A Critical Update on Psychological Interventions for Bipolar Disorders

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Although pharmacotherapy is the mainstay of treatment for bipolar disorder, the combination of evidence-based psychological interventions and drug treatment enhances overall effectiveness, mostly by further protecting patients from relapse/recurrence. In recent years, well-designed controlled studies have added weight to evidence favoring specific psychotherapy modalities for bipolar disorders. However, critical issues that may limit the benefits of psychotherapy in day-to-day clinical practice have emerged. In this article, we critically examine the effectiveness of psychosocial approaches to bipolar illness by reviewing the literature, which has been substantially enriched during the past 5 years. Recent studies further support the fact that psychoeducation and cognitive-behavioral therapy are effective in bipolar disorder, especially the early stages. Family interventions based on a psychoeducational model are also effective. Intensive psychotherapies may be more effective than short, managed care–based ones. Group psychoeducation seems to have long-lasting effects and to be cost-effective. Future studies should focus on neurobiological markers of response to psychotherapy and tailor interventions to specific subtypes.

Introduction

During the past 5 years, the use of psychological interventions in bipolar disorder (BP) has continued to grow. The bulk of research points to the need to combine efficacious psychological interventions in the long term with drug treatment in bipolar illness.

Despite recent and relevant advances in the pharmacotherapy and etiologic basis of BP, this condition often remains difficult to treat if we keep in mind functional recovery as a therapeutic target. Thus, most patients experience only a partial benefit from drug therapy—regarding both syndromal and functional recovery—and may still benefit from the combination of pharmacotherapy and psychological interventions. Indeed, BP is chronic and debilitating. Even during adequate drug treatment, it is characterized by high rates of recurrence and low remission rates with burdensome residual symptoms [1••], hampering the achievement of full functional recovery. Patients with BP spend as much as 47% of their lives with symptoms, mostly depressive [2]. Bipolar depression represents a particularly difficult-to-treat condition.

Lack of treatment adherence is another substantial problem among patients with BP. In one landmark article, Colom et al. [3] determined that only 60% of euthymic BP patients were fully adherent to medication. This may be partially due to lack of insight, misinformation, and stigma associated with bipolar illness. Other factors leading to poor outcome and nonadherence in BP patients are the high prevalence of persistent cognitive dysfunctions across different mood states and during remission [4,5,6•], psychiatric comorbidity [7,8], and side effects [9]. Finally, disrupted psychosocial and interpersonal functioning may persist between illness episodes [10•] and negatively affect quality of life.

Keeping all these problems in mind, several clinically based psychological approaches have emerged to cover the existent gap between theoretical efficacy and real world effectiveness of the treatment of bipolar illness [11,12]. Initially, four types of psychological interventions seemed to have some efficacy in preventing depressive and manic recurrences, stabilizing the course of the illness, or enhancing functioning at the middle term (1–2 years): cognitive therapy (CT) and other cognitive and behavioral techniques [13,14,15••,16•]; interpersonal and social rhythms therapy (IPSRT) [17]; family-focused therapy (FFT) [18,19] and similar forms of family psychoeducation (PE) [20••,21•]; and patients' group PE [22,23••] and other collaborative approaches that had a PE ingredient [24•,25••]. Results from systematic reviews and meta-analyses recently confirmed the benefits of psychological interventions as adjuncts to pharmacologic maintenance treatments to prevent relapse in BP [26••–28••].

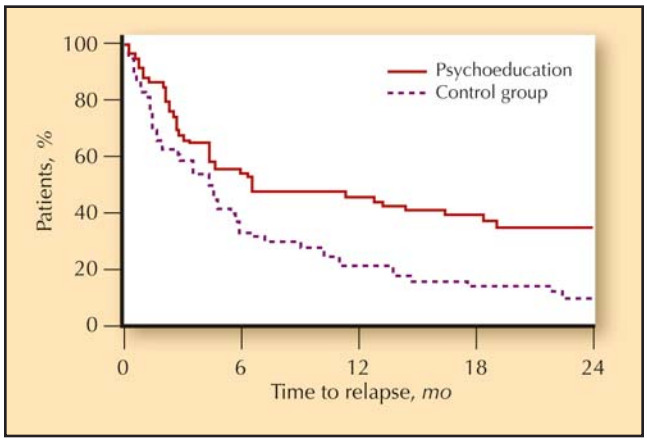

Figure 1. Survival curves (time to relapse) comparing a group of patients with bipolar disorder who received psychoeducation with a control group that did not.

