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Adjunctive Psychotherapy for Bipolar Disorder
A Systematic Review and Component Network Meta-analysis

David J. Miklowitz, PhD; Orestis Efthimiou, PhD; Toshi A. Furukawa, MD, PhD; Jan Scott, MD, PhD; Ross McLaren, BMBCh; John R. Geddes, MD; Andrea Cipriani, MD, PhD

IMPORTANCE Several psychotherapy protocols have been evaluated as adjuncts to pharmacotherapy for patients with bipolar disorder, but little is known about their comparative effectiveness.

OBJECTIVE To use systematic review and network meta-analysis to compare the association of using manualized psychotherapies and therapy components with reducing recurrences and stabilizing symptoms in patients with bipolar disorder.

DATA SOURCES Major bibliographic databases (MEDLINE, PsychInfo, and Cochrane Library of Systematic Reviews) and trial registries were searched from inception to June 1, 2019, for randomized clinical trials of psychotherapy for bipolar disorder.

STUDY SELECTION Of 3255 abstracts, 39 randomized clinical trials were identified that compared pharmacotherapy plus manualized psychotherapy (cognitive behavioral therapy, family or conjoint therapy, interpersonal therapy, or psychoeducational therapy) with pharmacotherapy plus a control intervention (eg, supportive therapy or treatment as usual) for patients with bipolar disorder.

DATA EXTRACTION AND SYNTHESIS Binary outcomes (recurrence and study retention) were compared across treatments using odds ratios (ORs). For depression or mania severity scores, data were pooled and compared across treatments using standardized mean differences (SMDs) (Hedges-adjusted *g* using weighted pooled SDs). In component network meta-analyses, the incremental effectiveness of 13 specific therapy components was examined.

MAIN OUTCOMES AND MEASURES The primary outcome was illness recurrence. Secondary outcomes were depressive and manic symptoms at 12 months and acceptability of treatment (study retention).

RESULTS A total of 39 randomized clinical trials with 3863 participants (2247 of 3693 [60.8%] with data on sex were female; mean [SD] age, 36.5 [8.2] years) were identified. Across 20 two-group trials that provided usable information, manualized treatments were associated with lower recurrence rates than control treatments (OR, 0.56; 95% CI, 0.43-0.74). Psychoeducation with guided practice of illness management skills in a family or group format was associated with reducing recurrences vs the same strategies in an individual format (OR, 0.12; 95% CI, 0.02-0.94). Cognitive behavioral therapy (SMD, −0.32; 95% CI, −0.64 to −0.01) and, with less certainty, family or conjoint therapy (SMD, −0.46; 95% CI, −1.01 to 0.08) and interpersonal therapy (SMD, -0.46; 95% CI, −1.07 to 0.15) were associated with stabilizing depressive symptoms compared with treatment as usual. Higher study retention was associated with family or conjoint therapy (OR, 0.46; 95% CI, 0.26-0.82) and brief psychoeducation (OR, 0.44; 95% CI, 0.23-0.85) compared with standard psychoeducation.

CONCLUSIONS AND RELEVANCE This study suggests that outpatients with bipolar disorder may benefit from skills-based psychosocial interventions combined with pharmacotherapy. Conclusions are tempered by heterogeneity in populations, treatment duration, and follow-up.

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Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: David J. Miklowitz, PhD, Department of Psychiatry and Biobehavioral Sciences, UCLA Semel Institute, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Room A8-256, Los Angeles, CA 90024 (dmiklowitz@mednet.ucla.edu).

There is increasing recognition that pharmacotherapy alone cannot prevent recurrences of bipolar disorder or fully alleviate postepisode symptoms or functional impairment.[1] Psychotherapy, when provided at all, is viewed as an adjunctive treatment.[2] Evidence from randomized clinical trials (RCTs) indicates that combining pharmacotherapy with manualized psychotherapies—including cognitive behavioral therapy (CBT), family-focused therapy, interpersonal and social rhythm therapy (IPSRT), and group psychoeducation—is more effective than pharmacotherapy alone in stabilizing symptoms and reducing recurrences among outpatients with bipolar disorder.[1,3,4] The comparative effectiveness of these approaches, however, has received scant attention.

Unfortunately, even carefully delivered psychosocial interventions are not effective for many patients with bipolar disorder, suggesting the importance of examining which therapy components (strategies, techniques, or formats) are essential for clinical effectiveness. The existing trial literature on bipolar disorder is heterogeneous, with few direct comparisons of modalities and a lack of clarity as to which treatments are effective in acute stabilization and which are effective in recurrence prevention. Network meta-analysis (NMA) aims to synthesize evidence across clinical trials so that all treatment options can be compared with each other, increasing the precision of effect estimates between interventions.[5,6] Component NMA, an extension of standard NMA, allows for the decomposition of complex interventions and estimates the effectiveness of their constituent components.[7,8]

There has been only 1 NMA of psychotherapies for bipolar disorder, to our knowledge; this NMA concluded that only caregiver-focused interventions (without patient participation) were associated with a significant reduction in the risk of recurrences in patients.[9] One editorial described a number of limitations of this analysis, notably that the primary conclusion was based on only 2 trials and that other key effectiveness trials (often featuring different interventions) were excluded.[10]

We performed a systematic review of the RCT literature and used NMA and component NMA to examine (1) whether any psychosocial interventions are associated with reduced episode recurrence and stabilizing symptoms in patients with bipolar disorder and (2) the outcomes of different therapy components (eg, provision of illness information or guided practice of illness management strategies or coping skills) or formats (ie, individual, family, or group). The primary outcome was illness recurrence, with secondary analyses of posttreatment depressive and manic symptom severity and acceptability (study attrition for any reason).

