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Review Article

Psychosocial treatments for bipolar disorder: cost-effectiveness, mediating mechanisms, and future directions

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Objectives: Randomized trials of adjunctive psychotherapy for bipolar disorder are reviewed, in tandem with discussion of cost-effectiveness, mediating mechanisms, and moderators of effects.

Methods: Systematic searches of the MEDLINE and PSYCHLIT databases yielded 19 randomized controlled trials of individual family and group therapies. Outcome variables included time to recovery, relapse or recurrence, symptom severity, medication adherence, and psychosocial functioning.

Results: Meta-analyses consistently show that disorder-specific psychotherapies [cognitive-behavioral therapy (CBT), interpersonal, family, and group] augment mood stabilizers in reducing rates of relapse (OR = 0.57; 95% CI: 0.39–0.82) over 1–2 years. Specific mediating mechanisms include, but are not limited to, increasing medication adherence, teaching self-monitoring and early intervention with emergent episodes, and enhancing interpersonal functioning and family communication. All therapies have strengths and weaknesses. One group psychoeducation trial, demonstrated effect sizes for recurrence that are at least equivalent to individual therapies, but findings await replication. Family interventions have been successfully administered in both single and multi-family formats, but no studies report the comparative cost-effectiveness of these formats. The best-studied psychotherapy modality, CBT, can have beneficial effects on depression, but findings are inconsistent across studies and vary with sample characteristics and comparison treatments.

Conclusions: Adjunctive psychotherapies can be cost-effective when weighed against observed reductions in recurrence, hospitalization and functional impairments. Future trials need to (i) clarify which populations are most likely to benefit from which strategies; (ii) identify putative mechanisms of action; (iii) systematically evaluate costs, benefits, and generalizability; and (iv) record adverse effects. The application of psychosocial interventions to young-onset populations deserves further study.

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Introduction

Psychotherapy is making a resurgence as an adjunct to pharmacotherapy in the outpatient management of bipolar disorder (BD). During the pre-pharmacological era, psychotherapy was proposed as the primary treatment for bipolar illness (1), but fell from favor with the rise in genetic and neurobiological models of the disorder (2, 3) and the introduction of lithium and other mood stabilizing medications. Until recently,

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psychotherapy was relegated to a supporting role, often with the sole purpose of encouraging medication adherence (4–6).

In the past two decades, randomized controlled treatment trials (RCTs) have found that adaptations of cognitive-behavioral therapy (CBT), family-focused therapy (FFT), group psychoeducation, interpersonal and social rhythm therapy (IPSRT) and systematic care management programs can be effective in hastening stabilization, delaying relapses, reducing symptom severity over time, or enhancing psychosocial and family functioning (7, 8). Effect sizes for these ''disorder-specific psychotherapies'' (DSPs) have ranged from 0.57 [odds ratio (OR); 95% confidence intervals (CI): 0.39–0.82] for reductions in any type of BD relapse to 1.2 (OR; 95% CI: 0.3–2.1) for improvements in social functioning. Recent psychiatric treatment guidelines have begun to incorporate recommendations derived from psychotherapy trials (9, 10).

Nonetheless, the push toward health care cost containment may lead to the erroneous conclusion that psychotherapy amounts to only good clinical practice–that is, teaching patients about the disorder and the necessity of medications (information that is readily available anyway), often delivered by individuals with no or minimal training. More intensive approaches may be costly in the short-term, but can be of greater benefit over the longer-term. A contention of this article is that to be effective, adjunctive psychosocial treatments must go beyond simply educating patients about the illness and the pharmacological strategies to avoid relapse.

The question of mediating mechanisms

A key weakness in the psychotherapy literature–and one that may contribute to the low uptake of specific therapies in community settings–is the lack of clarity about mediators of outcome: change variables which explain how a psychotherapy prevents relapse or stabilizes symptoms (11). In studies of depression and psychosis (12–14), a large proportion of the variance in outcome associated with any therapy is explained by the therapeutic alliance between the clinician and patient, although the role of working alliance has not been investigated in BD. In BD, other mediators may include proximal variables that are clearly targeted in therapy, such as the early identification of prodromal signs of relapse or medication adherence. In this view, the main function of psychotherapy is to catch symptoms early, to pave the way for earlier and more aggressive pharmacological prevention. However, many other 'distal mediators' could provide viable explanations for the effectiveness of various forms of psychotherapy (Table 1). Moreover, the variables mediating improvement in mania (e.g., enhanced medication adherence) may differ from those in depression (e.g., enhanced interpersonal functioning) (7).

Cost-effectiveness

Many psychosocial treatments are described as cost-effective because they are cheap to administer (e.g., 1-2 session psychoeducational workshops). Other treatments, although more resource intensive in the short term, have been shown to reduce costs associated with rehospitalization (15–17), which more than offsets the additional therapy-related costs that are incurred. This review will emphasize issues relevant to costs and benefits of psychotherapy in research and community settings.

Methods

This article systematically reviewed all randomized trials of adjunctive therapy for BD published between 1980 and 2008. Studies were identified through MEDLINE and PSYCHLIT searches using terms that included *randomized controlled treatment trial, psychotherapy, psychosocial treatment, psychoeducation, cognitive-behavior therapy, systematic care, family therapy, group therapy,* and *interpersonal therapy,* cross-referenced with *bipolar disorder*. The searches generated 19 RCTs of individual and group psychoeducation, systematic care, CBT, FFT, or IPSRT.