Although the underpinning theoretical models may have some differences, there is a considerable overlap in their actual targets. The main goals of PE (illness awareness, enhanced adherence, early warning sign detection, encouraging healthy habits, avoiding substance misuse) represent core elements of all such adjunctive psychosocial interventions. Intensive psychosocial interventions (FFT, IPSRT, cognitive-behavioral therapy [CBT]) that include PE to some extent as part of the compound are more effective than collaborative care in regard to recovery rates from an acute bipolar depressive episode over 1 year [29••]. Currently, most treatment guidelines include psychosocial interventions as sensible choices in bipolar depression and as maintenance treatment for BP [30,31].

This article critically examines the relevance and effectiveness of current psychosocial approaches in BP by conducting a systematic review of the recent literature.

Psychotherapy Modalities

Brief technique-driven interventions

To date, two randomized controlled trials (RCTs) have compared an experimental intervention (add-on) with treatment as usual, both with a follow-up of at least 1 year. Cochran [32] randomly assigned 28 stable BP patients to standard treatment (lithium alone) or standard treatment plus six sessions using cognitive and behavioral strategies to enhance treatment adherence. At the end of the sessions and during the 6-month follow-up, the psychotherapy group had significantly fewer relapses, better medication adherence, and less tendency to discontinue lithium (21% vs 57%). In the study by Perry and colleagues [33], 69 BP patients who had experienced a relapse within the previous 12 months were randomly assigned to receive routine care alone or routine care and 7 to 12 individual treatment sessions aimed at teaching them to identify the early symptoms of relapse. Patients who received the psychological intervention had a significant increase in time to first manic relapse and a 30% decrease in the number of manic, but not depressive, episodes over 18 months. Moreover, this group of patients had reduced hospital stays and showed a higher level of social functioning and better work performance.

Psychoeducation

PE goes beyond mere delivery of information, as information alone has no therapeutic effect [28••]; it is rather an information-based behavioral training aimed at providing BP patients with a theoretical and practical approach to understanding and coping with the consequences of their illness, which thus allows them to change their attitudes toward and beliefs about the illness, and provides specific coping strategies. PE enables patients to actively collaborate with the physician in some aspects of treatment.

Pioneering studies showed some changes in patients' attitudes toward lithium but provided no clinical outcome measures. European studies showed a significant decrease in noncompliant behavior and hospitalizations among PE patients. In 2003, our group published the first randomized clinical trial of the efficacy of group PE, showing prophylactic efficacy in the prevention of all types of bipolar episodes and increasing time to relapse at the 2-year follow-up (Fig. 1) [18]. The number of hospitalizations per patient was also lower among the PE group. This study had a reasonably large sample size (n = 120) and a random assignment of patients to a treatment condition (PE + standard pharmacologic treatment) or nonintervention (unstructured intervention + standard pharmacologic treatment). This design, which included a "placebo" intervention, is almost unique in the bipolar literature and is no doubt one of the strengths of the study. PE proved to be effective in improving treatment adherence. For instance, among patients on lithium, those who received PE had more stable lithium serum levels than those who did not [34]. However, it should also be stressed than in another smaller study by the same group, it was shown that despite adherence enhancement being established as one of the main components of PE, the other ingredients are efficacious as well, as shown by the fact that even patients without an adherence problem clearly benefited from being included in a PE group (Fig. 2) [35]. Interestingly, PE seems to be equally useful when provided to difficult-to-treat bipolar populations, such as those with Axis II comorbidity (Fig. 3) [7].

PE should be implemented only after the patient is reasonably euthymic, because of the frequent attentional and memory dysfunctions existing in mania and depression, plus, obviously, because of the behavioral symptoms of mania and depression, which may make group functioning difficult.

Thus far, psychological interventions are used mainly as add-on maintenance therapy, which, by definition, includes long-term efficacy. However, not many interventions have been tested over the long term. Moreover, some CBT interventions, such as those in the studies by Lam et al. [14] and Ball et al. [16•], indicated a progressive reduction in the effectiveness of CBT in BP over time, stressing the impor-

