A Randomized Controlled Trial of Psychoeducation or Cognitive-Behavioral Therapy in Bipolar Disorder: A Canadian Network for Mood and Anxiety Treatments (CANMAT) Study

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ABSTRACT

Objective: Bipolar disorder is insufficiently controlled by medication, so several adjunctive psychosocial interventions have been tested. Few studies have compared these psychosocial treatments, all of which are lengthy, expensive, and difficult to disseminate. We compared the relative effectiveness of a brief psychoeducation group intervention to a more comprehensive and longer individual cognitive-behavioral therapy intervention, measuring longitudinal outcome in mood burden in bipolar disorder.

Method: This single-blind randomized controlled trial was conducted between June 2002 and September 2006. A total of 204 participants (ages 18–64 years) with *DSM-IV* bipolar disorder type I or II participated from 4 Canadian academic centers. Subjects were recruited via advertisements or physician referral when well or minimally symptomatic, with few exclusionary criteria to enhance generalizability. Participants were assigned to receive either 20 individual sessions of cognitive-behavioral therapy or 6 sessions of group psychoeducation. The primary outcome of symptom course and morbidity was assessed prospectively over 72 weeks using the Longitudinal Interval Follow-up Evaluation, which yields depression and mania symptom burden scores for each week.

Results: Both treatments had similar outcomes with respect to reduction of symptom burden and the likelihood of relapse. Eight percent of subjects dropped out prior to receiving psychoeducation, while 64% were treatment completers; rates were similar for cognitive-behavioral therapy (6% and 66%, respectively). Psychoeducation cost $180 per subject compared to cognitive-behavioral therapy at $1,200 per subject.

Conclusions: Despite longer treatment duration and individualized treatment, cognitive-behavioral therapy did not show a significantly greater clinical benefit compared to group psychoeducation. Psychoeducation is less expensive to provide and requires less clinician training to deliver, suggesting its comparative attractiveness.

Trial Registration: ClinicalTrials.gov identifier: NCT00188838

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Bipolar disorder is a serious lifetime condition that is characterized by a pattern of elevated mood states (mania) and depressions and has a prevalence of 1%–3% worldwide.[1–4] Episodes are difficult to control and frequently recur, subsyndromal symptoms are common, and disability and mortality are high.[5–8] Numerous treatment guidelines offer detailed summaries of therapeutic strategies, but even with complex pharmacotherapy, relapses are common and residual symptoms may persist.[9–12] These limitations to pharmacotherapy have recently prompted various psychosocial interventions, including psychoeducation,[13] cognitive-behavioral therapy (CBT),[14] family focused therapy,[15] and interpersonal/social rhythm therapy.[16] Such interventions vary considerably in intensity (from a few to over 20 sessions) as well as modality (individual, group, or family therapy), variations that have major implications in terms of the cost and capacity for dissemination of these treatments. The largest bipolar CBT study[17] to date, involving an effectiveness rather than efficacy trial of individual CBT, failed to show any impact except in a small cohort of individuals with relatively few prior episodes. A study[18] of acute bipolar depression demonstrated that intensive psychotherapy—up to 30 sessions per year of CBT, interpersonal/social rhythm therapy, or family focused therapy—was modestly superior to a 3-session psychoeducational intervention in likelihood of recovery from depression.

Chronic disease management strategies have begun to be applied to bipolar disorder, with encouraging results.[19,20] In an extension of such thinking, a stepped care model for treatment has been proposed, which layers disease management and psychosocial treatments based on evidence, pragmatism, and feasibility including cost; this model, in turn, invites comparative effectiveness research.[21,22] We previously conducted a single-site study[23] of a brief versus long CBT intervention for bipolar disorder and found no major differences in outcomes. In view of earlier findings of the efficacy of CBT, we conducted a larger randomized controlled trial of 2 interventions added to existing pharmacotherapy in bipolar patients, hypothesizing that a properly powered study would demonstrate a superior outcome for a full course of CBT.

For Clinical Use

- Psychosocial interventions provide modest but definite effect in improving mood stability in bipolar disorder.
- Research comparing different interventions shows that brief, well-planned group psychoeducational interventions can be as effective as longer, individual cognitive-behavioral therapy (CBT) for bipolar disorder.
- Brief group psychoeducation requires less staff training and is more cost-efficient than longer, individual CBT for bipolar disorder.