Key Points

Question Which psychosocial interventions are associated with an improved course and medium-term outcomes of bipolar disorder?

Findings In a systematic review and network meta-analysis of 39 randomized clinical trials of adjunctive psychotherapy, there was evidence that family, cognitive behavioral, and psychoeducational therapies were associated with reduced episode recurrence vs treatment as usual in individuals with bipolar disorder. Cognitive behavioral therapy was associated with greater stabilization of residual symptoms of depression compared with treatment as usual.

Meaning This study suggests that outpatients with bipolar disorder receiving pharmacotherapy should also be offered psychosocial treatments that emphasize illness management strategies and enhance coping skills; delivering these components in family or group format may be especially advantageous.

Methods

Search Methods for Identification of Studies

We followed the specifications of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] statement and its extension for NMAs.[12] We focused on RCTs comparing an experimental psychotherapy plus pharmacotherapy with another form of psychotherapy plus pharmacotherapy or treatment as usual (TAU, defined as pharmacotherapy with routine monitoring visits) for adults or adolescents with bipolar disorder. The literature was searched from inception to June 1, 2019 (PROSPERO registration number CRD42015016085).[13] We searched MEDLINE, PsycInfo, Cochrane Library of Systematic Reviews, ClinicalTrials.gov, EU Clinical Trials Register, ISRCTN Registry, World Health Organization International Clinical Trials Registry, and the Australian New Zealand Clinical Trial Registry (search terms in eTable 1 in the Supplement). Trials were also located through searching reference lists of published and unpublished articles, conference proceedings, systematic reviews, and a prior NMA.[9] No language restrictions were applied.

Study Eligibility Criteria

The included RCTs focused on the alleviation of mood symptoms and/or the prevention of recurrences. We included only studies in which participants received medications per standard clinical practice, as operationalized by the original investigators. We excluded quasi-randomized trials and studies that examined psychotherapy as 1 element of multicomponent systematic care (eTable 1 in the Supplement). Two independent raters (including R.M.) selected studies and extracted the outcome data, as well as information on potential effect modifiers: age, sex, bipolar subtype, blinding of outcome assessors, and year of publication. The Cochrane tool was used to classify risk of bias.[14] When discrepancies occurred, a third rater (A.C.) was consulted, or the original study authors were contacted.

Trial Participants

Participants were outpatients or inpatients aged 12 years or older and of both sexes, with a primary diagnosis of bipolar disorder I or II or unspecified bipolar disorder according to *DSM-III* or *DSM-III-R*, *DSM-IV* or *DSM-IV-TR*, *DSM-5*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, or Research Diagnostic Criteria.[15-21] Participants could be in any clinical state or have any comorbid medical or psychiatric disorder at randomization.

Types of Interventions

Psychosocial interventions could be implemented with individuals, families, or groups and had to include in-person contact between the patient and a trained therapist (digital [ie, texting via smartphones], internet, or telephone formats were excluded). Two raters (D.J.M. and J.S.) classified each active intervention group as belonging to 1 of the following nodes (see operational definitions in eTable 2 in the Supplement): traditional CBT with cognitive restructuring, behavioral activation, and problem-solving (including dialectical behavior therapy components such as mindfulness and distress tolerance); standard-length psychoeducation (≥6 group or individual sessions); IPSRT; family or conjoint therapy (including family-focused therapy, multifamily groups, or caregiver-only groups); or functional remediation. The raters classified the control groups as the following: brief psychoeducation (≤3 sessions), supportive therapy, or TAU. Based on descriptions of each intervention and a prior review,[22] 2 raters (D.J.M. and J.S.) defined 18 therapy components (eg, cognitive restructuring and group format) and classified each trial group according to the presence or absence of each component.

Types of Outcomes

The primary outcome was the proportion of participants who experienced an episode recurrence of any type (depressed, manic, or mixed) during the first 12 months after randomization (or by the trial end point if follow-up was of shorter duration). When these data were unavailable, we imputed recurrence proportions at 12 months from survival curves or used the nearest available reported data. Secondary outcomes were depressive or manic symptoms at a common end point (12 months or the nearest available time point) and acceptability (study retention). Binary outcomes were compared using odds ratios (ORs). When studies used different rating scales to assess symptom severity (eTable 3 in the Supplement), data were pooled using standardized mean difference (SMD) scores (Hedges-adjusted *g* scores using weighted pooled SDs).[23]

Data Synthesis

Using the statistical package meta in R, version 4.0.2 (R Foundation for Statistical Computing),[24] we performed standard pairwise meta-analyses using a random-effects model for (1) the omnibus comparison of all experimental interventions (CBT, IPSRT, family or conjoint therapy, and standard psychoeducation) with all control interventions (brief psychoeducation, supportive therapy, and TAU) and (2) direct comparisons of any 2 interventions occurring in at least 2 studies. We then performed random-effect NMA to synthesize evidence from the entire network by integrating direct and indirect estimates for each comparison into a single summary effect, using the netmeta command in R.[25] League-tables with summary relative effect sizes (SMDs or ORs) for each possible pair of interventions were supplemented by an intervention effectiveness hierarchy using surface under the cumulative ranking curves.[26]

