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Psychological interventions for adults with bipolar disorder: A systematic review and meta- analysis

Matthijs Oud, Evan Mayo-Wilson, Ruth Braidwood, Peter Schulte, Steven H Jones, Richard Morriss, Ralph Kupka, Pim Cuijpers and Tim Kendall.

Correspondence to: moud@trimbos.nl

Abstract

Background Psychological interventions may be beneficial for bipolar disorder.

Aims Efficacy evaluation of psychological interventions for adults with bipolar disorder.

Methods A systematic review of randomised controlled trials.. Outcomes were meta-analysed using RevMan and confidence assessed using the GRADE-method.

Results We included 55 trials with 6010 participants. Moderate quality evidence associated individual psychological interventions with reduced relapses at post-treatment and follow-up, and collaborative care with a reduction in hospitalisations. . Low quality evidence associated group interventions with fewer depression relapses at post-treatment and follow-up, and family psycho-education with reduced symptoms of depression and mania at post-treatment.

Conclusions There is evidence that psychological interventions are effective for people with bipolar disorder. Limits were the very low quality of much of the evidence and therefore inconclusive. Further research should identify the most (cost)-effective interventions for each phase of this disorder.

Declaration of interest: RM and SJ are author on three included studies. .

Introduction

Bipolar disorder affects approximately 1.5% of the population, (1-5) and often takes a chronic course with recurrent manic, hypomanic, depressive, and mixed episodes. Bipolar disorder is associated with poor psychosocial functioning, (6) a high economic burden, (7-10) and early mortality. (11) People with bipolar disorder are symptomatically ill almost half of the time. (12) Although mania often results in hospitalisation, (13) depressive symptoms and episodes account for most illness-related disability. (1) In trying to long term manage the illness people with bipolar disorder use pharmacological interventions , but 60% of outpatients that start with maintenance treatment will have an episode within two years. (13) As an additional strategy, many people with bipolar disorder wish to use psychological interventions to improve symptoms and to reduce relapse rates. Previous meta-analyses have evaluated evidence for a specific psychological intervention (e.g., cognitive behavioural therapy (CBT), (14-18) family interventions, (17, 19) and psychoeducation (17, 18)) some during acute episodes and some during euthymic periods, with varying duration of intervention and follow-up. The number of relevant trials has tripled since the last meta-analyses, and a current review is needed to inform the selection of psychological interventions for each stage of bipolar disorder. . Given the need for a comprehensive evaluation, we conducted a systematic review and meta-analysis of psychological interventions for adults with bipolar disorder compared with control groups (treatment-as-usual, waitlist, attention control or an active intervention) on symptoms of depression and mania, response, relapse, discontinuation, hospitalisation, quality of life, and psychosocial functioning. This review informed the National Institute for Health and Clinical Excellence (NICE) guideline on the management of bipolar disorder (20) and the related Dutch Nederlandse Vereniging voor Psychiatrie (NVvP) and Trimbos-institute guideline, and the review is reported here following PRISMA guidelines. (21)

Methods

Eligibility criteria

We included randomised controlled trials of all individual, group, and family psychological interventions for adults (18 years and older). We also included service-level intervention with (elements of) psychological interventions (e.g. collaborative care). Eligible comparison groups were control groups (treatment-as-usual, waiting list or attention control) or other active interventions. Trials were eligible if at least 66% of the participants had bipolar disorder or if disaggregated data were reported for participants with bipolar disorder.

For trials also including participants with other mental disorders (e.g. unipolar depression or schizophrenia), we requested disaggregated data.

Search strategy

We searched CINAHL, Embase, Medline, PreMedline, PsycINFO, CDSR, DARE, HMIC, and CENTRAL from inception to January 2014 using terms for bipolar disorder and randomised clinical trials. (Appendix 1) Searches were not restricted by language. MO and RB assessed the eligibility of studies for inclusion and discussed disagreements with a third author (EMW). After our search, we searched the reference lists of the included studies, excluded studies, and previous reviews. We contacted study authors and experts to request additional reports of trials.

Assessment of bias

Studies were assessed and rated independently by two authors (MO, PC) using the Cochrane Collaboration Risk of Bias Assessment Tool. (22) Disagreements were discussed with a third author (EMW) and resolved by consensus. Each study was rated for risk of bias owing to sequence generation; allocation concealment; blinding of participants, assessors, and providers; selective outcome reporting (e.g., reporting incomplete data or not all of the outcomes measured); and incomplete data. Risk of bias for each domain was rated as high (seriously weakens confidence in the results), low (unlikely to seriously alter the results), or unclear.