METHOD

Study Design

This was a multicenter, randomized, parallel-group study of 2 types of adjunctive psychotherapy for bipolar disorder: either 6 sessions of group psychoeducation or 20 sessions of individual CBT, added on to naturalistic medication use. This 18-month study, using blinded outcome assessors, was conducted at academic medical centers linked to the Canadian Network for Mood and Anxiety Treatments (CANMAT) in Toronto, Montreal, Vancouver, and Hamilton, Canada, between June 2002 and September 2006. The study was approved by the institutional ethics board at each participating medical center, and written informed consent was obtained from all subjects. The study is registered with ClinicalTrials.gov (identifier: NCT00188838).

To ensure equivalent times to onset of psychotherapy, a permuted block randomization strategy in which blocks of 4 patients (the minimum group size for psychoeducation) were assigned to 1 of 2 treatment interventions was employed, with additional random generation of the assignment of treatment category to each block of 4. The computer generated sequences were kept in sealed opaque envelopes at the coordinating center until a site called for randomization.

Participants

Subjects were recruited by internal advertising using posted brochures, by community newspaper ads, and from outpatient psychiatry clinics. Subjects were 18–64 years of age and had bipolar disorder, type I or II, confirmed with the Structured Clinical Interview for *DSM-IV*.[24] Individuals were on treatment with a mood-stabilizing medication at study entry as established by bipolar treatment guidelines,[10,25] but medications were modified as necessary by the subject's usual physician during the study. Individuals had at least 2 episodes of significant symptoms or full episodes within the previous 3 years, but could not be in an episode in the month preceding randomization. Subjects were excluded only if they had current substance dependence, severe borderline personality disorder, antisocial personality disorder, life-threatening medical illness, acute suicidality or homicidality, or significant cognitive deficits or language problems.

Interventions

Individuals assigned to psychoeducation received 6 sessions of 90 minutes' duration drawn from a published manual.[26] The Life Goals manual includes a key psychoeducational component of 6 didactic sessions given by a therapist in a group format, with specific objectives and discussion points designed to elicit group member participation. Given the highly structured and detailed teaching, the group participation did not allow for the type of deep interpersonal sharing characteristic of classic group psychotherapy. Topics include illness recognition, treatment approaches, and coping strategies. The sessions culminate with explicit creation of a Personal Care Plan including an "Action Plan" for both depression and mania, to be instigated at the point of experiencing any symptoms of relapse or at exposure to historically observed personal triggers to relapse; these plans were shared with the therapists but not between subjects. Psychoeducation was delivered by experienced psychiatric staff (4 nurses, 2 psychotherapists, and 1 psychiatrist, done separately by site) after a brief training program (1 day plus supervision and feedback).

Individuals assigned to CBT received 20 individual sessions of 50 minutes' duration adapted from a published manual that organizes treatment into 3 stages.[27] The initial sessions (stage 1) focus on psychoeducation with respect to the diagnosis and course of bipolar illness and both psychological and pharmacologic treatments (including compliance). This psychoeducation is followed by a detailed life event history and individual goal-setting. In the subsequent sessions (stage 2), a range of cognitive and behavioral approaches are used to assist each subject to understand personal warning signs for onset of depressions and mania, along with a "relapse drill" of actions to take to mitigate risk of full episode relapse. In addition to traditional CBT strategies utilized in the treatment of depression, such as activity scheduling and cognitive restructuring, behavioral self-monitoring of mood and sleep are emphasized, as well as stimulus control measures to cope with hypomania and general mood instability. Also, a key emphasis is to facilitate cognitive restructuring of dysfunctional thoughts and assumptions through analysis of special automatic thought record sheets as well as through behavioral experiments. Sessions following the active treatment phase (stage 3) focus on continuing practice of techniques learned previously and on behavior changes strategies.

The CBT intervention employed individuals with at least a master's degree level of training and 1 year of experience with CBT; these individuals subsequently received a 2-day training program with periodic supervision and feedback (2 psychologists, 2 psychiatrists, 7 psychotherapists, 2 nurses).