The primary analyses of recurrences included only participants who completed the study. For sensitivity analyses, we assumed that patients who withdrew had a recurring outcome. For the secondary analyses of continuous symptom end points, we excluded studies that did not report the number of patients who completed the study. In sensitivity analyses, we imputed the number of patients who completed the study by multiplying the number randomized in the relevant study by the mean retention rate across the remaining studies. When *P* values, *t* values, 95% CIs, or SEs were reported, we calculated or imputed SDs.[27,28] We assessed statistical heterogeneity in the entire network by comparing the magnitude of the heterogeneity variance parameter (τ^2) from the NMA models with its empirical distribution.[6,29,30] We evaluated the presence of inconsistency globally using the design-by-treatment test[31] and locally using the back-calculation method comparing direct and indirect estimates.[32] We assessed small study effects, including publication bias, by examining asymmetry in the funnel plots of all interventions vs TAU.[33]

Component NMAs

We performed component NMAs in which the effect of each composite therapy was expressed as the sum of the effects of its constituent components.[7,8] The models estimate component-specific incremental odds ratios (iORs) for binary outcomes and incremental SMDs (iSMDs) for continuous outcomes. All component NMA models were conducted in a bayesian setting with analyses performed using OpenBUGS[34] and uncertainty expressed by 95% credible intervals (CrIs). In sensitivity analyses, we repeated all component NMAs in a frequentist setting using the discomb command in netmeta (eTable 4 in the Supplement).

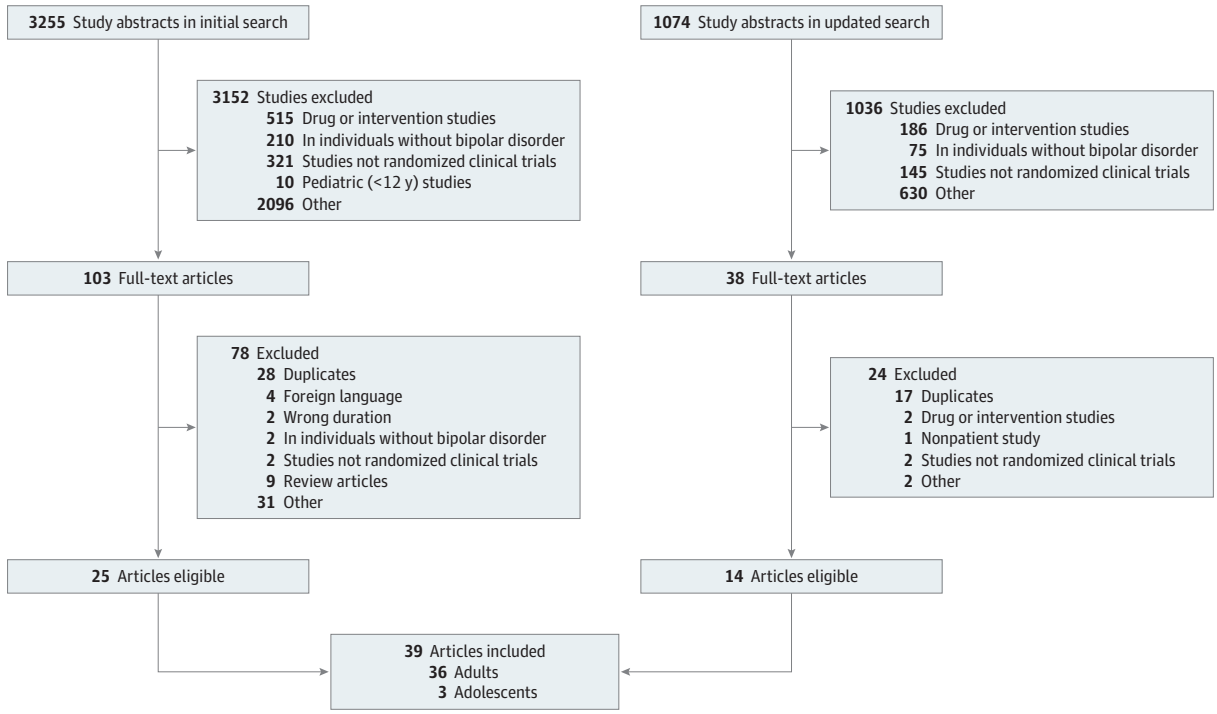
Results

Trial Characteristics

An initial search retrieved 3255 abstracts, with further examination of 103 published articles (**Figure 1**). Of these, 25 articles met full inclusion criteria. A further search using narrower search terms generated 1074 abstracts, from which 38 articles were examined and 14 met inclusion criteria. Thus, 39 RCTs were included, 36 enrolling adults and 3 enrolling adolescents. Of the 39 trials, 37 compared 2 intervention groups (eTable 5A in the Supplement). Of the 3863 trial participants (mean [SD] age, 36.5 [8.2] years), sex was reported for 3693 (2247 female participants [60.8%] and 1446 male participants [39.2%]). Most articles did not report racial or ethnic sample compositions. The geographical distribution and the number of published articles per 5-year interval are displayed in eFigure 1 in the Supplement. Risk of bias was rated as low in 17 studies, moderate in 19, and high in 3 (eTable 5B in the Supplement).