Data management

Service user outcomes included reduction of symptoms of depression and mania (response), relapse (any type, depression, mania or mixed), hospitalisation, quality of life, suicide, psychosocial functioning, and study discontinuation. We also extracted treatment format, number and length of sessions, method of recruitment, inclusion and exclusion criteria, age, sex, setting, study location and number of people with bipolar I disorder. For each study, the important study characteristics are reported in table 1.

Treatment in the acute phase typically aims at remission of the index episode, and if symptoms of the index episode reappear after a short period, the term "relapse" is often used. Long-term management aims to prevent future episodes, which are often called “recurrence”. (23) In this review, it was impossible to distinguish between “relapse” and “recurrence” because studies included both acutely symptomatic and euthymic participants without reporting disaggregated data; we have used the term "relapse" for both outcomes.

Statistical analysis

Psychological treatments developed for bipolar disorder may differ in the underlying therapeutic tradition (e.g. cognitive behaviour therapy, interpersonal therapy, psychoeducation) and delivery, but they share non-specific treatment factors (e.g. contact with a caring professional),(24) so their effects may be aggregated in meta-analysis to explore the range of potential effects. In this review, psychotherapies were aggregated by methods of delivery, including individual treatments, group treatment, family therapy, and collaborative care. Information about the effects of interventions with different therapeutic traditions were analysed in subgroups.

For continuous outcomes, we calculated the standardised mean difference (SMD), Hedges's *g*, for between-group differences. For dichotomous outcomes, we calculated the risk ratio (RR) for events. All outcomes are reported with 95% confidence intervals. Overall effects were calculated using random effects models. Continuous effects were weighted by the inverse of variance; dichotomous effects were weighted using the Mantel-Haenszel method. (22) Because time-to-event data were reported inconsistently, and often incompletely (e.g. as curves without associated events or statistics), we were unable to analyse these results; however, most studies were short and similar in duration, and hazard ratios would be similar to the relative risks reported here.

Missing data were noted for each outcome. When missing cases were not reported, we contacted the authors. If continuous outcomes were reported for completers as well as controlling for missing data (for example, imputed using regression methods), we used the data that controlled for missing data.

Statistical heterogeneity was assessed by visual inspection of forest plots, by performing the χ^2 test (assessing the P value), and by calculating the I^2 statistic, which describes the percentage of observed heterogeneity that would not be expected by chance. If the P value was less than 0.10 and I^2 exceeded 50%, we considered heterogeneity to be substantial. Meta-analyses of comparisons and subgroups were conducted using RevMan 5.2, (25) due to the few studies per type of intervention a meta-regression would not be meaningful and is therefore not conducted. Confidence in the results was assessed by MO and EMW using the GRADE method, (26) which is a structured assessment of the quality of evidence attending to the following factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results

Trial flow

Of 13,641 potentially relevant citations and four from other sources, we retrieved 59 papers, which were assessed for inclusion (Figure 1). Of these, three were excluded because only a minority of participants had bipolar disorder and we could not obtain disaggregated data, (27-29) and one was a trial of a measurement instrument. (30) Fifty five randomised controlled trials were, therefore, included, of which three were unpublished (31-33) at time of inclusion, one has recently been published and the others were published between 1984 and 2014. Seven were not included in the meta-analysis because they did not report useable outcomes, which remained unavailable after contacting the authors. (34-40)

Study characteristics

Table 1 presents study characteristics for each trial. Included studies randomised 6010 participants, ranging from 19 to 441 per study. Studies were conducted in North America (k=22), England and Ireland (k=12), Central Europe (k=11), Australia (k=5), Brazil (k=3), and Iran (k=2). Participants were recruited from outpatient (k=23) or inpatient settings (k=12), GP practices (k=2), Community Mental Health Teams (k=2), or advertising combined with (self) referral (k=16). In 52 studies a diagnostic interview was used to establish the presence of bipolar disorder, in one study participants themselves reported if they had bipolar disorder, another confirmed the diagnosis through a questionnaire, and one study only reported that bipolar disorder was an inclusion criterion.