All sessions were audiotaped: a random sample audit of approximately 20% of all sessions revealed comparable, high treatment fidelity for both interventions. Medications were prescribed by the subject's usual treating physician and recorded.

Effectiveness Outcomes

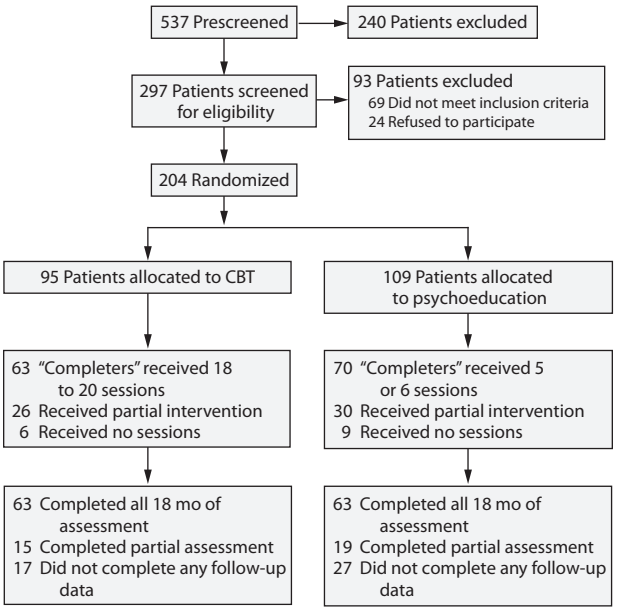
The principal outcome of the study was the degree to which the 2 treatments differed in the reduction of mood burden over the 72-week study period. Mood burden was ascertained using Longitudinal Interval Follow-up Evaluation (LIFE) scale scores for mania/hypomania and depression.[28] The LIFE is a semistructured interview and weekly retrospective rating system for depressive and manic/hypomanic symptoms that uses a 6-point scale on which 1 or 2 = no to minimal symptoms, 3 or 4 = clinically significant but subthreshold symptoms, and 5 or 6 = significant to severe syndromal symptoms. Key additional measures administered at entry and each follow-up assessment included (1) the Modified Social Adjustment Scale, integrated with the LIFE assessment tool[29]; (2) the 17-item Hamilton Depression Rating Scale[30]; and (3) the Clinician-Administered Rating Scale for Mania.[31] All follow-up assessments were conducted by trained assessors blind to the treatment assignment. Assessors were experienced research assistants who received additional training in the LIFE instrument and other scales at the start of the study. Interrater reliability assessments were conducted every 3 months for the LIFE during the study, involving complex fictional clinical vignettes that revealed various patterns of mood shifts over an 8-week span. Raters were to provide scores for these test scenarios for each week according to the LIFE; raters from the 4 sites showed concordant ratings over 90% of the time, and any rater with significant differences received additional review of the scoring criteria.

Statistical Analysis

Growth curve modeling was used to determine whether LIFE scores changed over the course of the study and whether the magnitude of this change differed across study groups. Separate models were developed for depression and mania scores. These models control for the relatedness of repeated measures taken on the same individuals and allow testing of differences in initial scores (intercept) and the rate of change (slope) across study groups. A series of Cox regression analyses (for depression and mania LIFE scores) was performed to determine whether the time to first recurrence differed significantly across study groups. Recurrence was defined as a LIFE score of 5 or 6. Mean depression and mania rating scale scores were compared between psychoeducation and CBT arms using a repeated measures approach for all the assessment times. Finally, we constructed a Kaplan-Meier survival curve and tested differential survival using a log-rank test.

Patient characteristics at study entry were compared between the 2 groups with the use of χ^2 tests and *t* tests where appropriate. The proportions of subjects who dropped out in each treatment arm were compared using χ^2 tests. For all comparisons, the traditional *P* value of less than .05 was considered significant. Calculations of sample size based on at least a moderate effect size (based on Cohen's criteria[32]) a priori yielded a target recruitment of 210 subjects, while 204 subjects were actually enrolled. Adequate enrollment together with observed effect sizes for the 2 treatments ranging from 0.28 to 0.35 indicates that the study was sufficiently powered to detect differences between groups.