Transitivity is assumed when it is equally likely that any patient in a network of treatment comparisons could have been given any of the treatments in the network. In the studies, blinding of outcome assessors, publication year, and proportion of patients with bipolar disorder I or II were balanced across comparisons. However, 2 of 4 comparisons of family or conjoint therapy with standard or brief psychoeducation were

Figure 1. PRISMA Flow Diagram



conducted for adolescents[35,36] and 1 such comparison was conducted for young adults.[37] Otherwise, the assumption of transitivity appeared to be valid.

Treatment-Level Comparisons on Prevention of Recurrences

Across 20 two-group trials that provided usable information, experimental interventions were associated with a lower probability of recurrence than control interventions (OR, 0.56; 95% CI, 0.43-0.74) (eTable 6 in the Supplement). Statistical heterogeneity for this pairwise meta-analysis was $\tau^2 = 0.16$. Findings were nearly identical when we assumed recurrences for participants who withdrew. There was weak evidence of small study effects or publication biases (eFigure 2 in the Supplement).

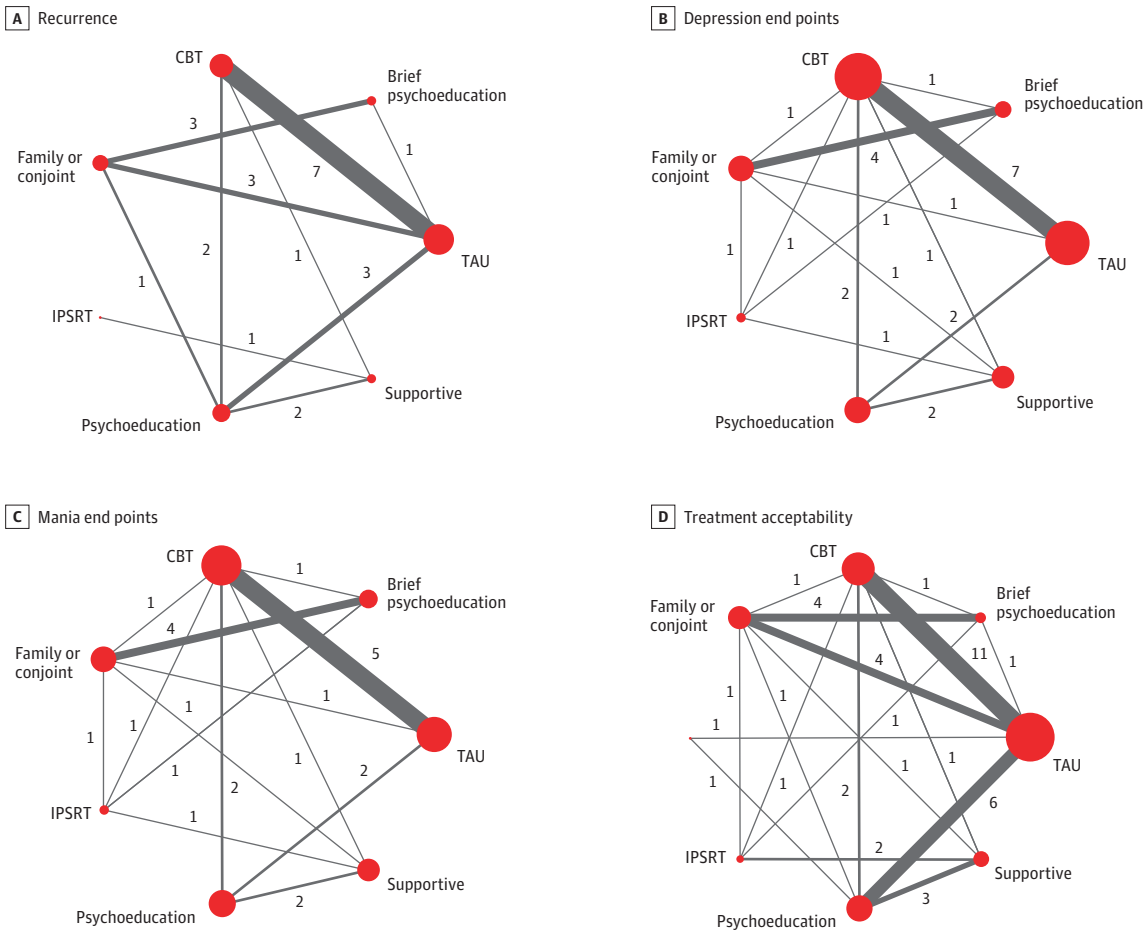
A total of 24 trials contained usable information for comparing associations of 2 therapy modalities with recurrence rates (**Figure 2**A; eTable 5A in the Supplement). There was no evidence of design-by-treatment inconsistency or local inconsistency (eTable 7 in the Supplement). Statistical heterogeneity (τ^2) was 0.35, similar to the values of τ^2 in Cochrane RCT reviews.[30] When examined by a standard NMA, family or conjoint therapy (OR, 0.30; 95% CI, 0.17-0.53), CBT (OR, 0.52; 95% CI, 0.34-0.79), standard psychoeducation (OR, 0.52; 95% CI, 0.32-0.84), and brief psychoeducation (OR, 0.34; 95% CI, 0.16-0.74) were associated with a more favorable outcome compared with TAU (**Table 1**). The highest surface under the cumulative ranking curve ranking was obtained for family or conjoint therapy (95%) (eTable 8 in the Supplement). A sensitivity analysis in which missing data were imputed yielded similar results (eTables 9 and 10 in the Supplement).

