), effect sizes and 95% confidence intervals were calculated for each clinical outcome category; confidence intervals were assessed for their inclusion of zero to test the significance of

Table 2. Effect Sizes (Cohen *d*[a]) for 4 Different Treatment Periods as a Function of Clinical Outcome Category

	Posttreatment			Posttreatment to 6-Month Follow-Up			>6 Months to 12-Month Follow-Up			>12-Month Follow-Up		
Outcome Category	*d*	No. of Effect Sizes per Outcome Category	95% CI	*d*	No. of Effect Sizes per Outcome Category	95% CI	*d*	No. of Effect Sizes per Outcome Category	95% CI	*d*	No. of Effect Sizes per Outcome Category	95% CI
Clinical symptoms	–0.44*	25	–0.59 to –0.29	–0.22*	8	–0.39 to –0.05	–0.38*	28	–0.52 to –0.23	–0.43*	5	–0.91 to –0.04
Cognitive-behavioral etiopathogenetic mechanisms	–0.49*	12	–0.72 to –0.25	–0.26*	4	–0.51 to –0.005	–0.69*	11	–0.13 to –0.09	–0.23*	3	–0.39 to –0.08
Quality of life and life/social adjustment	–0.36*	9	–0.54 to –0.18	–0.13	2	–0.3 to 2.7	–0.29	4	–0.87 to 0.29	–0.33	1	…
Relapse and/or recurrence	–0.28	5	–0.98 to 0.41	…	…	…	–0.14	5	–0.36 to 0.07	–0.29	7	–0.06 to 0.01
Treatment adherence	–0.53*	12	–0.71 to –0.35	–0.39*	7	–0.70 to –0.07	–0.36	2	–6.8 to 6.1	–0.38	1	…
Treatment costs	–0.10	4	–0.43 to 0.22	…	…	…	…	…	…	–0.005	4	–0.36 to 0.35

[a]Definition of categories for *d*: no effect (0–0.2), low effect (0.2–0.5), medium effect (0.5–0.8), and high effect (>0.8).
*Significant at $P<.05$.
Symbol: … = not applicable.

individual category effects, and between-group analysis of variance was used to investigate whether categories differed from each other. For follow-up categories (ie, posttreatment to 6 months; >6 months to 12 months; >12 months), several measure points of the same outcome were included in 1 follow-up category (eg, depression measures at 18, 24, and 30 months in the study were all included in the >12-month follow-up category). In this case, we computed the effect size for each measure point and then calculated the mean effect size for each follow-up category.

RESULTS

Posttreatment Analyses

Mean effect sizes, averaged for treatments within studies at various points, and the sample size for each study included in the analyses are presented in Table 1.

Our analysis revealed a significant benefit of CBT for patients diagnosed with bipolar disorder. Data analysis indicates a low to medium effect size ($d = -0.42$) of CBT at posttreatment (SD = 0.35). The 95% CI indicates that this effect size significantly differs from zero (95% CI, −0.51 to −0.34; $P < .05$). The number of patients was 770, and the number of effect sizes was 67.

Because bias can be introduced into effect-size calculations through variations in individual study sample size, we reran the analyses, correcting for sample size (computing D instead of d and variance of D [VAR D] instead of SD of d) (for more information, see reference 26). Results revealed a low effect size, but the 95% CI indicated that D ($D = -0.20$; VAR $D = 0.07$) significantly differed from zero (95% CI, −0.29 to −0.11; $P < .05$).

However, this global indicator is not very meaningful from a clinical point of view. It is possible that CBT has a greater impact on some outcomes and a smaller impact on others; therefore, it is important to find out the aspects in which CBT is clinically meaningful. Table 2 presents the mean effect sizes for each of the 6 clinical outcome categories.

As Table 2 shows, CBT has a low to medium significant effect on the clinical symptoms of bipolar disorder and a low to medium significant effect on the cognitive-behavioral etiopathogenetic mechanisms. The impact on the patient's quality of life and life/social adjustment is low to medium but still significant. For relapse and/or recurrence, the effect is low and nonsignificant. Finally, CBT has a medium significant effect on treatment adherence and no effect on treatment costs. Using analysis of variance, we found no significant differences between these outcome categories ($F_{6,61} = 1.21$, $P > .05$).

Follow-Up Analyses

From posttreatment to 6 months. The overall effect size of CBT was low but significant ($d = -0.27$, SD = 0.26; 95% CI, −0.39 to −0.16). After correcting for sample size, the overall effect size remained significant and in the same range ($D = -0.25$, VAR $D = 0.009$, $P < .05$). The number of patients was 80, and the number of effect sizes was 21.

