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Adjunctive Psychotherapy for Bipolar Disorder:

State of the Evidence

David J. Miklowitz, Ph.D.

From the Department of Psychology, University of Colorado; and the Department of Psychiatry, University of Colorado Health Sciences Center, Denver

Abstract

Objective—Psychotherapy has long been recommended as adjunctive to pharmacotherapy for bipolar disorder, but it is unclear which interventions are effective for which patients, over what intervals, and for what domains of outcome. This article reviews randomized trials of adjunctive psychotherapy for bipolar disorder.

Method—Eighteen trials of individual and group psychoeducation, systematic care, family therapy, interpersonal therapy, and cognitive-behavioral therapy are described. Relevant outcome variables include time to recovery, recurrence, duration of episodes, symptom severity, and psychosocial functioning.

Results—The effects of the treatment modalities varied according to the clinical condition of patients at the time of random assignment and the polarity of symptoms at follow-up. Family therapy, interpersonal therapy, and systematic care appeared to be most effective in preventing recurrences when initiated after an acute episode, whereas cognitive-behavioral therapy and group psychoeducation appeared to be most effective when initiated during a period of recovery. Individual psychoeducational and systematic care programs were more effective for manic than depressive symptoms, whereas family therapy and cognitive-behavioral therapy were more effective for depressive than manic symptoms.

Conclusions—Adjunctive psychotherapy enhances the symptomatic and functional outcomes of bipolar disorder over 2-year periods. The various modalities differ in content, structure, and associated mediating mechanisms. Treatments that emphasize medication adherence and early recognition of mood symptoms have stronger effects on mania, whereas treatments that emphasize cognitive and interpersonal coping strategies have stronger effects on depression. The placement of psychotherapy within chronic care algorithms and its role as a preventative agent in the early stages of the disorder deserve investigation.

Despite significant strides in the pharmacological treatment of bipolar disorder, most bipolar patients cannot be maintained on drug treatments alone. Up to 50% of bipolar I patients do not recover from acute manic episodes within 1 year, and only 25% achieve full recovery of function (1). Rates of recurrence average 40%-60% in 1-2 years even when patients undergo pharmacotherapy (2). Patients spend as much as 47% of their lives in symptomatic states, especially depressive states (3). Furthermore, only about 40% of patients are fully adherent with medication regimens in the year following an episode (4).

The ceiling on the effectiveness of pharmacotherapy has led to systematic investigations of the role of environmental stressors, and the corresponding role of adjunctive psychosocial treatments in the course of the disorder. Stressful life events and high levels of familial

expressed emotion are robust predictors of mood recurrences and delayed episode recovery in bipolar illness (5,6). Furthermore, 17 of 18 randomized, controlled trials (Table 1) have shown that individual, family, group, and systematic care treatments are effective in combination with pharmacotherapy in delaying relapses, stabilizing episodes, and reducing episode length.

Reviews (7-9) have concluded that psychoeducation is the active ingredient in most forms of psychotherapy for bipolar illness: a didactic, information-oriented approach to the illness. A close look at the trials, however, reveals important differences in the content and structure of the various treatments and significant differences between studies in the targeted patient populations, the nature of the control conditions, and the relevant outcome variables. Notably, some psychosocial modalities emphasize early recognition of mood symptoms, whereas others emphasize interpersonal relationships, communication skills, and stress management. Some forms of psychotherapy are effective when initiated during periods of sustained recovery, whereas other forms are effective when initiated immediately after an acute episode.

This article will examine the evidence for adjunctive psychosocial interventions for bipolar disorder, with a focus on five questions: 1) which treatments work at which stages of the illness? 2) how long should treatments last, and how enduring are their effects? 3) do the same treatments modify depressive and manic symptoms? 4) which functional domains (i.e., social, work, or family functioning or quality of life) are enhanced? 5) By what mechanisms do psychosocial treatments operate? The primary hypothesis is that treatments that emphasize medication adherence and relapse prevention strategies are more effective in controlling manic symptoms, whereas treatments that emphasize cognitive and interpersonal coping skills are more effective in controlling depressive symptoms.

Method

Studies were identified through MEDLINE and PsycINFO searches as well as existing reviews (7-9). The search terms included psychotherapy, psychosocial treatment, family therapy, individual therapy, group therapy, and psychoeducation. A total of 18 randomized trials were published between 1984 and 2008. One additional wait-list trial evaluated multifamily groups for youth with bipolar disorder and major depression, but the symptomatic outcomes have not yet been reported (10). Four general categories of psychotherapy were identified: psychoeducational (individual, group, and systematic care), family, cognitive-behavioral therapy, and interpersonal (Table 1).

Results

Individual Psychoeducation

The assumption behind psychoeducation is that when patients learn about bipolar disorder, develop relapse prevention plans, learn to stay adherent with medications, and implement illness management strategies (e.g., keeping regular sleep/wake cycles), they stay well for longer periods of time. Didactic information may reduce the stigma associated with the disorder and increase the likelihood that patients obtain necessary treatments (10).