Treatment-Level Comparisons of Depressive or Manic Symptoms

Twenty-one trials provided information on 12-month depression symptoms (Figure 2B). The common τ^2 was 0.10, close to the empirical median.[29] In treatment-level comparisons of depression end points, evidence suggested that CBT (SMD, -0.32; 95% CI, -0.64 to -0.01) and, with less certainty, family or conjoint therapy (SMD, -0.46; 95% CI, -1.01 to 0.08) and IPSRT (SMD, -0.46; 95% CI, -1.07 to 0.15) were associated with significantly improved outcomes compared with TAU (**Table 2**; eTable 11 in the Supplement). There was modest evidence for small study effects and publication bias favoring experimental interventions (eFigure 3 in the Supplement) and weak evidence for local inconsistency (eTable 12 in the Supplement). When imputing the number of patents who completed the study, sensitivity analyses favored the effects of CBT, IPSRT, and family or conjoint therapy vs TAU (eFigure 4, eTables 13 and 14 in the Supplement).

Nineteen trials provided data for pairwise comparisons of treatment effects on 12-month mania symptoms (Figure 2C). When examined by a standard NMA, evidence suggested that CBT (SMD, -0.32; 95% CI, -0.65 to 0.01), psychoeducation (SMD, -0.31; 95% CI, -0.70 to 0.08), and family or conjoint therapy (SMD, -0.35; 95% CI, -0.86 to 0.17) were associated with significantly improved outcomes compared with TAU, although with substantial uncertainty (eTables 15 and 16 in the Supplement). There was minimal evidence of inconsistency and no evidence of small study effects (eFigure 5 and eTable 17 in the Supplement). The findings did not change when we recalculated the NMA with imputation of missing data (eFigure 6 and eTable 18 in the Supplement).

Figure 2. Geometry of Networks for Treatment-Level Comparisons



Network structure for the 4 outcomes examined in this article. Nodes denote treatments, and lines denote trials performing the corresponding treatment comparison. The size of a node is proportional to the number of studies that included the corresponding treatment. The thickness of the lines corresponds to the number of studies performing each comparison (also indicated by the number on each line). CBT indicates cognitive behavioral therapy; IPSRT, interpersonal and social rhythm therapy; and TAU, treatment as usual.

Table 1. Pairwise and Network Meta-analysis for Treatment-Level Comparisons of Recurrence (Odds Ratios)[a]

Brief psychoeducation	NA	1.15 (0.60-2.20)	NA	NA	NA	0.34 (0.08-1.49)
0.66 (0.28-1.55)	**CBT**	NA	NA	0.89 (0.41-1.95)	0.81 (0.26-2.52)	0.52 (0.32-0.83)
1.15 (0.63-2.09)	1.75 (0.87-3.49)	**Family or conjoint therapy**	NA	0.51 (0.13-1.92)	NA	0.31 (0.16-0.62)
0.22 (0.04-1.15)	0.34 (0.08-1.46)	0.20 (0.04-0.92)	**IPSRT**	NA	1.76 (0.49-6.35)	NA
0.66 (0.28-1.58)	1.01 (0.61-1.68)	0.58 (0.29-1.16)	2.96 (0.72-12.11)	**Psychoeducation**	0.54 (0.28-1.03)	0.51 (0.26-0.99)
0.39 (0.14-1.08)	0.60 (0.30-1.19)	0.34 (0.14-0.82)	1.76 (0.49-6.35)	0.59 (0.33-1.06)	**Supportive**	NA
0.34 (0.16-0.74)	0.52 (0.34-0.79)	0.30 (0.17-0.53)	1.53 (0.35-6.62)	0.52 (0.32-0.84)	0.87 (0.43-1.76)	**TAU**

Abbreviations: CBT, cognitive behavioral therapy; IPSRT, interpersonal and social rhythm therapy; NA, not available; TAU, treatment as usual.

[a] The lower triangle shows results from network meta-analyses (including direct and indirect evidence) in terms of odds ratios for treatment in the column vs treatment in the row. Numbers smaller than 1 favor the column-defining treatment vs the row-defining treatment. Numbers in parentheses indicate 95% CIs. For example, the odds ratio for family or conjoint therapy vs TAU is 0.30 (95% CI, 0.17-0.53), which favors family or conjoint therapy vs TAU. The upper triangle shows results from pairwise meta-analyses for the treatment in the row vs the treatment in the column (direct evidence only). Odds ratios smaller than 1 in the upper triangle favor the row-defining treatment vs the column-defining treatment. Some cells are empty (NA) because there were no studies examining the corresponding comparison.

Component Analysis

Of 18 therapy components, 13 occurred in more than 2 intervention groups (**Table 3**). Interrater reliability on the presence or absence of these components in each group exceeded 80%. The specific components that were associated with lower recurrence rates were delivery of treatment in a

Table 2. Pairwise and Network Meta-analysis for Treatment-Level Comparisons of Depression End-Point Scores (Standardized Mean Differences)[a]