Figure 1. Enrollment, Treatment, and Assessments in a Randomized Controlled Trial of Psychoeducation Versus Cognitive-Behavioral Therapy (CBT) in Bipolar Disorder



RESULTS

Characteristics and Disposition of Subjects

Figure 1 displays the distribution of subjects throughout the study. At baseline, the 2 groups did not differ in demographic or clinical characteristics, as shown in Table 1. Key notable characteristics include the following: (1) 28% of the sample had bipolar II disorder; (2) recurrence rates were high, as 70% of the sample had experienced more than 10 mood episodes; and (3) comorbidity rates were high, as about half of the group had a lifetime anxiety disorder and about one-quarter had a lifetime substance use disorder.

Both groups were found to be similar with regard to initial medications, with 42% of each group receiving lithium, 43% of each group receiving valproate, and 31% of each group receiving an atypical antipsychotic. Specific medications at baseline used by the total sample included carbamazepine (6%), gabapentin (5%), lamotrigine (24%), olanzapine (14%), risperidone (6%), and quetiapine (15%).

Completion of Study

Close to two-thirds of subjects in each treatment were defined as completers (*P* = .75), with similar dropout rates of 6% in the CBT group and 8% in the psychoeducation group

Table 1. Baseline Characteristics of Subjects in a Randomized Controlled Trial of Psychoeducation Versus Cognitive-Behavioral Therapy (CBT) in Bipolar Disorder

Characteristic	Cognitive-Behavioral Therapy (n = 95)	Psychoeducation (n = 109)	*P* Value
Site, n (%)			.37
Toronto	34 (35.8)	35 (32.1)	
Hamilton	26 (27.4)	33 (30.3)	
Montreal	21 (22.1)	25 (22.9)	
Vancouver	14 (14.7)	16 (14.7)	
Gender, n (%)			.15
Male	35 (36.8)	51 (46.8)	
Female	60 (63.2)	58 (53.2)	
Age at baseline, mean (SD), y	40.9 (10.7)	40.9 (10.8)	
Education, n (%)			.13
Up to high school graduation	16 (16.8)	17 (15.6)	
Some university or university graduate	60 (63.2)	81 (74.3)	
Graduate studies	16 (16.8)	9 (8.3)	
Unknown	3 (3.2)	2 (1.8)	
Marital status, n (%)			.44
Married or common law	31 (32.6)	42 (38.5)	
Single	37 (38.9)	44 (40.4)	
Divorced, separated, or widowed	27 (28.4)	23 (21.1)	
Bipolar subtype, n (%)			.89
Type I	68 (71.6)	79 (72.5)	
Type II	27 (28.4)	30 (27.5)	
Age at first mood episode, mean (SD), y	22.2 (9.6)	22.0 (9.0)	
More than 10 episodes, n (%)	68 (71.6)	74 (67.9)	
Hospitalization, n (%)			.93
Yes	63 (66.3)	71 (65.1)	
No	32 (33.7)	37 (33.9)	
Missing	0 (0.0)	1 (1.0)	
Anxiety disorder (lifetime), n (%)	49 (51.6)	48 (44.0)	
Substance use disorder (lifetime), n (%)	24 (25.3)	29 (26.6)	
LIFE—mania score across 4 wk, mean (SD)	1.3 (0.7)	1.3 (0.6)	
LIFE—depression score across 4 wk, mean (SD)	2.5 (1.4)	2.4 (1.2)	
HDRS total score (17 items), mean (SD)	6.5 (4.8)	7.3 (5.0)	
CARS-M total score, mean (SD)	1.7 (2.6)	2.3 (3.5)	

Abbreviations: CARS-M = Clinician-Administered Rating Scale for Mania, HDRS = Hamilton Depression Rating Scale, LIFE = Longitudinal Interval Follow-up Evaluation.

prior to receiving any sessions (Figure 1). There were no clinical or demographic differences at baseline between eventual CBT dropouts and psychoeducation dropouts. Including all randomized subjects, CBT recipients attended a mean of 15 sessions, while psychoeducation recipients attended a mean of 5 sessions. Eighty-five percent of subjects in both groups who received at least 1 treatment session completed at least 1 follow-up assessment, with 67% of these subjects completing all 18 months of assessment and no differences between treatment groups ($P = .17$).