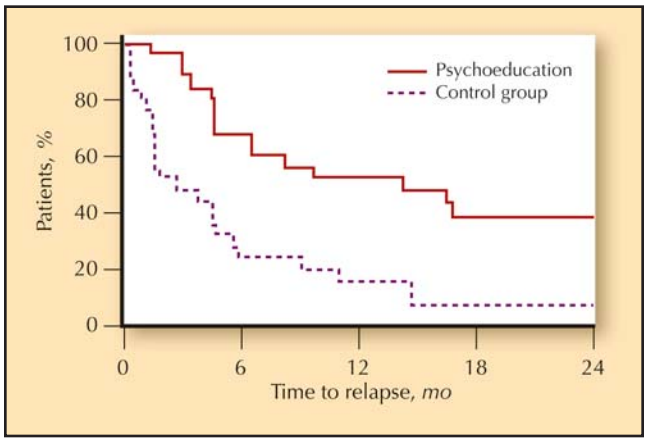

Figure 2. Survival curves (time to relapse) comparing a group of compliant patients with bipolar I disorder receiving psychoeducation with a control group that did not.

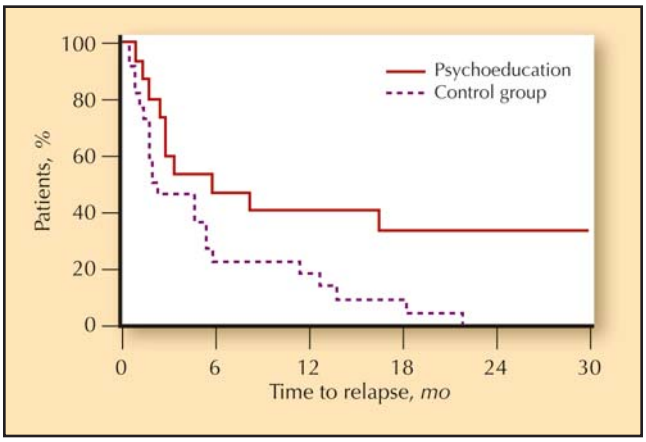

Figure 3. Survival curves (time to relapse) comparing a group of patients with bipolar disorder comorbid with a personality disorder receiving psychoeducation with a control group that did not.

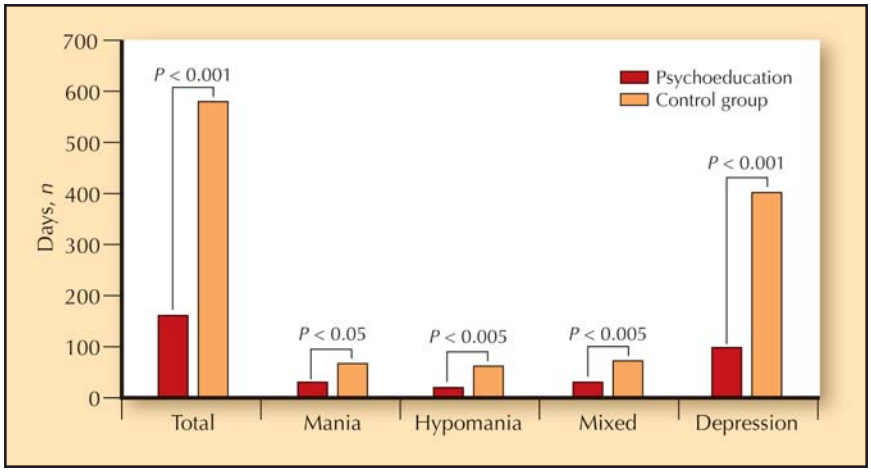

Figure 4. Time spent on an acute episode of bipolar disorder over 5 years. This graph compares psychoeducated and nonpsychoeducated patients.

tance of maintenance therapies or booster sessions at the expense of the feasibility and cost-effectiveness issues. In contrast, PE was the first psychological intervention to show very long-term efficacy (5-year follow-up) in BP, so it should mainly be considered as disease management training. In the 5-year continuation study of the 2003 randomized clinical trial [23••], PE patients showed a longer time to recurrence (log rank, 9.953; $P < 0.002$) than non-PE patients and fewer recurrences (3.86 vs 8.37; $F = 23.6$; $P < 0.0001$) of any type of polarity. Moreover, PE patients spent less time acutely ill, mainly due to less time spent in depression (364 days vs 399 days; $t = 5.387$; $P < 0.0001$), although the number of days spent on mania, hypomania, and mixed episodes was also lower among the PE patients (Fig. 4).

A very recent study explored long-term cost-effectiveness over an extended 5-year postintervention period following PE among BP patients [36••]. In the long term, PE patients used fewer mental health care resources with no additional health gain; costs were also reduced, particularly those related to hospitalizations.