Brief psychoeducation	0.16 (−0.56 to 0.89)	0.00 (−0.40 to 0.40)	0.15 (−0.57 to 0.88)	NA	NA	NA
−0.08 (−0.63 to 0.47)	**CBT**	−0.12 (−0.95 to 0.71)	−0.01 (−0.76 to 0.75)	−0.26 (−0.80 to 0.28)	0.68 (−0.13 to 1.48)	−0.33 (−0.69 to 0.03)
0.06 (−0.33 to 0.45)	0.14 (−0.38 to 0.66)	**Family or conjoint therapy**	0.11 (−0.72 to 0.94)	NA	−0.74 (−2.23 to 0.75)	−0.73 (−1.61 to 0.16)
0.06 (−0.55 to 0.66)	0.14 (−0.43 to 0.70)	−0.01 (−0.61 to 0.60)	**IPSRT**	NA	−0.11 (−0.86 to 0.63)	NA
−0.21 (−0.84 to 0.42)	−0.13 (−0.51 to 0.25)	−0.27 (−0.87 to 0.32)	−0.27 (−0.88 to 0.35)	**Psychoeducation**	−0.15 (−0.72 to 0.42)	−0.04 (−0.64 to 0.57)
−0.09 (−0.72 to 0.54)	−0.01 (−0.47 to 0.45)	−0.15 (−0.75 to 0.45)	−0.14 (−0.70 to 0.42)	0.12 (−0.33 to 0.57)	**Supportive**	NA
−0.40 (−0.99 to 0.18)	−0.32 (−0.64 to −0.01)	−0.46 (−1.01 to 0.08)	−0.46 (−1.07 to 0.15)	−0.19 (−0.60 to 0.22)	−0.31 (−0.83 to 0.20)	**TAU**

Abbreviations: CBT, cognitive behavioral therapy; IPSRT, interpersonal and social rhythm therapy; NA, not available; TAU, treatment as usual.

[a] The lower triangle shows results from network meta-analyses in terms of standardized mean differences for treatment in the column vs treatment in the row. Numbers smaller than 0 favor the column-defining treatment vs the row-defining treatment. Numbers in parentheses indicate 95% CIs. For example, the standardized mean difference for family or conjoint therapy vs TAU is −0.46 (95% CI, −1.01 to 0.08), which favors family or conjoint therapy vs TAU. The upper triangle shows results from pairwise meta-analyses (standardized mean differences) for the treatment in the row vs the treatment in the column (direct evidence). Standardized mean differences smaller than 0 in the upper triangle favor the row-defining treatment vs the column-defining treatment. Some cells are empty (NA) because there were no studies examining the corresponding comparison.

family format (iOR, 0.16; 95% CrI, 0.02-1.22) and encouraging patients to monitor prodromal symptoms (iOR, 0.22; 95% CrI, 0.04-1.35). The estimated heterogeneity was τ^2 = 0.19 (95% CrI, 0.00-1.42). Using the component NMA model, we estimated that psychoeducation with guided skill practice and self-monitoring delivered in a family or group format is more effective in reducing recurrences than the same 2 treatment components delivered in an individual format (OR, 0.12; 95% CrI, 0.02-0.94).

Cognitive restructuring (iSMD, -1.26; 95% CrI, -2.10 to -0.35), regulating daily rhythms (iSMD, -0.78; 95% CrI, -1.28 to -0.24), and, with less certainty, communication training (iSMD, -0.84; 95% CrI, -1.81 to 0.23) were the most potent components for reducing severity of depression (Table 3). The combination of these 3 components was estimated to be more effective than TAU (iSMD, -2.89; 95% CrI, -4.70 to -0.91). The least potent components (albeit with greater uncertainty) were behavioral activation (iSMD, 0.92; 95% CrI, 0.11 to 1.71) and individual therapy format (iSMD, 1.01; 95% CrI, -0.12 to 2.07). Analogously, cognitive restructuring (iSMD, -1.00; 95% CrI, -2.15 to 0.16) and regulating daily rhythms (iSMD, -0.42; 95% CrI, -1.08 to 0.28) were associated with greater stabilization of manic symptoms, whereas behavioral activation was associated with lesser stabilization (iSMD, 0.98; 95% CrI, -0.10 to 2.03) (Table 3). Fitting the component models in complete case analyses or in a frequentist setting yielded similar results for recurrence, depression, and mania (eTables 19-24 in the Supplement).

Treatment Acceptability

A total of 36 trials provided data on acceptability (retention rate) (Figure 2D). There were no overall differences between experimental and control interventions with regard to acceptability (OR, 1.02; 95% CI, 0.75-1.39) and no evidence of small study effects or publication biases (eFigure 7 in the Supplement). In the NMA model comparing specific interventions (heterogeneity τ^2 = 0.07), there was evidence that family or conjoint therapy (OR, 0.46; 95% CI, 0.26-0.82) and brief psychoeducation (OR, 0.44; 95% CI, 0.23-0.85) were associated with higher retention rates than standard-length (ie, ≥6 sessions) courses of psychoeducation (eTables 25 and 26 in the Supplement). There was less-certain evidence that family or conjoint therapy was associated with higher retention rates than CBT (OR, 0.64; 95% CI, 0.36-1.11) and TAU (OR, 0.61; 95% CI, 0.36-1.04), and no evidence of inconsistency (eTable 27 in the Supplement). In the component NMA, family format appeared to be the only component associated with a lower rate of attrition (iOR, 0.39; 95% CrI, 0.15-1.11; Table 3; eTable 28 in the Supplement).