Comparison groups varied across studies, and usually consisted of routine pharmacotherapy with or without case management. A few studies have included 'active' comparisons and/or treatment and control groups matched on time allocated for therapy and frequency of sessions.

Table 1. Potential mediators of the effects of adjunctive psychotherapy on illness outcomes in bipolar disorder

- Acquiring emotional self-regulation skills
- Acquiring balanced and less pessimistic attitudes toward the self in relation to the illness
- Improving family relationships and communication
- Improving social skills
- Decreasing self-stigmatization and increasing acceptance of the disorder
- Increasing external social and treatment supports
- Enhancing medication adherence
- Stabilizing sleep/wake cycles and other daily routines
- Improving ability to identify and intervene early with relapses

Results

Individual and group psychoeducation

Psychoeducation aims to increase a patient's knowledge and understanding of the disorder, to enable more effective coping in the future (18). However, the provision of generic support (which essentially represents good clinical practice) should be differentiated from the systematic use of structured psychoeducational interventions; we will focus on the latter.

Peet and Harvey (19) explored lithium adherence in patients allocated to a brief psychoeducation program (n = 30) or to usual treatment (n = 30). The intervention consisted of a videotaped lecture with illustrations of how lithium is used to treat BD, with one follow-up visit. Compared to usual treatment, there was a trend for greater self-reported adherence in the education group at six-week follow-up. A series of small scale trials of brief group psychoeducation of variable duration (6, 7.5 or 9 hours) undertaken in the 1980s by van Gent and colleagues (20, 21) demonstrated improvements in symptoms and functioning in group attendees over 15 months. Although these studies lacked the methodological rigor of modern RCTs, they helped shape current research.

In the largest trial of brief individual psychoeducation, Perry and colleagues (22) allocated 69 participants at high risk of BD relapse to usual treatment or usual treatment plus 6–12 sessions aimed at helping individuals to identify and manage early warning signs of relapse. Patients and professionals developed plans to avoid the evolution of isolated symptoms into full-blown BD episodes. In comparison to the control group, the intervention group had significantly fewer manic relapses (27% versus 57%) or days in hospital and higher levels of social and work functioning over 18 months. There was no effect on rates of depressive relapse, a common finding with briefer intervention packages.

An RCT focused on the use of group psychoeducation was undertaken at the University of Barcelona, Barcelona, Spain by Colom et al. (23). The key publication describes a randomized trial of 120 euthymic bipolar patients receiving standard treatments who were allocated to either (i) 21 sessions of a structured group psychoeducation program or (ii) 21 sessions of an unstructured support group, both attended by trained psychologists. Psychoeducation sessions employed lectures, role play, discussions of beliefs and attitudes, behavioral interventions and between-session homework assignments.

Attrition rates due to dropout and/or early relapse were non-significantly higher in the structured psychoeducation group. However, over two years, individuals who received group psychoeducation were significantly more likely to show an impressive range of clinical benefits such as lower relapse rates, lower hospitalizations rates (8% versus 36%), and higher, more stable plasma lithium levels (23, 24) than those allocated to the unstructured support group.

A longer-term naturalistic follow-up of this sample demonstrated that the additional health gains from this nine-month psychoeducation package are durable (25). Over 5.5 years, patients in psychoeducation had fewer relapses (mean = 3.86 versus 8.37) and spent much less time acutely ill than comparison patients (mean = 154 versus 586 days). In those admitted to hospital, the total number of days hospitalized was >50% shorter in psychoeducation participants (32 days versus 68 days over five years).

In a related publication, Scott et al. (17) reported different patterns of resource utilization but not significantly different total costs across the two treatment groups. Patients who received group psychoeducation were significantly more likely to attend scheduled outpatient appointments and significantly less likely to require costly emergency consultations. Over five years, there was a cost savings of about 5000€ per patient undergoing structured psychoeducation, which was attributable to fewer and shorter hospital admissions than observed in the comparison group. Interestingly, psychoeducated patients frequently sought further psychotherapy input (often self-funded), incurring an additional health care cost in the follow-up period. Seeking additional therapy may indicate a need for 'top-up' therapy to maintain gains from an earlier course of psychoeducation.

Further research is required to replicate the Barcelona findings, but it appears that group therapy can be a more cost-effective delivery format than individual therapy (26). As such, it would be helpful to understand the mediators of benefits; at this stage we know that improved medication adherence plays a role for some but not all individuals treated with group psychoeducation and lithium (24).

There are few studies of possible moderators of the effectiveness of group therapy for BD. Even et al. (27) explored predictors of participation in a hospital-based group psychoeducation program among 95 consecutive euthymic lithium-treated outpatients in a University clinic in Paris. Older and less well-educated patients, those with less initial knowledge about their treatment, and those

with a more external locus of control were less likely to participate in the program. Aggressive outreach to patients with these characteristics may be necessary to encourage engagement in group treatment.