In a 5-year outcome subanalysis, our group aimed to investigate whether PE plus medication could also be effective in a separate subpopulation of patients with BP II, a common condition demonstrating poor syndromal and functional recovery [37•]. Despite the small sample size ($n = 20$), this exploratory study provides initial preliminary evidence of the efficacy of group PE in preventing any type of mood episode recurrence and in increasing mean functioning levels in this subset of patients with BP. However, the question of whether a specifically BP II–tailored intervention would have yielded even better results is still open.

Cognitive-behavioral therapy

The classic approach to CBT is Beck's model. Basically, it assumes that maladaptive behavior and certain cognitive patterns cause psychiatric symptoms; thus, the treatment focuses on changing these patterns—through a logical discussion or behavioral activation—to improve symptoms. Recently, newer formulations of CBT have emerged that are more tailored to BP and focus on educative elements and stress the importance of sleep and habits [13].

To date, several well-designed studies testing CBT in BP have been carried out. In a large trial conducted in the United Kingdom and involving 253 difficult-to-treat BP I and BP II patients, Scott and colleagues [15••] showed that during an 18-month period, patients receiving individual CBT (22 sessions over 26 weeks) did not differ from those

treated as usual in regard to time to recurrence, duration of illness episodes, or mean symptom severity scores. A post hoc analysis revealed some efficacy of CBT in patients with a small number of episodes. However, when using this approach with veteran patients (≥ 12 episodes), CBT was not useful and may have even worsened the outcome [15••].

Lam and colleagues [13] reported that patients receiving group CBT had significantly fewer episodes, fewer hospitalizations, higher social functioning, and better medication adherence. A total of 44% of patients in the CBT group experienced a relapse over 1 year, compared with 75% in the control group. However, the same group of investigators showed that although over 30-month follow-up, the CBT group had significantly better outcomes in terms of time to relapse, the effect on relapse prevention was mostly limited to the first year. This could mean that as therapy became more distant, the beneficial effects became weaker. Further investigations should explore the possibility of booster sessions or maintenance therapy [14].

In an 18-month, randomized, long-term, controlled trial testing the efficacy of individual CBT in BP patients (euthymic, mildly depressed, or hypomanic at the time of initial assessment), some sustained effects in improving behavioral self-control and dysfunctional attitudes were found, but time to depressive relapse was longer in the CBT group only at a trend level [16•]. Again, many benefits from CBT were gradually lost upon withdrawal, suggesting the importance of maintaining psychological strategies.

In a pilot Canadian study, BP patients in full or partial remission from an index episode (n = 79) were randomly assigned to receive seven sessions of individual PE or seven sessions of PE followed by 13 additional individual sessions of CBT as maintenance therapy [38•]. Patients receiving CBT had 50% fewer days of depressed mood and fewer antidepressant dosage increases over 1 year. It should be noted that the duration of PE alone was shorter than that of CBT (only 7 sessions for PE vs 13 sessions for CBT). The authors themselves stressed the need for larger RCTs with equal treatment lengths.

These results lead to some considerations. First, one of the advantages of using psychological therapies as adjuncts to pharmacologic treatment should be the cost-effectiveness shown in the long term [36••]. In fact, if viewed only in the short term, adjunctive psychological interventions involve enhanced use of health care resources and increased costs. A reflection arising is whether long-term cost advantages are reduced by the weakening of the persistence of the effect of CBT after 1 to 2 years and the consequent need for booster sessions or even maintenance psychotherapy. Second, these findings seem to highlight the importance of an "information-based training" (principal mechanism of PE) for the efficacy of a certain psychological intervention to persist over time. In fact, shorter PE approaches, which merely provide information, seem to be less effective compared with more structured, longer PE strategies [23••].

Family-focused therapy

The burden of BP also affects caregivers, and the presence of stressful events within the family can be related to exacerbations of BP [39•]; for instance, expressed emotion has been described as an important predictor of relapse. On this basis, different family-focused interventions have been developed to work with groups of patients and caregivers separately and also together in the same group [18] or to run multifamily educational sessions [21•].