In the only randomized, controlled trial of individual psychoeducation (11), 69 remitted bipolar I patients were randomly assigned to pharmacotherapy plus routine care or pharmacotherapy plus 7-12 sessions of psychoeducation. Patients identified three or more symptoms that constituted the prodromes of manic or depressive episodes and rehearsed an early intervention plan (usually involving changes in medications) for when these symptoms appeared. The results over 18 months indicated clear benefits for individual psychoeducation on the likelihood of manic recurrences (27% of patients versus 57% in routine care) and the time to first manic recurrence as in but not on time to depressive recurrences. Possibly, the prodromal symptoms

of depressive recurrences are less distinctive than of manic recurrences, and the emergency treatment options less clear cut.

Group Psychoeducation

Group psychoeducation (GPE) has been administered in two formats: alone (as adjunctive to medications) or as part of a larger systematic care intervention. The results differ accordingly. In a study conducted in Barcelona, Spain, Colom et al. (12) randomly assigned 120 bipolar I and II patients to 9 months and 21 sessions of structured GPE or a 21-session unstructured support group. The structured GPE included lectures and exercises to enhance illness awareness, early detection and intervention with prodromal symptoms, medication compliance, and life style regularity, whereas the unstructured groups were supportive but not psychoeducational. Patients were free of comorbid disorders and had been in remission for at least 6 months. Over a 2-year study, the results strongly favored GPE: 67% of the GPE patients versus 90% of the unstructured group patients had recurrences. The effects extended to the number of days patients spent in the hospital, which may suggest that GPE facilitated early detection of manic episodes and a resulting decrease in their severity. Somewhat puzzling was the observation that patients were more likely to drop out of the structured groups (26.6%) than the unstructured groups (11.6%). Nonetheless, patients in GPE maintained higher lithium levels over the 2-year study.

The efficacy of GPE was also examined among bipolar adults with comorbid substance disorders (13). Bipolar I and II patients (N=62) were assigned randomly to 20 weeks of integrated group therapy or an equally intensive drug abuse counseling group. The integrated group focused on challenging cognitions relevant to the relapse and recovery processes of both disorders, whereas the drug counseling group focused on abstinence and coping with substance craving. Over 8 months, patients in the dual-focus groups had half as many days of alcohol use as those receiving only group drug counseling. The integrated groups did not prevent episodes of bipolar disorder; in fact, patients in the integrated groups had higher subsyndromal depression and mania scores than patients in the comparison group. The psychoeducation about mood disorders provided in the integrated groups may have increased the frequency with which patients recognized and reported mood symptoms.

Group Psychoeducation Within Systematic Care Models

Two studies have examined GPE within the context of overall systems of care. Working within 11 Veterans Administration (VA) settings, Bauer et al. (14) administered a collaborative chronic care treatment consisting of evidence-based pharmacotherapy, a nurse care coordinator assigned to each patient to enhance adherence to treatment, regular telephone monitoring of prodromal mood symptoms, and a structured "life goals" program consisting of 5 weekly followed by twice monthly group sessions for up to 3 years. The GPE focused on relapse prevention strategies, medication adherence, and illness management. Patients in a treatment-as-usual group received usual VA care, which included medication sessions and occasional psychotherapy.

The study contained 306 bipolar I patients, 87% of whom began as inpatients. Over 3 years, patients in the collaborative care intervention had 6.2 fewer weeks in affective episodes, 4.5 weeks of which were attributable to reductions in the length of manic episodes. There were no differences between the collaborative care and the treatment-as-usual groups in the length of depressive episodes. Broad effects of the care intervention were found on social and work functioning, quality of life, and treatment satisfaction. Of interest, the group differences were not statistically reliable until 2 years, suggesting a delayed effect of psychoeducation and facilitated collaboration with care providers.

A study with a nearly identical design—and the largest psychosocial study to date—was carried out in the Group Health Cooperative organization of Washington State, U.S. Simon et al. (15) randomly assigned 441 patients to a 2-year systematic collaborative care program or treatment as usual (typically medication management visits). The probability of a new manic episode was significantly lower in the systematic care group over the eight assessment points of the study. Patients spent an average of 5.5 fewer weeks with clinically significant symptoms of mania than those in treatment as usual. Like the VA study, there were no effects of systematic care on depression severity, weeks depressed, or depressive recurrences. Of interest, the effects on mania severity scores were only observed among the 343 patients with moderate to severe symptoms at entry.

Family Psychoeducation

Multiple randomized trials indicate that behavioral family therapy is an effective adjunct to neuroleptics in delaying psychotic recurrences and improving functioning among patients with schizophrenia (16). Likewise, several randomized, controlled trials have found that family psychoeducation is effective in enhancing the course of bipolar disorder (Table 1). One small-scale trial (N=33) found that acutely ill patients receiving an 11-month psychoeducational marital intervention had better medication adherence and greater improvements in functioning than those receiving pharmacotherapy alone (17). No effects of the marital intervention were observed on symptomatic outcome.