Systematic care management

Two large-scale studies have examined psychoeducation within a systematic care format. Both studies tested composite collaborative care models, one in a large Group Health Cooperative, Seattle, WA, USA (28), (n = 441); and the other, in 11 US Veterans Administration outpatient sites (16) (n = 306). Patients in these studies were in a variety of clinical states but most had been ill within the prior year. Systematic care consisted of five weekly group psychoeducation sessions followed by twice monthly sessions over 2–3 years, regular patient monitoring by a nurse care coordinator, and external monitoring of the physician's consistency with pharmacotherapy guidelines. Patients in the treatment-as-usual (TAU) condition received medication management and other routine adjunctive services. Findings were strikingly similar: patients in the systematic care treatment had fewer weeks in manic episodes than those in TAU. The Bauer et al. (16) study also found that patients in collaborative care had better social functioning, quality of life, and treatment satisfaction over two years. These therapy models showed no effects of treatment on depression.

Simon et al. (28) reported that the incremental cost of an observed reduction of 5.5 weeks in manic episodes was $1,251 per patient over two years. Bauer et al. (16) concluded that their program was cost neutral: the three-year intervention cost was $61,398 per patient in the experimental arm and $64,379 in the TAU arm, despite a net reduction of 6.2 weeks in affective episodes. Thus, systematic care programs can have clinical benefit without being more costly than usual treatment in mania prevention.

Cognitive-behavioral therapy

CBT is a primary treatment for major depressive and anxiety disorders, although its application to BD is relatively recent. The first trial of CBT was undertaken by Cochran (4) who allocated 28 new referrals to a lithium clinic to standard care with or without a six-session intervention to modify negative cognitions and/or other factors interfering with lithium adherence. Immediately post-intervention and at six-month follow up, the CBT participants were significantly less likely to terminate lithium treatment against medical advice (21% versus 57%), or to be hospitalized, than standard care patients.

The successful application of CBT in unipolar disorders is founded on an extensive and systematic approach to case conceptualization rather than brief, technique-driven models. These more comprehensive interventions have been adapted for use with BD populations by a number of CBT proponents. Lam and colleagues (29) undertook a pilot study of 25 euthymic bipolar patients randomized to 12-20 sessions of CBT or routine care and observed significantly fewer relapses in the CBT than the routine care group, along with greater improvements in social adjustment and better coping strategies for managing prodromal symptoms.

This team then undertook a larger-scale (n = 103) randomized trial of euthymic patients allocated to individual CBT plus mood stabilizers or to usual treatment (mood stabilizers plus outpatient support) (30). The intervention group had significantly fewer manic and depressive relapses (CBT group = 44%; control group = 75%), psychiatric admissions (15% versus 33%) or total days in episode (~27 days versus 88 days) over 12 months than the usual care group. A two-year follow-up (31) found that the between-group differences were significant for BD episodes and depressive episodes, but not manic/hypomanic episodes. Over 30 months, the CBT group spent 110 fewer days in BD episodes than control participants and exhibited significantly better mood ratings and social functioning. Most gains were observed in the first year of the study, once again suggesting that 'top-up' sessions may have a role to play in maintaining gains. An economic analysis revealed that the extra cost of providing CBT was offset by reduced resource utilization elsewhere, with costs for services used by individuals receiving CBT of about £10,350 over 30 months compared to £11,725 for individuals receiving usual care.

Lam et al. (32) explored predictors of CBT response. Notably, individuals with a very positive self image with highly positive appraisals of manic-like attributes (e.g., productivity, being outgoing) showed less response to CBT. Together with the findings for group psychoeducation (27), it can be hypothesized that patients who are less accepting of the realities of the illness, or who externalize its causes may be less likely to benefit from structured therapies.

A modified CBT model was implemented by Ball et al. (33) who allocated 52 patients with bipolar I or II disorders to a six-month trial of either

schema-focused CBT (use of imagery, narrative techniques, and reliving of early experiences) or usual treatment; both treatment groups also received mood stabilizers. Post-intervention, patients allocated to schema-focused CBT had less severe depression and reduced levels of dysfunctional attitudes, with a trend ($p = 0.06$) toward greater time to depressive relapse. At 18 month follow-up, scores on a clinical global impression scale showed a substantial difference in favor of CBT. The design and sample size of this trial leaves unanswered the question of any specific benefits of a schema-focused as compared to a 'relapse-prevention' style of CBT (31). However, it does suggest that, as in unipolar disorders, changes in dysfunctional attitudes may be a mediator of improvements in bipolar depression (34).

Given the overlap between the core elements of psychoeducation and individual CBT targeted at relapse prevention, some researchers have compared outcomes for patients randomized to psychoeducation alone with psychoeducation followed by CBT. In a Canadian trial, Zaretsky et al. (35) provided 79 participants with 7 sessions of individual psychoeducation and then allocated half the sample to an additional 13 sessions of CBT. Forty-six out of 79 participants completed the study. There were no significant between-group differences with regard to relapse, hospitalization or adherence rates or manic symptoms, but dysfunctional attitudes and days of depressed mood decreased significantly more over 12 months in the CBT group.