Discussion

In this NMA of 39 RCTs of patients with bipolar disorder, we confirm previous findings that pharmacotherapy in combination with manualized psychotherapy is associated with a more effective reduction in recurrences (OR, 0.56; 95% CI, 0.43-0.74) than pharmacotherapy with TAU. In addition, we

Table 3. Data on Incremental Effectiveness of Treatment Components Regarding Outcome Variables[a]

Component	Definition	Groups with component, No.[b]	iOR recurrence (95% CrI)	iSMD depression (95% CrI)	iSMD mania (95% CrI)	iOR dropout (95% CrI)
Psychoeducation: information only	Information giving without skill practice	7-11	0.95 (0.30 to 3.22)	0.25 (−0.57 to 1.06)	0.14 (−1.07 to 1.42)	1.27 (0.65 to 2.86)
Psychoeducation: information plus active skill practice	Information giving with skills development and practice	23-42	0.93 (0.27 to 3.46)	0.01 (−0.94 to 0.87)	−0.03 (−1.58 to 1.56)	1.09 (0.53 to 2.44)
Self-monitoring assignments	Patient tracks moods, prodromal symptoms, sleep, or thoughts	20-33	0.22 (0.04 to 1.35)	−0.13 (−0.71 to 0.58)	−0.17 (−1.25 to 0.95)	1.27 (0.55 to 2.94)
Self-management assignments	Patient learns to implement preventive strategies for managing early warning signs	17-30	1.70 (0.45 to 6.69)	0.38 (−0.36 to 1.07)	0.30 (−0.70 to 1.22)	1.34 (0.61 to 3.39)
Cognitive restructuring	Guided practice in challenging self-defeating thoughts and rehearsing adaptive thinking	10-16	0.64 (0.20 to 2.10)	−1.26 (−2.10 to −0.35)	−1.00 (−2.15 to 0.16)	1.08 (0.35 to 2.66)
Maintaining regular daily rhythms	Patient coached to regulate daily activities and sleep and wake schedules	12-21	1.63 (0.55 to 4.10)	−0.78 (−1.28 to −0.24)	−0.42 (−1.08 to 0.28)	1.15 (0.66 to 1.95)
Behavioral activation assignments	Patient coached to plan pleasurable activities to increase or modulate engagement with environment	3-6	0.69 (0.18 to 2.72)	0.92 (0.11 to 1.71)	0.98 (−0.10 to 2.03)	0.81 (0.30 to 2.18)
Behavioral problem solving	Patient coached on how to identify and define problems and generate, evaluate, and implement solutions	16-28	1.17 (0.39 to 3.22)	0.30 (−0.26 to 0.83)	0.10 (−0.64 to 0.88)	0.88 (0.43 to 1.86)
Interpersonal problem-solving	Patient encouraged to identify interpersonal habits and consider alternative behaviors	7-12	0.81 (0.08 to 8.94)	0.55 (−0.37 to 1.39)	0.73 (−0.47 to 1.90)	0.55 (0.17 to 1.72)
Communication training	Coaching families, couples, or groups on effective speaking and listening skills with in-session rehearsal	5-8	2.46 (0.07 to 74.4)	−0.84 (−1.81 to 0.23)	−0.80 (−2.23 to 0.63)	1.86 (0.46 to 6.49)
Group format	Sessions occur with other patients; includes multifamily groups	10-18	0.94 (0.18 to 4.76)	−0.12 (−0.99 to 0.78)	−0.05 (−1.42 to 1.29)	1.07 (0.49 to 2.16)
Family format	Sessions occur with patient's family members or spouse	11-15	0.16 (0.02 to 1.22)	0.93 (−0.34 to 2.15)	0.76 (−0.96 to 2.45)	0.39 (0.15 to 1.11)
Individual format	Sessions are limited to the individual patient	17-26	1.27 (0.23 to 5.21)	1.01 (−0.12 to 2.07)	0.41 (−1.17 to 1.95)	0.73 (0.29 to 1.95)

Abbreviations: CrI, credible interval; iOR, incremental odds ratios; iSMD, incremental standardized mean differences.

[a] Incremental odds ratios when the component was present vs absent, estimated in association with binary outcomes. Lower iORs indicate lower recurrence rates in treatments with the component. Incremental standardized mean differences when the component was present vs absent, estimated in association with continuous outcomes. Incremental standardized mean differences below 0 indicate that depression or mania scores were lower in treatments with the component.

[b] Number of treatment conditions in which the component was rated as present. There is a range because different numbers of studies qualified for inclusion in analyses of different outcome variables. The lower number refers to the depression and mania analyses, and the upper number to acceptability analyses.

demonstrate that family or conjoint therapy, CBT, and standard psychoeducation, with their focus on active skill training (eg, monitoring of prodromal symptoms), were each associated with a lower probability of recurrence than TAU. Family or conjoint therapy and brief psychoeducation were associated with lower attrition rates than standard psychoeducation. There was little evidence of inconsistency or small study effects in the networks, and heterogeneity was within expected ranges for all outcomes.[29,30] Sensitivity analyses did not alter the findings. Our findings are similar to the NMA results of Cuijpers et al,[38] who concluded that combining psychotherapy with pharmacotherapy is the best option for stabilizing episodes and preventing recurrences of major depressive disorder.

Cognitive behavioral therapy, IPSRT, and family or conjoint therapy appeared to have comparable outcomes for depression stabilization, although there was greater precision for the effect size estimates for CBT, which was evaluated in a larger number of trials. Few trials recruited patients in an acute mood episode, suggesting that our findings concerning symptom end points pertain mainly to stabilization of interepisode symptoms. We share the conclusion of Chatterton et al[9] that psychoeducation and CBT appear to be effective in stabilizing residual manic symptoms, and we add that regulating daily rhythms is more useful than behavioral activation in such circumstances. We stress that there is no evidence that cognitive restructuring is beneficial in acute mania. We do not share the conclusion reached by Chatterton et al[9] that caregiver-focused psychoeducation (without patients present) is the most effective approach to recurrence prevention or that no intervention is effective in stabilizing depressive symptoms. In our analysis, family therapy, CBT, and group psychoeducation—all modalities that include patients as active participants—were associated with significantly improved outcomes compared with TAU with regard to recurrence prevention and depression stabilization.