Our research group has conducted three trials of family-focused therapy, which consists of 21 sessions of psychoeducation, communication enhancement training, and problem-solving. Family-focused therapy emphasizes strategies for regulating one's emotions and enhancing interpersonal communication when facing conflicts (e.g., reflective listening; actively requesting support from family members). In the first trial (18), we randomly assigned 101 adult patients shortly after an acute manic, mixed, or depressive episode (81% hospitalized) to family-focused therapy and pharmacotherapy or two sessions of family-based crisis management and pharmacotherapy. Over 2 years, patients in family-focused therapy had a greater likelihood of survival without disease relapse (52%) than patients in crisis management (17%) and survived longer without recurrence (mean=73.5 weeks) than patients in crisis management (53.2 weeks). The effects of family-focused therapy were stronger on depressive ($p=0.005$) than manic symptoms ($p<0.05$). The effects of family-focused therapy on depressive symptoms appeared to be mediated by improvements in communication between patient and relatives in a laboratory-based family interaction task (19). In contrast, the effects of family-focused therapy on mania symptoms appeared to be mediated by improvements in patients' adherence with lithium and anticonvulsant regimens (18).

In a second trial (20), we examined family-focused therapy and pharmacotherapy versus an individual therapy and pharmacotherapy in 53 bipolar I patients hospitalized for a manic episode. The individual therapy was of identical frequency (21 sessions) and length (9 months) and contained many of the same psychoeducational elements as family-focused therapy. At 1 year, no differences emerged in recurrence rates. However, over a 1-2 year posttreatment period, patients in family-focused therapy had a 28% recurrence rate and a 12% rehospitalization rate, compared to a 60% recurrence rate and a 60% rehospitalization rate for individual therapy. Mean survival times prior to recurrences were also longer in the family-focused therapy group.

Our third randomized trial examined the effects of adjunctive family-focused therapy (21 sessions) or a 3-session psychoeducational treatment on subsyndromally or acutely ill adolescents (mean age=14.5) who had had at least one episode of bipolar spectrum disorder in the prior 3 months (21). Adolescents assigned to family-focused therapy had more rapid recoveries from depressive states, spent less time in acute depressive episodes, and had a more

favorable trajectory of depressive symptoms over 2 years than adolescents receiving pharmacotherapy and brief psychoeducation. The effects of family-focused therapy were not significant for manic symptoms.

Multifamily Psychoeducation Groups

Presumably, working with multiple families at once could be more cost-effective than working with families individually. Miller and associates (22,23) assigned 92 acutely ill (75% manic) bipolar I patients to pharmacotherapy alone, pharmacotherapy plus 12 sessions of single-family therapy (based on problem-centered systems therapy), or pharmacotherapy plus six sessions of multi-family psychoeducation groups. Over 28 months, no differences emerged between the three groups in time to recovery or recurrence. However, patients from families that were initially high in conflict or low in problem-solving and who received either form of family therapy had approximately half as many depressive episodes per year and spent less time in depressive episodes than those who received pharmacotherapy alone. There were no effects of either family intervention on mania symptoms and no differences in the outcomes of patients who received single family therapy or multifamily groups. The study is consistent with the family-focused therapy trials in showing stronger effects of family intervention on depressive than manic outcomes.

One study examined the effects of caregiver psychoeducation groups that did not involve patients (24). Participants were caregivers (62 parents and 45 partners) of 113 bipolar I and II patients treated at a bipolar clinic at the University of Barcelona, Spain. Patients had to be euthymic for 3 months, free of any other axis I disorder, and living with relatives. The caregivers were randomly assigned to 12 weeks of group psychoeducation or treatment as usual (pharmacological care for patients without caregiver groups). Similar to the family-focused therapy model, the caregiver groups focused on illness management skills (e.g., early detection of prodromes), medication adherence, and effective communication and problem-solving.

Over a 12-month posttreatment follow-up, patients whose relatives attended the groups had longer survival times prior to hypomanic or manic recurrences than patients in treatment as usual but did not differ on time to depressive or mixed episodes. Thus, caregivers may have been able to identify and intervene with patients' manic prodromes without the input of the patients. In contrast, patient involvement may be necessary to extend the benefits of multifamily groups to the alleviation of depressive symptoms.

Cognitive-Behavioral Therapy

Some bipolar patients have pessimistic explanatory styles in the depressive phases and overly optimistic explanatory biases in the manic or hypomanic phases of the illness (5). These thinking biases are the target of cognitive restructuring strategies. Cochran (25) examined a six-session individual cognitive-behavioral therapy (CBT) in a small-scale randomized, controlled trial involving 28 stable bipolar I patients. The goal of the CBT was to alter cognitions and behaviors that interfered with lithium compliance. Relative to standard care (lithium alone), the intervention was successful over a 6-month follow-up in promoting compliance, reducing the proportion of patients requiring hospitalization and reducing the proportion of patients with mood episodes attributable to noncompliance.