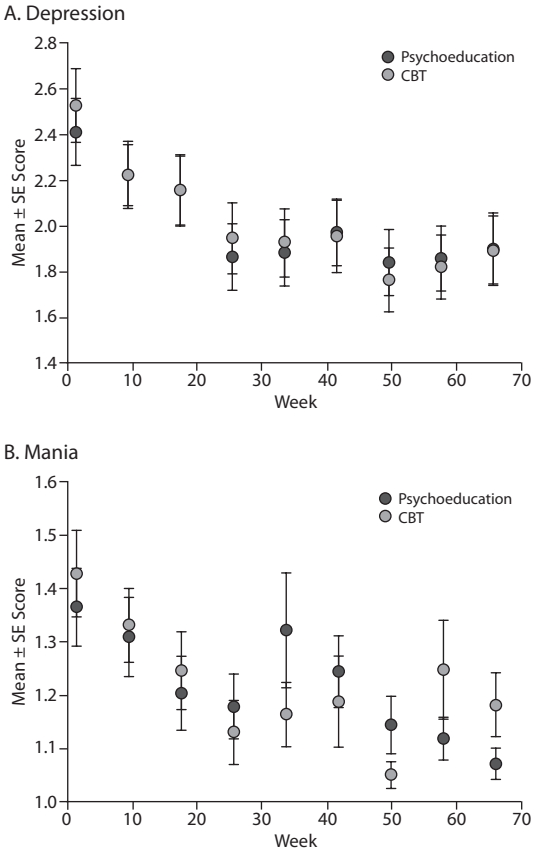
Treatment Outcomes

Our principal outcome was the comparison of LIFE scores across the study, a measure of mood burden over time. Both groups showed significant decline in LIFE scores over time ($P < .01$ for both groups); there were no differences between groups (Figure 2). There were no differences in scores on periodic symptom rating scales for either depression ($P = .89$) or mania ($P = .96$) during the study. Further analysis by number of previous episodes did not show any differential benefit by treatment group, dichotomizing around either ≤ 5 previous episodes ($P = .89$) or 10 previous episodes ($P = .97$). Next, a survival analysis was done, with 95 of the 204 subjects experiencing a depression recurrence and 59 subjects experiencing a recurrence of hypomania or mania. The proportions of those experiencing recurrence did not differ by group. After those who dropped out prior to recurrence or did not have a recurrence during the study were censored—leaving an effective sample size of 153—time to recurrence was calculated, again revealing no differences between treatment groups (Figure 3; $P = .76$ for depression; $P = .46$ for mania). In addition, the 2 groups were compared on changes in ratings of depression and mania over time with the standard rating scales; both groups showed a similar and significant decline in LIFE ratings. No significant differences in outcomes were seen by site. Additional post hoc exploration of the data revealed that baseline subthreshold symptoms or comorbidity did not influence outcome by treatment subtype; across the entire sample, baseline symptoms were associated with slightly more depressive symptoms over time.

Medication Use and Compliance

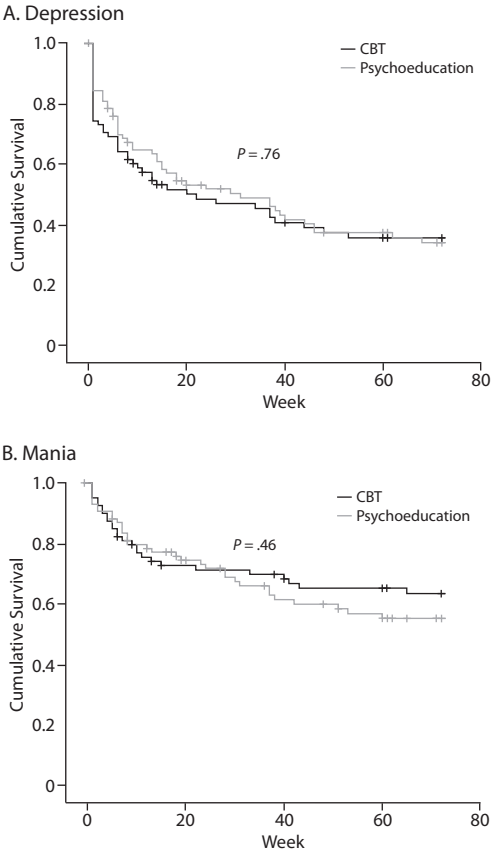
No significant differences in medication between groups were observed. Use of lithium and valproate use remained at baseline levels throughout the study, with absolute use of atypical antipsychotics also remaining constant. Antidepressants were used by approximately 50% of the entire sample