A four-site Canadian trial (S. Parikh and colleagues; personal communication, June 29, 2008), the final results of which are still pending, randomly assigned 204 patients in full or partial remission to 20 weekly sessions of CBT or 6 group psychoeducation sessions, both adjunctive to pharmacotherapy. Preliminary results show no between group differences in outcome, but without a 'no psychotherapy' control group, it cannot be determined whether the lack of difference is because both groups had equally good or equally poor outcomes.

In contrast to the efficacy studies targeted at relapse prevention in euthymic individuals, Scott and colleagues (36, 37) explored the benefits of CBT when offered to representative patients with BD drawn from UK public mental health services. In a pilot study, Scott et al. (36) examined the effect of 20 sessions of CBT in 42 patients with BD; 30% met criteria for a current mood episode and 60% met criteria for substance abuse/dependence, personality disorders, or other Axis I disorders. Participants were initially randomized to the intervention group or to a 'waiting list' control group who received CBT after a six-month delay. Compared with subjects on the wait-list, those who received immediate CBT experienced significant reductions in symptom levels and improvements in global functioning, work and social adjustment. Follow-up of all those who received CBT suggested a substantial reduction in BD episodes in the 18-month post-intervention phase as compared with the equivalent pre-intervention phase. Although moderators were not formally studied, it was noted that CBT participants who showed significantly reduced and less volatile activation scale scores did especially well with the intervention.

Scott and colleagues (37) then undertook a large scale ($n = 252$), five-site pragmatic effectiveness trial of adjunctive CBT compared with usual treatment in individuals at high risk of BD relapse. There were minimum exclusion criteria (high suicide risk, severe personality disorders); many participants were symptomatic and/or had comorbid disorders (30% were depressed; >40% had a comorbid substance misuse disorder). Over 18 months, 52% of all participants experienced a relapse but there was no differential relapse rate in CBT compared with TAU.

Whereas this trial did not reveal main effects for the adjunctive CBT treatment on any primary outcome variable, post hoc analyses revealed that individuals with fewer (<12) lifetime BD episodes benefited more from CBT with regard to relapse than those with more (≥ 12) episodes. Post hoc analyses also revealed that individuals receiving CBT while in a depressive episode ($n = 78$; CBT = 41, TAU = 37) met recovery criteria about five weeks earlier than those receiving usual treatment (median days to recovery: CBT = 73 versus TAU = 118) (37). In contrast, clinicians reported anecdotally that a small subgroup of patients with multiple comorbidities, many prior BD episodes, and complex social problems experienced symptom exacerbations because they were either too emotionally labile or were 'stressed' by trying to engage in CBT.

It is noteworthy that CBT for BD has been tested in more randomized trials than any other psychological approach for BD. The different investigators have used interventions which, although all coming under the rubric of CBT, employed different models (schema focused, CBT added to psychoeducation) or had different emphases (CBT for relapse prevention in euthymic individuals versus CBT for acute and continuation treatment). The studies also differed considerably in sample characteristics (i.e., recovered versus

subsyndromally or syndromally ill) at study entry. Thus, cross-trial comparisons yield inconsistent conclusions. Nonetheless, most meta-analyses to date have concluded that CBT plays its part in the outpatient management of BD, with the most robust benefit being the prevention of depressive relapses (38–42).

Family-focused therapy

Developments in the family psychoeducational treatment of schizophrenia (43–45) were influential in the creation of similar approaches in bipolar disorder. The FFT model consists of 21 sessions of psychoeducation for the patient and family members (typically, parents or spouse), followed by training in communication and problem-solving skills. The approach includes development of a relapse prevention plan, examination of the attitudes toward medications, as well as communication exercises (e.g., active listening; constructive feedback) aimed at reducing high expressed emotion interchanges (46).

In the Colorado Treatment-Outcome Project (47), 101 bipolar I patients, 80% of whom began as hospital inpatients, were randomly assigned following an acute episode to FFT and pharmacotherapy or crisis management and pharmacotherapy. Patients in FFT received 21 sessions in nine months, whereas those in crisis management received 2 sessions of family-based psychoeducation followed by telephone monitoring and crisis intervention sessions over nine months. Over two years, patients in FFT were three times more likely to remain remitted without relapsing, with less severe depressive ($p = 0.005$) and manic ($p < 0.05$) symptoms. The effects of FFT on depression were mediated by improvements in patient/relative interactional behavior, whereas improvements in manic symptoms were mediated by improved medication adherence, which was higher in the FFT than the crisis management group.

A second RCT (15) systematically examined the effects of FFT in comparison to an adjunctive individual therapy that covered similar psychoeducation topics in 21 sessions over nine months. Bipolar I patients ($n = 53$) were recruited shortly after a hospitalization for a manic episode. No differences in the treatment modalities were observed in the first year, but in a 1–2 year post-treatment follow-up only 12% of the patients in FFT required rehospitalization compared with 60% of the patients in individual therapy. Post-treatment rates of symptomatic recurrence were 28% in FFT and 60% in individual therapy.

In a two-site randomized trial, Miklowitz et al. (48) assigned 58 adolescent bipolar patients to an age-appropriate version of FFT plus pharmacotherapy or a three-session psychoeducational treatment (enhanced care) plus pharmacotherapy. Patients entered in a variety of clinical states and met diagnostic criteria for bipolar I, bipolar II, or BD not otherwise specified. The results over two years indicated a significant advantage of FFT in time to recovery from initial depressive symptoms, amount of time in a depressed state, and the trajectory of depressive symptoms over two years; but benefits did not extend to manic symptoms.