Lam et al. (26,27) identified 103 bipolar I and II patients who were in recovery but had had at least three episodes in the past 5 years. Patients were randomly assigned to pharmacotherapy plus 12-18 individual CBT sessions over 6 months or pharmacotherapy plus routine care. The results over 1 year favored the CBT group (44% relapsed) over the routine care group (75%). Patients in CBT also had fewer hospitalizations and days in the hospital, better social functioning, and better medication adherence than those in routine care. At 30 months, the

group difference in relapse rates was only significant for depressive relapses. Depression severity scores and days spent in depressive episodes were lower among CBT patients over 12 but not 30 months.

A single-site randomized, controlled trial (N=52) in Australia generally confirmed these results (28). Bipolar I and II patients who were euthymic or mildly symptomatic were randomly assigned to medication and 6 months (20 sessions) of CBT and “emotive techniques” (imagery, narratives, and reliving early experiences) or medication with brief psychoeducation (treatment as usual). Patients in CBT had lower depression scores at 6 months and tended to have longer times to depressive relapses over 18 months ($p=0.06$) but did not differ in overall relapse rates. Patients in CBT also had greater improvements in the severity of depressive symptoms relative to the 18 months preceding the study. As in the Lam et al. (27) trial, the benefits of CBT on depression scores diminished over time, suggesting that booster sessions may be necessary for the maintenance of gains.

A five-site U.K. study of 253 bipolar I and II patients examined CBT in community centers serving highly recurrent patients (29). Most of the patients were “high risk” by virtue of having comorbid disorders (e.g., substance dependence), at least one episode in the prior year, current active symptoms (32% in acute episodes), or other risk factors. Patients in CBT underwent 22 sessions over 26 weeks, although patients attended an average of only 14 sessions (identical to the Lam et al. [26] trial). The primary results were negative: over 18 months, patients in CBT did not differ from those in treatment as usual on time to recurrence, duration of illness episodes, or mean symptom severity scores. A post hoc analysis revealed that CBT was effective in delaying recurrences among patients with fewer than 12 prior episodes.

A maintenance randomized, controlled trial in Canada examined the effects of CBT in addition to individual psychoeducation (7,30) among 79 fully remitted or minimally symptomatic bipolar I and II patients on stable medications. All subjects received seven individual sessions of psychoeducation derived from a structured CBT manual; half also received 13 individual sessions of CBT. There were no differences in relapse or rehospitalization rates between the two study arms, but the patients in CBT had 50% fewer days of depressed mood and fewer antidepressant dosage increases over the study year.

Parikh and colleagues (personal communication, June 29, 2008) have recently concluded an effectiveness study of CBT versus psychoeducation across four Canadian sites with bipolar I and II patients (N=204) in full or partial remission. This 18-month trial compared pharmacotherapy plus 20 weeks of individual CBT to pharmacotherapy plus 6 sessions of group psychoeducation (14). Because the full results of this trial have not been published, it is not included in Table 1. Preliminary results, however, have shown no differences in outcome between the two interventions. The effectiveness of group psychoeducation cannot be assessed in this study because of the lack of a no-psychotherapy control.

The results of these trials yield inconsistent conclusions regarding the effectiveness of CBT. CBT may be more effective among recovered and less recurrent patients than among severely ill, highly recurrent patients. The effects of CBT on depressive outcomes appear to be more robust than on manic outcomes, except when medication compliance is the focus of treatment (25). Alternatively, differences among the studies in sample populations (e.g., number of prior episodes, clinical status at admission), therapy training procedures, consistency of the intervention components across settings, and other site or protocol variables may account for the discrepant results. For example, Lam et al. (26) examined recovered patients, whereas Scott et al. (29) included patients in a variety of clinical states, some of whom were not on mood stabilizers. Thus, conclusions regarding the status of CBT as a maintenance treatment await systematic trials that examine the moderating effects of patient, treatment, and setting variables.

Interpersonal and Social Rhythm Therapy

The interpersonal and social rhythm therapy approach, an adaptation of interpersonal psychotherapy for depression, derives from two observations: bipolar disorder is often associated with poor interpersonal functioning, especially during the depressive phases (31); and disruptions into sleep/wake cycles can precipitate manic episodes (32). Accordingly, interpersonal and social rhythm therapy has two objectives: to resolve key interpersonal problems related to grief, role disputes, interpersonal conflicts, or interpersonal deficits; and to stabilize social rhythms (i.e., when patients arise, go to sleep, exercise, or socialize). Initiated during the postepisode period, patients are instructed to track and regulate their daily routines and sleep/wake cycles and identify events (e.g., changes in job hours) that could provoke changes to these routines.