What do our findings suggest about treating outpatients with bipolar disorder? When the goals center on prevention of recurrences, patients should be engaged in family or group psychoeducation with guided skills training and active tasks to enhance coping skills (eg, monitoring and managing prodromal symptoms) rather than being passive recipients of didactic education. When the immediate goal is recovery from moderately severe depressive or manic symptoms, cognitive restructuring, regulating daily rhythms, and communication training may be associated with stabilization. It is unclear whether CBT techniques work best in an individual format; in this NMA, family and group formats were more closely associated with depression improvement than individual formats.

Limitations

The analyses were limited by small sample sizes and sparsely connected networks. Many of our conclusions are based on indirect rather than direct comparisons (eg, IPSRT vs TAU). We cannot draw conclusions about the comparative effectiveness of psychotherapy for patients with severe illness vs those with moderate or mild illness. Recruitment of acutely ill patients with bipolar disorder, particularly those with mania, into psychotherapy trials is neither feasible nor ethically justifiable unless therapy is initiated after stabilization of symptoms with pharmacotherapy. Randomized clinical trials that are adequately powered to examine interactions between treatments and levels of illness severity require considerable commitments of time and expense.

In the 39 RCTs, the durations of therapy (3-12 months) and the follow-up intervals (6-60 months) were variable. Thus, we were unable to evaluate whether the associations of experimental interventions or their constituent components with outcomes were enduring or whether treatments would need to be revisited with booster sessions over time. Also, there was considerable variability in choice of assessment instruments. Consensus regarding a common assessment battery for drug or psychotherapy trials of bipolar disorder would enable cross-study findings to be compared more reliably. We recommend inclusion of clinician-rated assessments of weekly symptoms and mood polarity,[39,40] as well as patient-rated electronic diaries of mood and medication use.[41,42]

Most of the RCTs used study retention as a proxy for treatment acceptability. Other potentially informative definitions of acceptability, such as frequency of session attendance, medication adherence, or patients' ratings of helpfulness, were rarely reported. We recommend that future trials include these more nuanced measures to offer insight into this important aspect of clinical management.

Although our results suggest the effectiveness of family interventions, several of the relevant trials concerned adolescent or young-adult populations. Younger patients are more likely than older patients to have family supports,[43] and adult patients without family members are less likely to recover from depressive episodes and more likely to be hospitalized than those with family members.[4] For patients without family supports, group psychoeducation or CBT and IPSRT are recommended.

None of the RCTs examined the comparative contributions of psychotherapy and pharmacotherapy to outcomes. Systematic examinations of whether pharmacotherapy regimens can be simplified (without loss of effectiveness) when combined with specific psychosocial protocols would be of considerable value. Last, although we were rigorous in our literature search, we cannot exclude the possibility that we failed to identify relevant published trials.

Conclusions

Despite these limitations, there is enough evidence from this NMA and other systematic reviews[1-3,9] to conclude that health care systems should offer combinations of evidence-based pharmacotherapy and psychotherapy to outpatients with bipolar disorder. This recommendation is in line with the guidelines of the Canadian Network for Mood and Anxiety Treatments[44] and the UK Improving Access to Psychological Therapies program.[45] Implementing this recommendation will require a considerable reallocation of mental health resources. In a US survey of 1627 adults with bipolar disorder,

1448 (89%) were receiving medications for bipolar disorder, but only 820 (50.4%) were also receiving psychotherapy.[46]

Psychotherapy in these RCTs was delivered by well-trained clinicians who received supervision throughout the trials. As with suboptimal pharmacotherapy, if the quality of therapy is substandard, benefits will not hold up in clinical practice. The widespread availability of evidence-based psychotherapies for bipolar disorder in community care will depend on the development of well-scaled methods for disseminating clinician training and monitoring treatment fidelity. Systematic studies of telehealth and internet-based psychotherapy may enhance progress toward these objectives. Finally, there is a need to evaluate the most effective combinations of therapy components for patients with different illness presentations treated across public and private settings. All of these strategies are required to translate the benefits of adjunctive psychotherapies into effective personalized treatments for individuals with bipolar disorder.

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Author Affiliations: Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles (Miklowitz); Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, United Kingdom (Miklowitz, Geddes, Cipriani); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Efthimiou); Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan (Furukawa); Department of Clinical Epidemiology, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan (Furukawa); Brain and Mind Centre, The University of Sydney, Sydney, Australia (Scott); Institute of Neuroscience, Newcastle University, Newcastle, United Kingdom (Scott); Oxford Health National Health Service Foundation Trust, Warneford Hospital, Oxford, United Kingdom (McLaren, Geddes, Cipriani).

Author Contributions: Drs Miklowitz and Efthimiou had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Miklowitz, Efthimiou, Furukawa, Scott, Geddes, Cipriani.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Miklowitz, Efthimiou, Furukawa, Scott, Geddes.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Miklowitz, Efthimiou, Scott, Geddes, Cipriani.
Administrative, technical, or material support: Miklowitz, McLaren, Cipriani.
Supervision: Miklowitz, Geddes, Cipriani.

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