Multifamily approaches

The FFT approach has been criticized because clinicians work with one family at a time rather than with several families simultaneously. A wait-list controlled study of a multifamily psychoeducation group was recently completed with 175 school-aged bipolar (70%) and unipolar depressed (30%) children. The groups included didactic information, stress management, communication skills, and coping with mood escalation. Over one year, children who participated with parents in the groups showed greater improvement in mood symptoms than children on the wait-list, although no data were presented on recovery or recurrence rates. Benefits of the groups extended to parents' ability to advocate for the health needs of their children (49).

A group at Brown University Medical Center, Providence, RI, USA (50–52) randomly assigned 92 acutely ill bipolar I patients to (i) pharmacotherapy alone or pharmacotherapy plus (ii) 12 sessions of single-family problem-centered therapy, or (iii) 6 sessions of multifamily group psychoeducation. There were no between-group differences in time to recovery or relapse. A secondary analysis revealed that patients from families with high conflict or low problem-solving at pretreatment who received either form of family therapy had half as many depressive episodes per year, and spent less time in depressive episodes than patients from high conflict families allocated to pharmacotherapy alone. The effects of the family interventions did not extend to manic symptoms, although the patients in the multifamily groups were less likely than the controls to be re-hospitalized during follow-up (52).

The Barcelona group examined caregiver psychoeducation groups which excluded patients (53). Participants were 113 caregivers of bipolar I and II patients; the patients were euthymic, currently

undergoing pharmacotherapy, free of other Axis I disorders, and living with these caregivers. Half of the caregivers received 12 weeks of group psychoeducation and half received no intervention. Caregiver groups focused on early detection of prodromes, medication adherence, and effective communication and problem-solving. Over 12 months, patients whose relatives attended the groups had longer survival times prior to hypomanic or manic recurrences than patients in the control condition, but did not differ on time to depressive or mixed episodes.

These studies raise the question of whether family therapy can be done in shortened packages (6–12 sessions); with or without patients present; and with several families at once. It is difficult, however, to compare the studies directly. Patients in these studies differed in clinical condition at entry and the therapy durations, content and assumptions differed considerably. Moreover, economic analysis of multifamily and single family models would need to extend beyond health care resource utilization by the patient and take into account indirect or opportunity costs incurred by caregivers such as costs of time away from employment, change in employment status, as well as the alleviation of burden (physical or psychological stress) that may impede quality of life.

Other issues to consider when involving families are highlighted by a treatment preference study conducted at the Veterans Administration Hospital, Denver, CO, USA (54) where patients with bipolar, schizophrenic, or schizoaffective disorder and their families were allowed to choose among three treatment options: (i) individualized FFT (21 sessions), (ii) peer-led multifamily educational groups (12 sessions), (iii) brief (3 session) family psychoeducation, or no family treatment. Of 133 referrals, 58 (43.6%) chose no treatment. Of the remaining 75, 42 (56.0%) chose the individualized FFT approach; 28 (37.3%) requested multifamily groups and 5 (6.7%) opted for brief family treatment. Furthermore, caregivers of bipolar patients were significantly more likely than caregivers of schizophrenia or schizoaffective patients to choose individualized family therapy. Collectively, these studies suggest the importance of including caregivers in the psychoeducational treatment of bipolar patients and modeling economic costs of real world service delivery, where families may or may not choose to receive input.

Interpersonal and social rhythm therapy

The IPSRT model (55, 56) has two aims: (i) to stabilize daily and nightly routines or 'social rhythms' (i.e., when patients arise, go to sleep, eat, socialize, etc.) and (ii) to resolve interpersonal problems that co-existed with the most recent illness episode. Stabilizing social rhythms involves tracking daily routines and sleep/wake cycles and keeping routines even during events that would ordinarily change routines (e.g., preparing for an exam; taking a transatlantic flight). As in the interpersonal psychotherapy (IPT) approach to unipolar disorders, IPSRT involves helping the patient resolve issues relevant to grief over loss, role transitions, interpersonal disputes, or interpersonal deficits (57, 58).

Frank et al. (55) randomly assigned 175 bipolar I patients following an acute illness episode to pharmacotherapy and (i) stabilization with weekly IPSRT sessions or (ii) stabilization with weekly intensive clinical management (review of symptoms, adherence monitoring, psychoeducation) sessions. Patients who met criteria for 'stabilization' were then re-randomized to pharmacotherapy plus IPSRT or intensive clinical management, with monthly sessions over two years. Patients who received IPSRT during the acute phase had longer periods of stability prior to recurrences in the maintenance phase than patients who received intensive clinical management in the acute phase. The effects of IPSRT were most pronounced in patients who succeeded in stabilizing their social rhythms during the acute phase. Patients receiving IPSRT acutely also showed greater improvement in vocational functioning during the acute phase than patients in intensive clinical management (56). In contrast, there were no differences in the outcomes of patients assigned to IPSRT or clinical management during the maintenance phase. The results suggest that IPSRT may be an effective intervention if initiated immediately following an acute episode. In contrast, CBT and group psychoeducation may be more beneficial if initiated after a sustained period of euthymia.