In a single-center trial of this modality, 175 acutely ill bipolar I patients were assigned randomly to pharmacotherapy and weekly interpersonal and social rhythm therapy or pharmacotherapy and weekly clinical management sessions (33). Once recovered, patients were again assigned randomly to interpersonal and social rhythm therapy or clinical management for a 2-year maintenance period, with sessions tapered to monthly. The results generally supported the efficacy of interpersonal and social rhythm therapy. Patients who received interpersonal and social rhythm therapy during the acute phase had longer well intervals in the maintenance phase than patients assigned to clinical management in the acute phase. Interpersonal and social rhythm therapy was most effective in delaying recurrences in the maintenance phase when patients succeeded in stabilizing their social rhythms during the acute phase. In contrast, interpersonal and social rhythm therapy initiated during a period of recovery was no more effective than clinical management in preventing recurrences over 2 years. Secondary analyses revealed strong effects of interpersonal and social rhythm therapy relative to clinical management on depressive recurrences and a marginally significant effect on suicide attempts (34,35).

A Comparison of Treatments for Bipolar Depression: STEP-BD

Few of the trials reviewed above compared two or more active treatments. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; [references 36,37]), an effectiveness study carried out in 15 U.S. sites, 293 acutely depressed patients with bipolar I or II disorder were randomly assigned to medication or any of four evidence-based psychosocial treatments: 30 weekly and biweekly sessions of family-focused therapy, interpersonal and social rhythm therapy, CBT, or a three-session psychoeducational control called collaborative care. Unlike prior studies, the primary outcome variable was recovery from an acute depressive episode. Treatments were carried out by therapists who received limited training and supervision (an 8-hour workshop in each modality followed by monthly teleconferences).

Over 1 year, being in any of the three intensive psychotherapies was associated with a faster recovery rate (169 days versus 279 days) from acute depression than being in collaborative care (36). Patients in intensive treatment were also 1.58 times more likely to be well in any month of the 1-year study than patients in collaborative care. Rates of recovery by 1 year did not differ significantly across the intensive modalities: family-focused therapy=77% (mean time to recovery=103 days), interpersonal and social rhythm therapy=65% (127.5 days), and CBT=60% (112 days). Patients in intensive psychotherapy also had greater gains in functional outcomes, including relationship functioning and life satisfaction, even after functioning scores were adjusted for concurrent levels of depression (37).

The results of STEP-BD underline the power of adjunctive psychosocial approaches, but also their limitations. Despite the availability of up to 30 sessions of care, patients attended an

average of only 14.3 (SD=11.4) sessions. Only 54% of the patients had family members available to assist in family-focused therapy or other treatments. Psychotherapies affected relationship functioning but not vocational functioning; possibly, cognitive rehabilitation programs such as those for schizophrenia could be adapted to bipolar disorder (38). Nonetheless, bipolar patients with acute depression appear to require more intensive psychotherapy than is typically offered in community care. Possibly, the common ingredients of these intensive psychotherapies—such as teaching strategies to regulate mood states and resolve key interpersonal or family problems—contribute to more rapid recoveries and better functioning after a depressive episode.

Discussion

Psychotherapy is an effective adjunct to pharmacotherapy in relapse prevention and episode stabilization among bipolar patients. The active treatments reviewed here are associated with 30% to 40% reductions in relapse rates over 12- to 30-month periods. Although not as well studied, patients who receive intensive psychosocial treatment have better functional outcomes than those who receive routine pharmacological care over 1-2 year periods. Beneficial effects of group, systematic care, family, CBT, and interpersonal and social rhythm therapy approaches can be observed for at least 1 year after their termination. Across studies, treatment models containing 12 or more sessions consistently perform better than comparison treatments of three or fewer sessions. Although no particular modality emerged as superior to others, the results suggest that the modalities operate through different change mechanisms, and in turn affect different outcome variables.

These conclusions must be tempered by the substantial differences among studies in inclusion criteria, targeted outcomes, control groups, therapist training and monitoring procedures, and durations of treatment and follow-up. Most of the studies are single-site with inadequate sample sizes to test hypotheses about moderating and mediating variables. Multisite effectiveness studies with well-defined treatment protocols are just beginning to be done (14,29,36). Thus, inferences regarding the effectiveness of specific models of psychotherapy for bipolar disorder are best viewed as promising but preliminary. Hypotheses to be examined in the next generation of research on psychosocial interventions are highlighted next.

Depression Versus Mania

Although not all studies report the effects of psychosocial interventions on depressive versus manic outcomes, some preliminary conclusions can be drawn. Manic symptoms are most consistently associated with medication nonadherence, life events that promote goal striving, and sleep/wake cycle disruption (5,32). In parallel, interventions that focus on the early identification of prodromal symptoms (including sleep disruption) and compliance with medications are more effective in ameliorating manic than depressive symptoms. In contrast, patient- and family-centered approaches that focus on cognitive and behavioral skills for managing interpersonal or familial relationships—such as communication and problem-solving strategies for high-conflict situations—appear to be more effective for depressive than manic symptoms. Indeed, impairment in interpersonal and family functioning, including high expressed emotion and caregiving burden among relatives, is more consistently correlated with patients' depressive than manic symptoms (2,31,37,39-42).

Which Patients Benefit Most From Psychotherapy?