Figure 2. Longitudinal Interval Follow-up Evaluation (LIFE) Scores by Treatment Group: Eight-Week Aggregate Intervals



Abbreviation: CBT = cognitive-behavioral therapy.

Figure 3. Survival Curves for Recurrence With Depressive or Manic Episode



Abbreviation: CBT = cognitive-behavioral therapy.

during the course of the study. Medication compliance was excellent on patient interview for both groups.

DISCUSSION

We investigated the effectiveness of a brief psychoeducational intervention conducted in a group format in comparison to a longer cognitive-behavioral intervention delivered individually in addition to existing pharmacotherapy in subjects with bipolar disorder. Both approaches have substantial data supporting a positive effect in reducing mood burden and rates of relapse in bipolar disorder. We found no differences in overall mood burden or rates of relapse in this randomized controlled trial conducted in 4 sites across Canada. Both treatments were associated with significant decreases in overall mood burden over the 18-month study period. Since similar percentages of each treatment group were completers, low CBT compliance was not a concern as in an earlier study.[17] Our original hypothesis postulating superior outcomes for CBT was not confirmed. While the study was not powered as an equivalency trial, the significant ($P < .01$) time effects of each treatment and earlier studies demonstrating the efficacy of psychoeducation invite speculation that the briefer psychoeducation may be as effective as a full course of CBT. Furthermore, since the group psychoeducation was highly scripted and did not allow for sharing of the key product—a personal coping plan—between participants, it is unlikely that the therapeutic factors associated with formal group psychotherapy could explain the efficacy of psychoeducation.

The lack of superiority of CBT invites many possible explanations. The brief training of experienced CBT therapists could have resulted in poor fidelity. However, all 4 study sites are established academic research centers with experience in delivering CBT; it is unlikely that all 4 could have failed to deliver adequate therapy, particularly since 2 sites had been delivering bipolar CBT for several years, including in our previous study.[23] Furthermore, random audit of audiotaped CBT sessions showed good fidelity to treatment for all therapists except for 1 whose treatment was restricted to 2 subjects. More plausibly, CBT did not prove superior to psychoeducation because it simply is not superior. The robust findings of CBT in unipolar depression rest in part on the fact that a relevant CBT model exists; for bipolar disorder, no satisfactory theoretical CBT model exists.[33] Common to all psychosocial interventions in bipolar disorder is early symptom recognition and response, perhaps most purely demonstrated in the study by Perry and colleagues[34] in

which a relapse drill was strikingly effective in preventing relapse into mania. As Parikh and Scott have noted, "CBT in bipolar disorder is currently a generic, nonspecific psychoeducation intervention that incorporates some cognitive and behavioral techniques, not a specific empirically driven approach based on a cognitive formulation and primarily focused on cognitive style and processing."[33(p425)]

Study limitations include subject recruitment primarily from academic medical centers; these subjects may not be fully representative of bipolar patients in the community. While individuals had to be on appropriate bipolar medication treatments at the outset of the study, subsequent medication use was naturalistic. However, no significant differences on medication use between groups was found, thus removing this as a potential confound. Finally, the lack of an untreated control group is a genuine weakness; it is possible that both psychoeducation and CBT were equally ineffective, ie, this study is not a negative study about the superiority of CBT but instead a failed trial. The fact that the improvement seen in each arm over time mirrors that seen in earlier controlled trials by Lam et al[14] and by Simon et al[19] suggests that each treatment indeed had efficacy.