A comparison of treatment models: The STEP-BD Program

Most of the above-cited trials reported time to first BD relapse or actuarial relapse rates for an active treatment compared with an inactive treatment condition, or an equally intensive but nonspecific comparison (e.g., the supportive group arm of the Barcelona psychoeducation study). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (59) examined the effects of different forms of psychotherapy, and different medication algorithms, for acutely depressed bipolar I and II patients treated at 15 US sites. The design emphasized effectiveness strategies,

including (i) minimal training of therapists (a weekend workshop followed by monthly supervisory teleconferences), (ii) clinically significant outcomes (time to recovery and amount of time well), and (iii) delivery of DSPs in sites which had not previously administered these treatments.

The therapy RCT ran alongside a six-month trial comparing mood stabilizers plus antidepressants to mood stabilizers plus placebo (n = 366). In the therapy RCT (n = 293), three forms of psychotherapy (CBT, FFT, or IPSRT) given over nine months were compared to a three-session collaborative care intervention (CC). Over one year, time to recovery from acute bipolar depression did not differ across the FFT (median 103 days), CBT (112 days) and IPSRT (128 days) conditions, although all were shorter than time to recovery in the collaborative care condition (146 days). Furthermore, intensive psychotherapy was associated with a greater probability of staying well over one year, better psychosocial functioning, and higher life satisfaction than collaborative care (60).

In an exploratory analysis of the patients who participated in both trials (n = 236), the main effect of psychotherapy (intensive versus collaborative care) was significant in predicting time to recovery over one year ($p = 0.04$), whereas the main effect of medication strategy (mood stabilizer plus adjunctive antidepressant or adjunctive placebo) was not ($p = 0.24$). When only considering recovery within the first six months, intensive psychotherapy was more likely than collaborative care to be associated with depressive recovery (OR = 1.62), whereas no differences emerged between the two medication strategies (OR = 1.09). Studies that provide direct comparisons of mood stabilizers plus adjunctive psychotherapy versus mood stabilizers plus adjunctive antidepressants for bipolar depression are clearly warranted.

Discussion

This review concludes that adjunctive psychotherapy can be effective in preventing BD relapse or recurrence, reducing symptom severity, and possibly, hastening time to recovery from acute BD depression over 1–2 year periods. There is also limited evidence that psychotherapy may lead to improvements in social functioning. Most of the DSPs that had an impact on depression (the greatest symptom burden in BD) (61) involved at least 12 sessions, and the effects appeared to be largely maintained, although in some cases weakened, in the 1-2 year post-intervention period.

Active ingredients and mediating mechanisms

Few of the studies examined the active ingredients of DSPs. The content of treatments ranged considerably from study to study, and included a focus on early identification of prodromal symptoms (22), medication adherence (4), sleep/wake cycle stabilization (55), cognitive restructuring (30), and family communication styles (47, 62). It is not clear whether these different foci are correlated with differences in the durability of treatment effects, the relative effects of the DSPs on mania versus depression, or their effects on psychosocial functioning.

It is noteworthy that effective therapies share a number of characteristics in common regarding how the model is shared with the patient (and the family as appropriate), how it is delivered, and the overall structure of the treatment (see Table 2). These common characteristics help to distinguish DSPs from generic good clinical practice approaches (63).

Recently, we attempted to identify the hypothesized active ingredients of existing DSPs through a survey of clinicians involved in the RCTs reviewed (64). The questionnaire asked clinicians to quantify (on a 1–3 frequency scale) the extent to which they used each of 17 treatment strategies in experimental and control conditions. Not surprisingly, CBT was distinguishable by the therapists' greater use of cognitive restructuring and behavioral activation relative to other treatments, whereas communication training was a distinctive feature of family interventions. However, other techniques were commonly used in several approaches, with IPSRT, CBT, and group psychoeducation all incorporating interventions to stabilize sleep/wake cycles and daily routines.

Table 2. Shared characteristics of disorder-specific psychotherapies (DSP)

1. Each DSP offers a specific individualized formulation or conceptualization of the problems experienced with bipolar disorder
2. The model of therapy is shared openly with the patient and (where appropriate) the family
3. There is a clear rationale for the techniques used, which are applied in a way that appears logical to the patient
4. There is an emphasis on psychoeducation and skill development, with transfer of learning outside of therapy sessions
5. Change is attributed to the patient's, not just the therapist's efforts
6. The patient (and family) is encouraged to use illness management techniques post-therapy, increasing the likelihood that benefits will be durable

Interestingly, most of the comparison treatment conditions contained some elements of psychoeducation, including information about medications and side effects, the importance of adherence, and community advocacy for the patient. The comparison treatments were most clearly distinguished from the experimental treatments by the lack of systematic employment of interventions and the absence of therapeutic ingredients such as: problem-solving regarding stressful events or experiences (including stigmatization), communication training, cognitive restructuring, or sleep/wake cycle regulation. These components are candidates for the 'active ingredients' by which DSPs confer clinical benefits relative to usual care or nonspecific psychotherapy.