Patient attributes, notably initial clinical state and the history of recurrences, may moderate the effectiveness of certain psychosocial modalities. CBT and some forms of group psychoeducation (12,24) appear to be more effective with recovered than acutely ill or subsyndromal patients, whereas family therapy, interpersonal and social rhythm therapy, and

systematic care interventions produced benefits among patients who began in moderately or acutely ill states. One study found that CBT was more effective than treatment as usual among patients with fewer than 12 prior episodes but less effective among patients with 12 or more episodes (29). It is not clear whether CBT is more efficacious earlier in the course of the disorder, with younger patients, or with patients who are less recurrence prone. The cognitive impairments associated with highly recurrent bipolar disorder may make the core tasks of CBT (i.e., identifying and challenging cognitions) too difficult to negotiate. Ideally, future effectiveness trials would test these hypotheses directly by stratifying participants on recovery status or illness history variables before assigning them to treatment or control conditions.

Patients in families with high levels of conflict or impairment show greater stabilization of depressive symptoms in family therapy than patients in families with low levels of impairment (23,42). Possibly, family therapy should be reserved for depression-prone patients who, following an acute illness, return to families that are high in marital or parent/offspring conflict, criticism, or hostility; show deficits in problem-solving; or have difficulty meeting the practical and emotional needs of family members (43). Future studies should examine which aspects of family affect, communication, and problem-solving are most essential to the process of recovery from bipolar depression.

Further differences among the treatment modalities may emerge from studies of axis I and axis II comorbidity. Attention deficit hyperactivity disorder, anxiety disorders, and substance abuse or dependence disorders are frequently comorbid with bipolar illness (44), but data on the treatment of comorbid patients are surprisingly scant. In a secondary analysis, Frank et al. (33) found that interpersonal and social rhythm therapy was less effective among patients with comorbid medical or anxiety disorders. Co-morbid borderline personality disorder was also associated with a more difficult course of interpersonal and social rhythm therapy (45). To address diagnostically complex patients, existing psychosocial treatment manuals should be supplemented with evidence-based strategies for treating anxiety disorders (e.g., prolonged exposure for posttraumatic stress disorder, [46]), borderline personality disorder (47), and substance use disorders (48).

Psychosocial Mechanisms

The psychotherapy literature is hampered by its lack of grounding in basic studies of psychosocial processes and cognitive vulnerability factors. Most of the trials proceeded without explicit reference to the longitudinal studies of life events stress, reward sensitivity, dysfunctional goal pursuit, neuroticism, or distorted styles of information processing in bipolar disorder (5,6). Measuring stressful life-event, personality variables, or cognitive vulnerability factors before the initiation of psychosocial treatments may help to identify subgroups of patients who are more and less likely to benefit from certain approaches. For example, cognitive styles associated with mania—such as unrealistic appraisals regarding goal attainment or a sense of “hyperpositive self”—are associated with a poorer response to CBT (49).

Identifying treatment mediators (change mechanisms) in the biological or psychological domains will be essential to the development of psychosocial treatments that are more efficient and have greater longevity of effects (50). Current candidates for treatment-associated mediators in bipolar disorder include enhanced adherence to mood stabilizer regimens (17, 18,25,26,51), increased knowledge of the disorder, leading to greater access to appropriate care (10,24), regularity of sleep/wake cycles and daily rhythms (33), improved family communication (10,19), reductions in dysfunctional attitudes (30), and earlier recognition of prodromal symptoms (11,24,26). The variables mediating improvement in manic symptoms (e.g., medication adherence) appear to be different from the variables mediating improvement in depression (e.g., enhanced communication between patients and caregivers) (5,18,19).

No studies have examined pretreatment to posttreatment changes in neural structure or function among bipolar patients undergoing psychotherapy, although such studies have been undertaken in other disorders (52). The correlates of response to psychotherapy in bipolar disorder might include increased activation of the dorsolateral and ventrolateral prefrontal cortices, decreased activation of the amygdala, or increased activation of the rostral anterior cingulate (53,54).

Treatment Algorithms

A clear (if unintended) conclusion of the trials is that bipolar disorder is a highly chronic, disabling, and recurrent illness, and our existing treatment options are inadequate for maintaining long-term stability. Even with optimal psychotherapy and pharmacotherapy, recurrences occurred in 50%-75% of patients in 1 year (Table 1). Chronic care models, in which patients move in and out of intensive treatments as required by their clinical state, may be more cost-effective over the long term than “one-shot” intensive approaches.

Researchers investigating chronic care models should follow the lead of psychopharmacology researchers in implementing pragmatic trials that mirror decision making in clinical practice. Pragmatic trials can help determine whether adjunctive psychotherapy has greater or lesser benefits at different points in an algorithm, such as following the failure of an adjunctive antidepressant or a second mood stabilizer. A practical trial may establish, for example, that acutely manic patients need to be adequately stabilized with pharmacotherapy prior to the initiation of psychosocial interventions, whereas acutely depressed patients may benefit from the simultaneous initiation of drug and intensive psychosocial treatments, as was done in STEP-BD. Once stabilized, patients may be tapered to less frequent psychosocial sessions. Management protocols may differ depending on the stage of the patient’s disorder.