Across all trials, the median of the mean age of participants was 40 years (range 26 to 55), the median percentage who were female was 58% (range 1% to 77%) and the median percentage of participants with bipolar I disorder was 81% (range 42% to 100% and one study with 0%). Four studies included participants experiencing a depressive episode at baseline, (41-44) six studies included both participants experiencing depressive and manic episodes, (35, 36, 45-48) and 32 studies included only euthymic participants. Twelve studies (38, 39, 49-58) included a mix of euthymic and symptomatic participants at baseline, of which only two studies (49, 58) provided disaggregated data.

Interventions

Trials included a variety of interventions (Table 2) and comparison conditions and were grouped in nine comparisons. The first five comparisons were interventions compared with treatment as usual (individual treatment, group treatment, family therapy, collaborative care, integrated cognitive and interpersonal therapy). Four comparisons included interventions compared with other active interventions (“head-to-head” trials).

Outcomes

Table 3 lists the continuous measures used in the trials by outcome type. Dichotomous data were also reported. Response was determined through clinical interviews (e.g. SCID), cut-off points on diverse scales (e.g. when scoring symptomatic at baseline and at a follow-up scoring on the YMRS<11 for manic response or Bech–Rafaelsen scores < 6 for depression response) or a percentage of reduction on a scale (e.g. 50% on the HAM-D for a depression response). In most trials, participants had to score above a cut off score for a period of time (e.g. two months) to be considered responsive. Relapse in most cases was determined with a clinical interviews, for example with the Structured Clinical Interview for DSM (SCID-LIFE), Schedule for Affective Disorders and Schizophrenia (SADS) and the Mini-International Neuropsychiatric Interview (M.I.N.I.). Other trials established relapse in participants with a score above a cut-off point on a depression (e.g. HAM-D>12) or mania scale (e.g. YMRS>20 for mania); in some, a combination of the two scales was used to evaluate the presence of mixed episodes. Five studies assumed that a relapse had occurred based on chart reviews or hospitalisation records.

Risk of bias

Each risk of bias item is presented as percentages across all studies in table 4 and for each studied independently in table 5. No trials were at high risk of bias for random sequence generation; however, the method of randomisation was not reported in 15 trials. Allocation concealment was unclear in 25 trials and low risk in 30 trials. Blinding of participants and providers in trials of psychological interventions is impossible, so all were at high risk of bias *per se*. Nine trials only used self-report measures and 32 trials reported blind assessor rated outcomes, these 41 trials were at low risk of bias for blinding. However, eight studies did not have blinded assessors and these were considered to be at high risk of bias. In six studies, it was unclear if assessors were blinded. For incomplete outcome data, 25 trials were at low risk of bias and 24 were at high risk of bias because of the number (more than 10%) of missing cases or because missing cases were excluded from the analyses. In six studies, the handling of missing data was not described.

Reporting bias

Risk of reporting bias could not be assessed indirectly (e.g., using funnel plots or statistical methods) because there were few studies for most comparisons and the studies were of similar size. We used direct methods to assess risk of reporting bias by checking trial registrations and by contacting authors. There was a high risk of reporting bias in 22 trials, including seven studies that did not report any usable data. In addition to the outcomes we

analysed, several trials also reported incomplete results that could not be included in the meta-analysis. Only 11 studies were prospectively registered, but 23 others were assessed to be at low risk of bias because authors provided missing data or confirmed that all outcomes were published.

Overall quality of the evidence

Using the GRADE method, (26) many outcomes were downgraded because of risk of bias (e.g., inappropriate handling of missing data). Nearly all results were downgraded at least one level because of imprecision (the analyses included few participants or events). Results for relapse following individual interventions, hospitalisation following collaborative care, and study discontinuation during interpersonal and social rhythm therapy were of moderate quality. Most other evidence was of low or very low quality. Studies also reported controlled comparisons at follow-up, but most outcomes were of very low quality.

Quantitative data synthesis

Across nine comparisons, results of the meta-analyses suggest that psychological interventions may be associated with symptomatic improvement, and fewer relapses and hospitalisations. The majority of these low to moderate quality outcomes are summarized per comparison and presented in table 6 (post-treatment) and table 7 (follow-up) with reasons for downgrading, for all outcomes per comparison and subgroups we refer to Table 8 and 9.