As shown in Table 2, CBT had a significant low effect size for clinical symptoms and cognitive-behavioral etiopathogenetic mechanisms and a low to medium effect size for treatment adherence. Cognitive-behavioral therapy had no significant effect on quality of life and life/social adjustment.

From >6 months to 12 months. The overall effect size of CBT was low to medium and was significant ($d = -0.41$, SD = 0.54; 95% CI, −0.57 to −0.26). After correcting for sample size, the overall effect size was still significant ($D = -0.23$, VAR $D = 0.04$, $P < .05$). The number of patients was 636, and the number of effect sizes was 50.

Cognitive-behavioral therapy had a significant low to medium effect size for clinical symptoms and a significant medium to large effect size for cognitive-behavioral etiopathogenetic mechanisms; CBT had no significant effect on quality of life and life/social adjustment, on relapse and/or recurrence, and on treatment adherence (see Table 2).

Greater than 12 months (maximum, 30 months). The overall effect size of CBT was low but significant ($d = -0.27$, SD = 0.30; 95% CI, −0.40 to −0.13). After correcting for sample size, the overall effect size was no longer significant ($D = -0.06$, VAR $D = 0.03$, $P > .05$). The number of patients was 459, and the number of effect sizes was 21.

As seen in Table 2, CBT had a significant low to medium effect on clinical symptoms and a low but significant effect on cognitive-behavioral etiopathogenetic mechanisms; it had no significant effect on relapse and/or recurrence and treatment cost. For quality of life and life/social adjustment and for treatment adherence, we had only 1 effect size, in favor of CBT: $d = -0.33$ and $d = -0.38$, respectively.

Other Analyses

Only 1 study in the sample delivered CBT in group format, while the others were based on individual intervention; therefore, the 2 types of intervention could not be compared. However, an analysis of the absolute values shows that the largest effect size across all studies was obtained by using group CBT ($d = -0.93$), although the result was not significant ($P > .05$) and included only 2 effect sizes and 14 patients (see Table 1).

DISCUSSION

In general, the overall effect size of adjunctive CBT compared to standard treatment (eg, medication) in bipolar disorder was significant (low to medium), both at posttreatment and during follow-ups. However, considering that all studies compared CBT plus pharmacotherapy to pharmacotherapy alone rather than to placebo, a significant low to medium effect size can reflect clinical significance. As we have already mentioned, in clinical work, this general effect size has no special meaning. A more important question is

concerned with the particular clinical conditions for which CBT work and the clinical conditions in which CBT has no observable influence.

Our data indicate that, at posttreatment, CBT has a clear impact on symptoms and on cognitive-behavioral etiopathogenetic mechanisms (low to medium effect size). This finding provides indirect support for the cognitive-behavioral theory because we found no situation in which CBT impacted on symptoms but not on hypothesized cognitive-behavioral mechanisms (or vice-versa). A significant effect of CBT is also noticeable for treatment adherence (medium effect size) and quality of life and life/social adjustment (low to medium effect size). The intervention has no significant effect on relapse and/or recurrence and treatment cost. Thus, adding CBT to medication as part of the treatment package for patients diagnosed with bipolar disorder entails significant benefits without increasing the costs. Cognitive-behavioral therapy should therefore be supported as a recommended treatment, adjunct to medication for these patients. This conclusion is in line with the recent recommendation of the National Institute for Health and Clinical Excellence (http://www.nice.org.uk/) and with findings of other recent reviews.[11]

However, during follow-up, the effects of CBT were not so clear. At 6 months, CBT had a significant but low effect size, which slightly increased at 6 to 12 months (low to medium effect size) and then decreased again at >12 months (low but significant effect size). But if we look at the effect sizes corrected for sample size, the picture is different: at 6 months and at >6 to 12 months, CBT had a significant but low effect, which was lost at >12 months. One study,[21] involving a large sample, seems to be responsible for the change in the stability of CBT effects during follow-up. Results of this study need, therefore, to be replicated to get a clear picture of the effects of CBT during follow-up.

The type of effects in all 3 follow-up categories was quite consistent, with CBT having a significant impact on symptoms and cognitive-behavioral mechanisms. The impact on adherence was significant at 6-month follow-up, and we found a similar trend at >12-month follow-up; the effect was not significant at >6 to 12 months, but we had only 2 effect sizes in this category, and, taking into account that the overall effect was low to medium ($d = -0.36$), we can say that there was a favorable trend for CBT to positively impact on treatment adherence. The influence of CBT on quality of life and life/social adjustment and on relapse and/or recurrence was not significant at follow-ups. This issue is a critical one that should be explored in future studies, and CBT interventions should be more focused on improving these aspects. Considering that the impact of CBT on quality of life and life/social adjustment was significant at posttreatment, the question of why it was lost during follow-up merits future investigations.