Pragmatic trials may also be able to address whether patients in intensive psychotherapy can be maintained on fewer mood stabilizers or atypical antipsychotic agents (or lower dosages) than patients receiving medication alone. Some patients—such as bipolar II patients who have prolonged periods of stability or only mild residual depression—may be able to be weaned from pharmacotherapy altogether and maintained on psychosocial treatment alone, with pharmacotherapy to be reinitiated if symptoms return.

Finally, patients with early-onset bipolar disorder are at risk for a host of poor outcomes, notably rapid cycling, lengthy episodes, polarity switches, and deteriorations in functioning (55). Given the possibly neurotoxic effects of repeated episodes on the developing juvenile brain, introducing psychosocial interventions early in the course of the disorder (even during the preonset period) may decrease long-term chronicity, psychosocial impairment, and caregiver burden. Pragmatic trials may clarify the optimal content, format, and intensity of interventions initiated prior to the disorder’s onset.

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Randomized, Controlled Trials of Psychotherapy for Bipolar Disorder

TABLE 1

Study/ Country	Experimental Treatment	Control Treatment	N	Condition at Entry	Treatment Length	Length of Study	Recovery	Relapse or Recurrence	Severity of Symptoms	Effects on Depression Versus Mania	Psychosocial Functioning	Moderators of Effects
Perry et al. (1999) (11) (U.K.)	Individual psychoeducation	Routine care	69 bipolar I and II	Remitted but 1 or more relapse in last 12 months	7-12 sessions	18 months	Not applicable	Psychoeducation associated with delays of manic recurrences	Not reported	Mania effects only	Better social functioning and employment in psychoeducation at 18 months	Not reported
Colom et al. (2003) (12) (Spain)	Group psychoeducation	Unstructured support groups	120 bipolar I and II	Euthymic for at least 6 months, no comorbid disorders, in continuous treatment for ≥2 years	21 weeks	2 years	Not applicable	Recurrence lower in group psychoeducation than comparison subjects	Not reported	Significant effects on both	Not reported	Not reported
Weiss et al. (2007) (13) (U.S.)	Integrated group therapy	Drug counseling groups	62 bipolar I and II	Moderate mood symptoms plus substance use disorders	20 sessions over 20 weeks	8 months	Not reported	No differences in recurrence or weeks ill	More severe symptoms in integrated groups	No differences	Fewer days per month of alcohol use in integrated groups	Not reported
Bauer et al. (2006) (14) (U.S.)	Collaborative chronic care	Treatment as usual	306 bipolar I and II	All in acute episode, 87% hospitalized	5 weekly groups followed by twice monthly for up to 3 years	3 years	Not reported	No differences in number of hospital days	Care program associated with 6.2 fewer weeks in mood episodes	4.5 fewer weeks in manic episodes; no differences in manic and depression symptoms over time	Care program associated with better social functioning, quality of life, treatment satisfaction	Not reported
Simone et al. (2006) (15) (U.S.)	Systematic care program	Treatment as usual	441 bipolar I and II	One mental health contact in last year; 343 symptomatic at entry	5 weekly group sessions followed by twice monthly for up to 2 years	2 years	Not reported	Probability of manic episodes lower in care program over 24 months	Fewer weeks in manic episodes, lower mania ratings in care program	No effects of treatment on depression	Not reported	Treatment effects only among patients who began with substantial symptoms
Clarkin et al. (1998) (17) (U.S.)	Marital psychoeducation	Treatment as usual	33 bipolar I	In episode	25 sessions over 11 months	11 months	Not reported	No differences	No differences	Not reported	Global functioning and medication adherence better in marital group	Not reported
Miklowitz et al. (2003) (18) (U.S.)	Family-focused therapy	Crisis management (three sessions)	101 bipolar I	Recently episodic and hospitalized, partially stabilized	21 sessions over 9 months	2 years	Not reported	Family-focused therapy associated with longer delays prior to relapse	Family- focused therapy associated with lower symptom severity	Family-focused therapy more effective with depression than mania	Family-focused therapy associated with better medication adherence, better family communication	High family expressed emotion associated with better family- focused therapy response
Rea et al. (2003) (20) (U.S.)	Family-focused therapy	Individual psychoeducation (21 sessions)	53 bipolar I	Recently manic and hospitalized, partially stabilized	21 sessions over 9 months	2 years	Not reported	Family-focused therapy associated with delayed recurrences and rehospitalizations	Not reported	Not reported	Not reported	Poor premorbid adjustment predicted better family- focused