The FFT model developed by Miklowitz et al. [40] is the most widely used family intervention. The treatment goal is to improve family functioning using a combination of communication, problem solving, and coping strategies training; PE; and relapse prevention techniques. Miklowitz et al. [40] carried out an RCT of 21 sessions of FFT (n = 31) compared with care as usual and a brief, two-session family intervention (n = 70). After 1 year of follow-up, patients assigned to the longer psychosocial treatment group had fewer relapses, longer time to relapse, and significantly lower nonadherence rates than patients assigned to the shorter intervention [40]. Patients receiving FFT showed greater improvement than the control group in depressive symptoms, but no differences were observed in manic symptoms. The benefit was greater for those living in families with high expressed emotions. At the 2-year follow-up, the results were sustained and even improved, with the FFT group showing fewer relapses than the standard care group (71% vs 47%) [14]. On the other hand, Miklowitz and colleagues [41] reported that the combination of FFT and individual psychotherapy is also a powerful add-on treatment for BP patients in remission. Rea and colleagues [19] randomly assigned 53 BP patients with a recent admission with mania to 21 sessions of FFT (n = 28) or 21 sessions of individual support and problem-solving treatment. The active treatment phase was 9 months, with a follow-up of an additional 15 months after therapy. Although there were no significant differences in the relapse rates of the two groups during the first year, at the 2-year follow-up, the respective relapses were 60% for those receiving individual treatment and 28% for the FFT group, and those receiving FFT were also significantly less likely to be rehospitalized during the follow-up period.

In a recent RCT, Reinares and colleagues [20••] assessed the effect of PE on the course of illness of medicated euthymic BP patients whose caregivers had received PE (n = 57) compared with controls (n = 56). The experimental group showed significant improvement in time to first recurrence and prevention of manic/hypomanic, but not depressive, episodes compared with the control group.

Miller and colleagues [21•] investigated the efficacy of two different adjunctive family treatments (single-family therapy and multifamily PE groups) as additions to pharmacotherapy for BP I patients (n = 92) during a 28-month follow-up period. The family therapy condition received a relatively brief (10–15 sessions) problem-focused family treatment, while the multifamily group received six PE sessions with family members from multiple families. The first

study reported no differences in recovery and recurrence rates between treatment conditions [42]. In the last study, no significant main effects were found for the treatment condition on primary outcome measures (number of episodes per year and percentage of time spent ill). However, when researchers considered BP patients from families with high levels of impairment, the addition of either family intervention improved the course of illness, with nearly half the number of depressive episodes and fewer depressive symptoms than patients in the pharmacotherapy-alone group. Another report from the first study showed patients receiving pharmacotherapy plus multifamily PE intervention had a lower percentage of hospitalizations compared with the other two groups (pharmacotherapy alone or pharmacotherapy + family therapy) [43•].

Interpersonal social rhythm therapy

IPSRT is a version of the Klerman and Weissman interpersonal therapy adapted to fit the needs of bipolar patients. Interpersonal therapy was formerly a psychodynamic approach reformulated as a newer behaviorally focused interpersonal therapy that was time limited and allowed for a simple and reliable assessment of its results.

In this kind of intervention, special emphasis is placed on helping patients recognize the impact of interpersonal events on their social and circadian rhythms, as well as on providing patients with PE about their illness and stressing the importance of adherence to treatment.

Frank et al. [17] conducted a two-stage RCT (n = 175). In the acute phase, BP I patients with a current episode were randomly assigned to IPSRT or intensive clinical management (ICM). After patients were stabilized, they entered phase two, in which they were reassigned to IPSRT or ICM for a 2-year maintenance period. The results of this study showed no differences between the IPSRT and ICM groups in time to stabilization. Patients assigned to IPSRT in the acute treatment phase survived longer without a new mood episode independent of their assignment to maintenance treatment (P = 0.01). Patients in the IPSRT groups had more regular social rhythms at the end of the acute phase, and the ability to increase the regularity of daily routine during the acute treatment was associated with reduced likelihood of recurrence during the maintenance phase, supporting its inclusion in BP treatment routines.

Other group psychological interventions including psychoeducation: systematic care models

Castle and colleagues [44•] recently published a pilot study on group psychological intervention for BP. This intervention is based on a collaborative approach; it provides PE and includes introductory skills training in certain CBT skills. BP patients (n = 84) were randomly assigned to the intervention arm, a structured group-based therapy (12 group sessions and 3 booster sessions) as an adjunct to treatment as usual, or the control arm, which consisted of treatment as usual plus weekly phone calls. At the 12-month follow-up, there was a positive trend toward reduction in relapse and an improvement in social relationships for patients receiving group intervention.