As with most meta-analytic research, this study has several shortcomings. First, one could argue that the effect size is not due to the specific mechanisms engaged by CBT, but to the general influence of common factors involved in psychotherapy (eg, placebo effect, attention).[4] Because we found only 2 randomized trials[6,22] comparing CBT to other forms of psychosocial interventions in bipolar disorder, adjunctive to medication in both, we could not rigorously investigate this aspect. However, considering that the effect of CBT on bipolar disorder symptoms was consistently associated with a similar change in cognitive-behavioral mechanisms, this finding can be interpreted in favor of the specific effects of CBT.

Second, some comparisons were limited by the sample size. Only 3 studies[17,21,22] had over 100 patients; the other studies involved small samples. This limitation will be corrected when more studies involving large samples are published.

Third, an important issue in meta-analysis is related to the "file-drawer" problem. Researchers who found nonsignificant results may not have published these findings, thus biasing the present results in a direction favoring CBT. Although we believe this is not the case here (for example, see Scott et al[21]), we calculated the number of studies with an effect size of zero that would be needed to reduce the present effect size (the general effect size at posttreatment) to zero.[26] We found that 52 studies (for d) or 30 studies (for D) with no effect would be needed to reduce the effect size we found to zero. We believe this number is unlikely considering that many of the published studies report nonsignificant effects. As we have mentioned before, the study by Scott et al,[21] because of its large sample size and nonsignificant outcomes, seriously influences the results against the effect of CBT. Therefore, it is very important that future studies address these aspects using large samples.

To summarize, we believe that CBT should be used as an adjunctive intervention to medication for patients diagnosed with bipolar disorder because of its positive effects at posttreatment and some positive effects at follow-up. Notably, the inclusion of CBT does not seem to increase the overall treatment costs. Thus, although the effects are not high (they are in the low-medium range), taking into account that adjunctive CBT does not increase costs, it should be implemented; any added clinical value is important in these severely affected patients. This conclusion is in line with other qualitative reviews[10,11] and the recommendation of the National Institute for Health and Clinical Excellence.

Having said that, we must also strongly emphasize the idea that future CBT treatments should develop innovative techniques aimed at (1) increasing their effect on various outcomes, (2) generating new effects on outcomes less impacted now (eg, recurrence, relapse), and (3) maintaining the effects once generated over a longer period of time. For example, in these studies, cognitive restructuring was typically focused on changing distorted cognitions (cold cognitions), in the form of automatic thoughts and/or schemas, rather than on changing appraisal/evaluative

cognitions (hot cognitions).[28] However, in the case of affective disorders, appraisal might be more relevant than cold cognitions.[29] Future CBT packages should consider specific interventions for changing appraisal (eg, evaluative irrational beliefs[30]). Indeed, in a recent study, David and colleagues[31] found that a focus on irrational beliefs in the treatment of major depressive disorder has a better outcome at 6-month follow-up compared to medication and CBT, based mainly on restructuring automatic thoughts and schemas. Future studies should therefore explore this aspect.

Finally, we believe that a more rigorous pattern should be followed by authors and required by editors of scientific journals when considering such aspects as outcome categories, results reporting, and follow-up intervals, etc, in randomized trials relating to bipolar patients. One of the major difficulties we were confronted with in conducting this analysis involved the tremendous heterogeneity of results and reporting styles. This can be seen both as a limitation of the study and also as an opportunity for future developments. As a limitation, the heterogeneity draws attention to the fact that meta-analysis cannot in itself clarify and reconcile major positive and negative findings. Well-designed, large-scale clinical trials are needed to firmly answer this question on the reconciliation of positive and negative findings in independent studies, dwelling on a coherent research methodology, developed and promoted by the main professional organizations in the field, based on expert guidelines and consensus. Establishing and following some common general guidelines in evaluating and presenting the impact of psychotherapeutic interventions in bipolar disorder would certainly be to the benefit of accuracy and clarity in the field. In other words, beyond summarizing the present state of this domain and discussing clinical implications, the present study also suggests guidelines for future research in the field (theory level) and argues for a more coherent approach to this topic from a methodological point of view, with both aspects having practical implications.

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