Study/ Country	Experimental Treatment	Control Treatment	N	Condition at Entry	Treatment Length	Length of Study	Recovery	Relapse or Recurrence	Severity of Symptoms	Effects on Depression Versus Mania	Psychosocial Functioning	Moderators of Effects
Miklowitz et al. (21) (2008)	Family-focused therapy for adolescents (13-17 years)	Brief psychoeducation (three sessions)	58 bipolar I, II, not otherwise specified	Recently episodic, partially stabilized	21 sessions over 9 months	2 years	Family- focused therapy associated with faster recovery from depression	No differences in time to recurrence, but episodes of depression shorter in family- focused therapy	Family- focused therapy associated with less severe depression over 2 years	Family-focused therapy more effective with depression than mania	Not reported	therapy response Not reported
Miklowitz et al. (2004), 2008, 22, 23 (U.S.)	Single family therapy, multifamily groups	Treatment as usual	92 bipolar I	All recruited in acute episode; 69/92 had acute mania, 84/92 hospitalized	12 single family or 6 multifamily sessions	Up to 28 months	No differences	No differences	Treatment by family impairment interaction on number of depressive recurrences and time depressed	Effects of family therapy greater on depression than mania	Not reported	Family impairment associated with better response to family therapy
Reinas et al. (24) (Spain)	Multifamily groups for caregivers	Treatment as usual	113 bipolar I, II	All euthymic for 3 months, lived with caregivers; no axis I comorbidity	12 weekly 90- minute group sessions over 3 months	15 months	Not applicable	Fewer patients in experimental condition had relapses (42% versus 66%)	Not reported	Significant effects on hypomanic or manic relapses (17.5% versus 37.5% in treatment as usual) but not depressive relapses	No effects on medication adherence	Not reported
Cochran (1984) (25) (U.S.)	Cognitive- behavioral therapy	Standard care	28 bipolar I, II	Stable	6 weekly sessions	6 months	Not reported	Cognitive- behavioral therapy associated with fewer hospitalizations (14% versus 57%) by 6 months	Not reported	Not reported	Not reported	Not reported
Lam et al. (2003), 2005, 26, 27 (U.K.)	Cognitive- behavioral therapy	Minimal psychiatric care	103 bipolar I	In full remission or only mild symptoms; ≥2 episodes in last 2 years	12-18 individual sessions in 6 months	30 months	Not applicable	Lower relapse rates and fewer hospital days in cognitive- behavioral therapy at 12 months; fewer depressive relapses by 30 months	Less severe depression scores in cognitive- behavioral therapy over 12 months	Cognitive- behavioral therapy more effective with depression than mania	Better social functioning in cognitive- behavioral therapy at 24 months	Sense of hyper- positive self associated with poorer outcomes of cognitive- behavioral therapy
Ball et al. (2006) (28) (Australia)	Cognitive- behavioral therapy	Treatment as usual	52 bipolar I, II	In full remission or only mild symptoms; ≥1 episode in previous 18 months	20 weekly sessions over 6 months	18 months	—	Longer time to depressive relapses in cognitive- behavioral therapy (p=0.06)	Less severe depression scores in cognitive- behavioral therapy at 6 months but not at 18 months	Cognitive- behavioral therapy more effective with depression than mania; trend (p=0.08) toward lower mania	Less dysfunctional attitudes and less social disability in cognitive- behavioral therapy at 6 months but not	Not reported

Study/ Country	Experimental Treatment	Control Treatment	N	Condition at Entry	Treatment Length	Length of Study	Recovery	Relapse or Recurrence	Severity of Symptoms	Effects on Depression Versus Mania	Psychosocial Functioning	Moderators of Effects
Scott et al. (2006) (29) (U.K.)	Cognitive- behavioral therapy	Treatment as usual	253 bipolar I and II	Variable; 32% in episode	22 sessions over 26 weeks	18 months	Not reported	No differences	No differences	scores at 18 months	18 months; no differences in medication compliance Not reported	Cognitive- behavioral therapy more effective than treatment as usual among patients with <12 prior episodes Not reported
Zaretsky et al. (2007, 2008) (7, 30) (Canada)	Cognitive- behavioral therapy plus individual psychoeducation	Individual psychoeducation (7 sessions)	79 bipolar I and II	Full or partial remission	20 weekly sessions	1 year	Not applicable	No differences	50% fewer days of depressed mood in cognitive- behavioral therapy	Cognitive- behavioral therapy more effective with depression than mania	No differences	No differences
Frank et al. (2005) (33) (U.S.)	Interpersonal and social rhythm therapy	Individual clinical management	175 bipolar I	Depressed, mixed, or manic	Weekly in acute phase until recovery, biweekly then monthly for 2 years	2 years	No differences	Interpersonal and social rhythm therapy during acute phase associated with longer survival during maintenance phase	No differences	Not reported	Not reported	Interpersonal and social rhythm therapy less effective in patients with medical or anxiety disorders Not reported
STEP-BD (Miklowitz et al., 2007) (36, 37) (U.S.)	Interpersonal and social rhythm therapy family-focused therapy, Cognitive- behavioral therapy	Brief psychoeducation (three sessions)	293 bipolar I and II	Acutely depressed	30 sessions over 9 months	1 year	Patients intensive therapy recovered more rapidly	Patients in intensive therapy 1.58 times more likely to stay well	Not reported	Effects only on depression	Intensive therapy improved total functional, relational, life satisfaction	Not reported