During the past few years, several studies have been published on the usefulness of collaborative care packages containing PE as a core element. Bauer et al. [24•] developed a team-based care model conceptually similar to the 1970s lithium clinic (Life Goals Program). The program consists of patient PE to improve self-management skills, simplified clinical practice guidelines, and use of a nurse care coordinator in collaboration with a supervising psychiatrist to enhance continuity of care and information flow. The authors reported a significant reduction (14%) in weeks spent in affective episodes for the treatment condition, primarily mania (23%), with no significant effects on time spent in depression. The intervention was cost neutral while achieving a net reduction in affective episodes of 6.2 weeks [24•].

Simon and colleagues [25••] reported the results of a 2-year effectiveness trial evaluating another multicomponent long-term care program (Systematic Care Program) for BP. The study showed a reduction in the mean level of manic symptom severity and in time spent in mania. Again, no significant differences were observed in the frequency or severity of depression between the two groups.

Discussion

Unsolved questions and future research

Putting aside positive evidence, we believe that limitations and gaps should be focused on in the effort to improve techniques and to identify specific "intervention packages" that could suit—as much as possible—each individual patient with any BP subtype. The critical points emerging are constituted by 1) treatment-intrinsic factors, 2) patient-intrinsic factors, and 3) factors associated with the natural history of the disorder.

Treatment-intrinsic factors

Beyond apparent similarities, every psychological intervention possesses a specificity that renders it more effective for a given aspect or a given phase of the disorder [45•]. Future research should attempt to identify the core ingredients of treatment as a function of their relative impact on the phase of illness and on the polarity of episodes [46•] and to compare them in terms of their ability to induce clinical changes.

Patient-intrinsic factors

Participants in clinical trials are generally selected on the basis of highly restrictive inclusion and exclusion criteria and thus constitute selected samples that usually do not correspond to people commonly seen in real world clinical practice.

Factors associated with the natural history of the disorder

A recent interesting staging model proposed steps of increasing severity in the natural course of BP similar to

staging models used in other medical disciplines [47••]. In the most advanced stages of illness, stable damage is likely to have occurred that involves structural and functional brain modifications comprising neuroplasticity changes. These changes with time would render the patient less able to use coping strategies to address stressful events; this would facilitate the occurrence of new episodes according to a self-feeding mechanism [48••]. Some consensus in the literature indicates that the later we intervene during advanced stages of illness, the higher the severity, the greater the cognitive impairment [4,5], and the weaker the response to psychological treatments [15••,22]. Hence, it is important to initiate therapy during the early stages of illness to modify its natural course and improve its outcome [49•,50••]. A last but important consideration concerns the duration of the effects of psychological interventions after they are terminated. Evidence suggests that the effects of CBT generally decay after 1 to 2 years [14,16•]. Group PE is the only psychological treatment for which there is evidence of efficacy 5 years after termination [23••]. We may speculate that one of the mechanisms through which the persistence of PE's effect over time could be explained is the induction of neuroplasticity through increased synthesis of its neurobiological mediators (ie, brain-derived neurotrophic factor [BDNF]), which is held to be involved in long-term memory storage [51•]. The involvement of long-term memory could explain the persistence of the effect of PE over time. Neurotrophic factors such as BDNF could be used as biological predictors of response to psychological interventions in the effort to unveil hitherto unidentified biological mechanisms of psychotherapy. A shift in that sense has been made in interpersonal therapy provided for depression, in which it has been shown that another neuroplasticity molecule, phosphorylated cyclic adenosine monophosphate reactive element binding protein, but not BDNF, could be used to distinguish responders from nonresponders [52•]. However, to claim that BDNF-related, neuroplasticity-dependent long-term memory is involved in the long-term effects of PE, we should also test the same set of markers in CBT to determine whether the lack of involvement of long-term memory may account for the loss of the strength of its effects after 1 to 2 years. Further comparative studies testing the duration of the efficacy of psychological interventions in time are needed; furthermore, the role of "refresher" or booster sessions must be assessed against this background. In our opinion, for the above reasons, longer interventions are preferred over short-term ones [22].

Conclusions

The evidence for the use of psychological interventions as prophylactic adjunct to medication in BP is quite conclusively positive. However, further studies are needed to target interventions according to patient and illness characteristics. One obvious target would be BP II, for which only very preliminary evidence in favor of PE is available thus far. Research is also needed in other areas related to effectiveness in the acute phase of BP, in the timing of the intervention, and in whether booster psychological sessions are needed after the completion of the psychotherapeutic program. Future studies should investigate possible biological mechanisms of action of psychological interventions and neurobiological measures as predictive markers of response.