Further research is needed to determine which core ingredients of psychotherapy are associated with differential effects on depressive and manic outcomes. The pattern of findings suggests that brief interventions emphasizing medication adherence or early identification and intervention with prodromal symptoms (4, 22, 53) have significant effects on manic symptoms but virtually no impact on depression. The more extended DSPs, especially those developed from therapies applied to major depressive disorder or schizophrenia, have stronger effects on depression than mania (7, 63). Beyond these general observations, we do not know which specific strategies are essential to stabilizing patients with bipolar depression or mania, how long patients must be exposed to these interventions, or whether the strategies should vary with the clinical presentation or illness history of patients. The latter factors are particularly important for mental health services as clinical and personal characteristics are often critical moderators of the benefits of an apparently efficacious DSP.

Studies examining the pathways from specific treatment techniques to change variables to clinical outcomes will be essential to moving the field forward (11). As an example, a study of CBT could be constructed such that changes in dysfunctional attitudes during acute treatment could be compared with changes in patients' attributions about BD (dispositional or situational) and their ability to recognize and intervene with prodromal symptoms of mania during maintenance treatment. That is, the mediators of treatment efficacy could be different during the acute and maintenance phases of treatment. To draw an example from the depression literature, changes in negative expectations (hopelessness) predated symptom improvement in one trial of CBT; in contrast, decreased hopelessness followed symptom improvement during antidepressant treatment (65). During maintenance treatment, changes in explanatory style occurred later in CBT, after the majority of symptom stabilization had already occurred. Changes in explanatory style, however, mediated the effects of CBT on relapse prevention (34, 65, 66).

Studies that examine Theory of Mind tasks (ToM) (the ability to 'mentalize' and infer one's own and others' thoughts, intentions, or feelings) before and after psychosocial treatments could determine whether improvements in neural activation patterns that subserve social cognition are observed, and how such improvements map onto clinical or functional gains (67). For example, responders to IPSRT or FFT who show improvements in the ability to mentalize might show enhanced prefrontal cortical activation in ToM tasks. In turn, this level of enhanced activation might correlate with pre/post-treatment gains in social or family functioning.

Cost-effectiveness

As this review demonstrates, therapies that cost more in the initial stages of treatment, and that require greater therapist skill and more sessions are most likely to be associated with health gains and/or reductions in resource utilization in the medium to longer term. As an example, the STEP-BD comparison of up to 30 sessions of intensive therapy (FFT, IPSRT, or CBT) with 3 sessions of collaborative care found that intensive therapy was associated with a shorter time to recovery from depression, a greater likelihood of ongoing stability, and enhanced psychosocial functioning. Thus, in the psychotherapy of BD, "you get what you pay for." Moreover, the total cost of treatment is not an adequate reflection of the clinical and social needs of individual patients as better outcomes are often associated with greater resource utilization (e.g., a patient with greater insight seeking extra therapy to enhance quality of life, not just prevent relapses). Hence, calculating incremental cost-effectiveness ratios will be more informative if the assessment of cost versus benefit extends beyond the intervention phase. If the analysis includes medium to longer term follow-up, the additional costs of the resources utilized during the initial phase are readily offset by a relatively small reduction (about 10%) in the number of occupied hospital bed-days. Given that the likelihood of hospital admission among individuals receiving usual treatment is significantly greater than among those receiving adjunctive DSPs (OR = 1.49; 95% CI: 1.05–2.11) and admissions are usually of longer duration, the economic argument begins to shift in favor of DSPs.

The next generation of RCTs will need to include assessments of treatment, illness costs, benefits and 'opportunity costs' (e.g., loss of earnings to attend appointments, costs of training of therapists). Extending the monitoring of resource use beyond the health system to social care and other systems is especially important if cost estimation is to be combined with cross-disease assessments of impairment (e.g., quality of life indices or years lived with disability). This type of research is more easily undertaken in some settings or countries than in others, but such studies will mean that psychotherapy speaks the international languages of health and general economics. This is even more crucial given the current global fiscal climate.

Length of treatment

How many sessions are optimal for the bipolar patient? Patients in the STEP-BD randomized study were expected to attend up to 30 sessions in nine months, but the average patient attended about half the course of therapy (median = 13 sessions), with a range of 0-30 sessions. Attending about 13–15 of the scheduled therapy sessions is a remarkably consistent cross-study finding (26), but trials do not always allow the flexibility we can exercise in real world clinical practice. The optimal length of treatment will vary with the time since the onset of the last episode, the complexity of the illness or co-morbid problems identified, the availability of social supports, and the response to (and adherence with) medications.

A naturalistic study using a STEP-BD naturalistic cohort (n = 148) found that patients who had more severe levels of depression responded better to more frequent (i.e., weekly) psychosocial sessions than less frequent (i.e., monthly) sessions, whereas the reverse was true for patients who began with milder levels of depression (68). Possibly, less frequent 'check-ins' may be sufficient for stable patients, mirroring the maintenance therapy models that are frequently instigated for those with highly recurrent depression. In contrast, in some instances, therapy 'breaks' may help some patients with complex problems to pace themselves, master new skills, and then return to therapy to move into a new phase of learning (63). Determining the optimal length of treatments will require pragmatic trials which test different treatment durations and frequencies at different phases of the illness or in different sub-populations.