Our study was notable in several ways. First, we explicitly designed an effectiveness study, including subjects with comorbidities and few exclusionary criteria (only 1 subject was excluded for substance dependence, and none for personality disorder). Individuals both in remission and with subsyndromal symptoms were enrolled. By including patients with varying degrees of symptoms and concomitant conditions, our sample was more likely to be representative of a modal bipolar patient. Interventions were chosen for both efficacy and practicality, with deliberate comparison of different modalities and duration of treatment. The principal outcomes were selected to detect overall mood burden by capturing symptom expression along a full continuum from well to full relapse, over an 18-month period. Our findings of potential equivalency between treatments mirrors findings of other large effectiveness studies, such as the Sequenced Treatment Alternatives to Relieve Depression study and the Clinical Antipsychotic Trials of Intervention Effectiveness in schizophrenia.[35,36]

Our findings are particularly relevant in terms of generalizability with regards to both cost and ease of training. Our extensive experience (more than 13 years) of training both research therapists and clinicians in CBT[37] and in psychoeducation for bipolar disorders,[23] and our experience in training and supervising therapists in earlier trials,[23] (including 1 unpublished study, Parikh et al) led to our decision to have brief yet highly refined training. For study recruitment reasons, we had set the usual group size at 4 for psychoeducation, with a total paid time for treatment delivery of 2 hours for each 90-minute session, or 12 hours of staff time. Twenty hours of staff time paid at $60 per hour yielded a CBT cost of $1,200 per participant. Using the same hourly rate (higher than the actual rate typically paid to nurses), the psychoeducation intervention for 4 subjects cost $720, or just $180 per participant. Furthermore, usual clinical care groups in psychoeducation are often larger, further reducing costs. The cost advantages to employing psychoeducation rather than CBT thus are quite striking. Scott and colleagues[38] found a further cost-benefit advantage from group psychoeducation intervention, which lowered overall costs by reducing health care utilization over 5 years. The fewer training requirements for psychoeducation, the use of nurses as the most readily available treatment provider, and the use of brief training methods for that intervention all speak to the opportunity for rapid uptake of psychoeducation across different health care systems and treatment settings.

Existing psychosocial studies suggest similar effect sizes for each of the different interventions, with no evidence to support a comparative advantage for any particular approach. Difficulty in making specific treatment recommendations based on these initial efficacy studies may reflect inherent limitations of efficacy-based research paradigms. These limitations reinforce the value of research designs that reflect the effectiveness of treatments under "real world" conditions.[39] Recent major studies in bipolar depression, unipolar depression, and schizophrenia have therefore utilized effectiveness designs.[11,35,36] In that spirit, this study extends the efficacy research on psychoeducation and CBT into the realm of effectiveness. Our results suggest that despite all the advantages that are associated with CBT—longer treatment duration, individual treatment, more highly trained psychotherapists, and close supervision—CBT did not show significant benefit over group psychoeducation. Provision of a brief group psychoeducation program, which should be less expensive and easier to disseminate, was no different in outcomes from CBT for bipolar disorder. This positioning of psychoeducation as a more "effective" treatment invites formal testing of a stepped care approach[21] to bipolar disorder with individuals initially receiving psychoeducation and reserving additional psychosocial interventions for those with enduring symptoms.

Drug names: carbamazepine (Carbatrol, Equetro, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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Author contributions: Dr Parikh and Mr Velyvis had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. **Study concept and design:** Parikh, Zaretsky. **Acquisition of data:** Parikh, Zaretsky, Velyvis, Young, Patelis-Siotis, MacQueen, Yatham, Beaulieu, Cervantes. **Analysis and interpretation of data:** Parikh, Zaretsky, Velyvis, Streiner, Arenovich,

Levitt, Kennedy. **Drafting of the manuscript:** Parikh, Velyvis. **Critical revision of the manuscript for important intellectual content:** Parikh, Zaretsky, Beaulieu, Yatham, Young, Patelis-Siotis, MacQueen, Levitt, Arenovich, Cervantes, Velyvis, Kennedy, Streiner. **Statistical analysis:** Parikh, Velyvis, Arenovich, Streiner. **Obtained funding:** Parikh. **Administrative, technical, or material support:** Parikh, Zaretsky, Young, Yatham, Levitt, Kennedy, Beaulieu, Cervantes. **Study supervision:** Parikh, Zaretsky, Beaulieu, Cervantes, Yatham, Young, Patelis-Siotis, MacQueen.

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