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Disclosure

Dr. Vieta has served as a consultant, advisor, or speaker for Almirall, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, Janssen-Cilag, Jazz Pharmaceuticals, Lundbeck, Merck Sharp & Dohme, Novartis, Otsuka America Pharmaceutical, Pfizer, Sanofi-Aventis, Servier, Schering-Plough, and UCB.

Dr. Scott has given lectures or served on advisory boards for AstraZeneca UK, Janssen-Cilag, Eli Lilly and Company, and Otsuka Pharmaceutical.

Dr. Colom has served as an advisor or speaker for AstraZeneca, Bristol-Myers Squibb, Pfizer, GlaxoSmithKline, Eli Lilly and Company, Sanofi-Aventis, Otsuka America Pharmaceutical, Tecnifar, and Shire. No other potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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23.•• Colom F, Vieta E, Sánchez-Moreno J, et al.: **Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial.** *Br J Psychiatry* 2009, **194:**260–265. (Published erratum appears in *Br J Psychiatry* 2009, **194:**571.)
This study evaluated the long-term efficacy of PE for BP at 5-year follow-up. The authors found that PE patients continued to benefit from the effects of PE without the need for any booster session. Time to recurrence was longer for PE patients, who showed fewer recurrences and spent less time acutely ill.
24.• Bauer MS, McBride L, Williford WO, et al.: **Collaborative care for bipolar disorder: Part II. Impact on clinical outcome, function, and costs.** *Psychiatr Serv* 2006, **57:**937–945.
In this two-part article, the authors summarized the development of a collaborative care intervention in BP and reported on the positive clinical, functional, and overall cost outcomes of the trial at 3-year follow-up.
25.•• Simon GE, Ludman EJ, Bauer MS, et al.: **Long-term effectiveness and cost of a systematic care management program for bipolar disorder.** *Arch Gen Psychiatry* 2006, **63:**500–508.
This RCT showed the effectiveness of multicomponent care management in BP at 2-year follow-up. The results showed a significant positive effect on manic episode frequency and severity for the experimental group compared with the control group (usual care). No significant difference was found for depression.
26.•• Scott J, Colom F, Vieta E: **A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders.** *Int J Neuropsychopharmacol* 2007, **10:**123–129.
This meta-analysis reviewed RCTs of adjunctive psychological therapies (PE, CT, IPSRT, FFT) compared with standard psychiatric treatment alone to evaluate reduction in relapse rates in individuals with BP. The use of psychological therapies as an adjunct to medication is likely to be clinically effective and cost-effective and to contribute to a significant improvement in quality of life among stabilized individuals with BP.
27.•• Beynon S, Soares-Weiser K, Woolacott N, et al.: **Psychosocial interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials.** *Br J Psychiatry* 2008, **192:**5–11.
In this review, the authors aimed to determine whether psychosocial interventions could be effective in reducing relapse in people with BP. The results showed that CBT and group PE were effective for relapse prevention in stable individuals. Family therapy also may be beneficial as an adjunct to pharmacologic maintenance treatments.