Choosing treatments based on moderators of response

Identifying treatment moderators – the conditions and subpopulations for whom various forms of psychotherapy are most effective – may be the most efficient way to cut the costs of psychosocial treatments. Moderation is usually demonstrated by observing an interaction between treatment conditions (i.e., active treatment versus usual treatment) and patient or family variables measured prior to treatment (11). Unfortunately, few studies have been adequately statistically powered to identify moderators. In most cases, moderators are discovered post hoc, necessitating later independent replication. Nonetheless, knowing that a DSP works particularly well for one subgroup and not another is important in developing treatment plans under conditions of limited resources. As an example, Scott et al.'s CBT trial (37) had a sufficient sample size to allow a 'dismantling' analysis that identified a sub-group of CBT responders who had < 12 prior BD episodes. This analysis was then replicated with the group psychoeducation sample of Colom et al. (23) who also found that patients who had ≥ 12 prior episodes showed no benefit from the active compared to the control intervention (38). These findings may indicate that intensive therapy should be considered at an early point in the 'illness career' of individuals with BD rather than after multiple episodes.

Meta-analyses of existing datasets will help to identify moderators. For example, there are now at least five studies of CBT in which the moderating effect of number of prior episodes could be examined; however, this analysis would require researchers to pool the data for *each individual participant* in each study (not just group means and SDs). Likewise, existing datasets could be collapsed to determine if certain forms of treatment (notably, CBT or psychoeducation) are more effective when given to stable and recovered patients, whereas other treatments (notably, FFT or IPSRT) are more effective for patients who have recently had an acute episode. Finally, those trials that included health economic assessments could identify cross-trial characteristics of high resource utilizers, particularly 'outliers' such as patients who continue post-therapy to be high utilizers, or continue to require frequent hospitalizations despite receiving apparently adequate services.

Unfortunately, even with accurate identification of the subpopulations most in need of psychosocial care, limited financial resources and availability of trained therapists make the administration of full-length DSPs unfeasible for most BD patients in the majority of clinical settings. Standardized psychoeducation protocols that can be easily delivered in public health/primary care settings may be reasonable alternatives to personalized

care, especially if these protocols are supplemented with telephone follow-up, bibliotherapy, or internet-based self-care materials. Primary care and internet-based approaches to treatment are gaining traction in the treatment of depression (34). However, these approaches may be best viewed as supplements to, rather than substitutes for more labor-intensive approaches to BD. Until we have clear evidence, it is likely that primary care or internet-based approaches will be more suitable to those with less severe or recurrent forms of BD, or perhaps those with bipolar spectrum disorders or cyclothymia.

Psychosocial interventions for youth at risk for bipolar disorder

Another unexplored territory is the applicability of psychosocial interventions for children or adolescents at risk for BD. Risk for BD increases with the combination of a positive family history of BD in a first-degree relative (especially if three generations are affected) and the presence of subsyndromal but impairing mood swings [i.e., cyclothymia or manic/hypomanic episodes of short duration; subsyndromal mixed presentations (69–71)]. Furthermore, those who experience three or more recurrences of depression or severe depressions with psychotic symptoms before the age of 25 years are at high risk of *conversion* from unipolar to bipolar disorders (71). Although current methods for identifying high risk individuals lack specificity, neural markers – notably, changes in amygdalar volume or changes in the activation of amygdalar/prefrontal circuitry in response to emotional challenges (72–74) – may ultimately help to identify populations at risk. Administering briefer versions of DSPs targeted toward the unique difficulties of high risk youth (for example, restructuring self-defeating cognitions, working toward stabilization of sleep/wake cycles, reducing family conflict related to a parent's or sibling's bipolar illness) could have the effect of delaying the onset of BD among at-risk youth, or at least minimizing its severity and impairment once manifest. Preventing the neurotoxic effects of early episodes before the illness becomes chronic, and minimizing the psychosocial sequelae of early episodes may do much to prevent the long-term disability caused by bipolar illness.

Conclusion

In summary, research on adjunctive psychotherapy for BD has grown exponentially in the last two decades. Although trials are still predominantly efficacy rather than effectiveness studies, we are beginning to put important pieces of the jigsaw into place regarding what works for whom and under what circumstances. There is, however, no room for complacency. Meta-analyses of trials suggest that replication of studies is essential to help us understand if the impressive results achieved in one research center are generalizable to other settings (41).

As well as estimating benefits and health gains from adjunctive psychotherapy, we need to elucidate whether there are adverse effects for some individuals offered psychotherapy, and to develop some consensus on the best methods for reporting tolerability or undesirable effects of psychotherapy. In the Scott et al. trial (37), patients with ≥ 12 episodes did not respond well to intensive CBT and some may even have deteriorated as a consequence. Determining what variables (other than number of prior episodes, which correlated with a number of other poor prognostic indicators) predict a poor response to psychotherapy is as important as identifying predictors of good outcome from these combined treatments. Finally, we need to consider what modifications to current therapy models might be needed to more specifically target the needs of special populations of BD patients, notably those with extensive histories of relapse, bipolar II disorder with high levels of intermorbid depression, rapid cycling, early-onset, or poor prognostic co-morbidites (i.e., anxiety, substance abuse, and Axis II disorders) (75). The message is clearly that we are at the start rather than the end of a long journey.

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