28.•• Miklowitz DJ: **Adjunctive psychotherapy for bipolar disorder: state of the evidence.** *Am J Psychiatry* 2008, **165:**1408–1419.
The author examined 18 trials of individual and group PE, systematic care, family therapy, interpersonal therapy, and CBT for BP. He concluded that adjunctive psychotherapy enhances the symptomatic and functional outcome of BP over a 2-year period.
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This RCT from the Systematic Treatment Enhancement Program for Bipolar Disorder examined the effects of four disorder-specific psychotherapies in conjunction with pharmacotherapy on time to recovery after an episode of bipolar depression. The results showed that intensive psychosocial treatment as an adjunct to pharmacotherapy was more beneficial than brief treatment in enhancing stabilization of bipolar depression.
30. Yatham LN, Kennedy SH, Schaffer A, et al.: **Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) Collaborative Update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009.** *Bipolar Disord* 2009, **11:**225–255.
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32. Cochran SD: **Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders.** *J Consult Clin Psychol* 1984, **52:**873–878.
33. Perry A, Tarrier N, Morriss R, et al.: **Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment.** *BMJ* 1999, **318:**149–153.
34. Colom F, Vieta E, Sánchez-Moreno J, et al.: **Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels.** *Bipolar Disord* 2005, **7(Suppl 5):**32–36.
35. Colom F, Vieta E, Reinares M, et al.: **Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement.** *J Clin Psychiatry* 2003, **64:**1101–1105.
36.•• Scott J, Colom F, Popova E, et al.: **Long-term mental health resource utilization and cost of care following group psychoeducation or unstructured group support for bipolar disorders: a cost–benefit analysis.** *J Clin Psychiatry* 2009, **70:**378–386.
This study demonstrated the importance of taking a long-term overview of the costs versus benefits of adjunctive psychological therapy in BP. In the long term, compared with an unstructured support group intervention, PE is less expensive and more effective.
37.• Colom F, Vieta E, Sanchez-Moreno J, et al.: **Psychoeducation for bipolar II disorder: an exploratory, 5-years outcome subanalysis.** *J Affect Disord* 2009, **112:**30–35.
This exploratory subanalysis of the 5-year outcome of PE in a subpopulation of BP II patients showed lower rates of depressive and hypomanic recurrences and higher levels of functioning in people receiving PE. Dedicated treatment trials are needed for this subset of individuals with BP.
38.• Zaretsky A, Lancee W, Miller C, et al.: **Is cognitive-behavioural therapy more effective than psychoeducation in bipolar disorder?** *Can J Psychiatry* 2008, **53:**441–448.
This pilot study examined the efficacy and benefit of adding a course of CBT to a standard course of brief PE as maintenance therapy for BP. Participants who received CBT in addition to PE experienced 50% fewer days of depressed mood during the course of 1 year.
39.• Reinares M, Vieta E, Colom F, et al.: **What really matters to bipolar patients' caregivers: sources of family burden.** *J Affect Disord* 2006, **94:**157–163.
The aim of this study was to assess caregivers' subjective burden. The results showed that the highest levels of distress were reported regarding patient behavior (irritability, hyperactivity, sadness, and withdrawal), and they were also related to patients' jobs and social relationships.
40. Miklowitz DJ, Simoneau TL, George EL, et al.: **Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy.** *Biol Psychiatry* 2000, **48:**582–592.
41. Miklowitz DJ, Richards JA, George EL, et al.: **Integrated family and individual therapy for bipolar disorder: results of a treatment development study.** *J Clin Psychiatry* 2003, **64:**182–191.
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This third report from the original study by Miller and colleagues [42] showed that BP I patients receiving multifamily PE intervention had fewer hospitalizations compared with other treatment conditions.
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This pilot study showed the efficacy of a group-based psychosocial intervention in reducing rates of relapse and improving function and quality of life among people with BP.
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This article aimed to determine the clinical and therapeutic relevance of longitudinally predominant polarity for BPs' long-term outcome. Prevention of depression is crucial for the maintenance treatment of BP II patients, whereas prevention of mania and depression would be equally important in the case of BP I patients.
47.•• Berk M, Hallam K, McGorry PD: **The potential utility of a staging model as a course specifier: a bipolar disorder perspective.** *J Affect Disord* 2007, **100:**279–281.
In this article, the authors propose a staging model for BP similar to those used in clinical medicine. Its potential usefulness lies in its ability to inform on treatment choice and prognosis. It could also be used as a course specifier.
48.•• Kapczinski F, Vieta E, Andreazza AC, et al.: **Allostatic load in bipolar disorder: implication for pathophysiology and treatment.** *Neurosci Biobehav Rev* 2008, **32:**675–692.
This article introduces and explains the concept of allostatic load, which offers an important clue as to why patients who suffer recurrent mood episodes are clinically perceived as less resilient. Allostatic load also can explain the cumulative disruptive health effects of intermittent episodes and stressors.
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This article develops the rationale for early intervention in BP and stresses the importance of early initiation of appropriate therapy to improve clinical outcome and prevent the sequelae of untreated illness.
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This RCT examined the benefits of FFT for adolescents and pharmacotherapy in the 2-year course of adolescent BP. FFT is effective in combination with pharmacotherapy in stabilizing bipolar depressive symptoms among adolescents.

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In terms of neuropathological findings, recent data suggest that changes in neuronal plasticity, particularly in cell resilience and connectivity, are the main findings in BP. Data from differential lines of research converge to BDNF as an important contributor to the pathophysiology of BP.

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This study identified an intracellular biological marker of response to psychotherapy in depression. Responders to interpersonal therapy (assessed after 6 weeks with the Hamilton Depression Rating Scale) show increased phosphorylated cyclic adenosine monophosphate reactive element binding protein after 1 week (two sessions) as compared with nonresponders.