Individual psychological interventions

The search identified 15 RCTs (n=1580) of face-to-face and interactive online psychoeducation (49, 58-63) cognitive (behavioural) therapy (33, 41, 50, 51, 64-67) and medication adherence therapy. (68) Interventions were compared with treatment as usual. Eleven trials enrolled participants who were euthymic at baseline, four trials enrolled a mix of participants experiencing acute episode of mania or depression and participants who were euthymic. (49-51, 58)

Seven trials (n=637) reported low quality evidence that individual psychological interventions were associated with a small reduction in symptoms of depression at post-treatment. (49, 50, 58, 64-67) Six trials (n=365) reported moderate quality evidence that individual psychological interventions reduced the risk of relapse at post-treatment. (50, 63-65, 67, 68) However, three trials found no difference in effect on symptoms of mania. (64, 66, 67) One trial with few events was inconclusive regarding the risk of hospitalisation. (68)

Eight trials (n=532) reported moderate quality evidence that individual psychological interventions were associated with a reduction in relapse at follow-up. (58, 62-65, 67, 68)

There was low quality evidence from three trials (n=214) that individual psychological interventions might be associated with a reduction in hospitalisations, but the confidence interval was compatible with both a reduction and an increase in the effect. (33, 63, 67, 68)

Group psychological interventions

The search identified 12 RCTs (n=914) of group interventions including psychoeducation, (47, 69-72) cognitive behavioural therapy, (31, 73, 74) mindfulness therapy, (75, 76) social cognition and interaction training, (77) and dialectical behaviour therapy. (42) Interventions were compared with treatment as usual except for two studies that compared psychoeducation with attention control. (69, 70) In ten trials participants were euthymic at baseline (31, 69-77), one study included participants experiencing an acute episode of mania or depression (47) and another included people who were currently depressed.

Eight trials (n= 423) reported very low quality evidence of a small effect on depression outcomes at post-treatment favouring group interventions. (31, 42, 47, 72, 74-77) Six trials (n=375) found no effect on manic symptoms. (31, 47, 72, 74, 75, 77) Furthermore, the two studies comparing psychoeducation to attention control (n=170) found low quality evidence for a reduction in any type of relapse, but the confidence interval was compatible with both a reduction and increase in the effect. (69, 70) The two studies did find evidence for a reduction in depressive and manic relapses. Also, the two studies together with a trial comparing CBT with treatment as usual (n=205) reported low quality evidence that group interventions might be associated with a reduction in hospitalisations, but the confidence interval was compatible with both a reduction and increase in the effect. (69, 70, 74)

Results at follow-up in five studies (n=333) reported low quality evidence of a reduction in depressive relapses. (69, 70, 72, 73, 75) Also, four studies (n=274) reported a reduction of relapses into mixed episodes. (69, 70, 72, 73) However, effects on depressive symptoms (31, 72, 75) and hospitalisation (69, 70) were inconclusive.

Family psychoeducation

The search identified seven RCTs (n=409) of family psychoeducation. Two trials included psychoeducation for participants and their family members (48, 78) and in five trials only family members received psychoeducation. (56, 79-82) Interventions were compared with treatment as usual. Five trials enrolled participants who were euthymic at baseline, one trial enrolled participants who were experiencing acute episode of mania or depression or were

euthymic at baseline (56) and another included only participants who were in an acute episode of mania or depression. (48)

One trial (n=43) found low quality evidence of medium effect in reduction of depressive and manic symptoms favouring family psychoeducation at post-treatment. (56)

At follow-up, three trials (n=228) reported low quality evidence of a reduction in relapse. (78, 79, 81) One trial (n=113) reported a reduction in manic relapses. (81) One study (n=57) reported a very large effect on reduction of the number of hospitalisation, but there were only nine events in the study. (79)

Collaborative care

The search identified five RCTs (n=1058) on collaborative care compared with treatment as usual. Two trials on collaborative care started with euthymic participants, (45, 83) three trials recruited participants in an episode. (52-54)

In comparison to treatment as usual, two trials (n=123) reported low quality evidence of small effect favouring collaborative care on depressive symptoms and no effect on manic symptoms at post-treatment, but the effect estimates were imprecise. (52, 53) One trial (n=234) found no difference in reduction of relapses. (54) However, two trials (n=572) reported moderate quality evidence suggesting collaborative care reduced the number of hospitalisations at post-treatment. (54, 83)

Integrated Cognitive and Interpersonal Therapy

The search identified one RCT (n=212) with a group of participants that were randomised to integrated cognitive and interpersonal therapy or treatment as usual. (32) Participants in the intervention group could choose to follow individual or group integrated cognitive and interpersonal therapy. Outcome data were presented for the whole intervention group versus treatment as usual.

The trial reported low quality evidence at post-treatment of a medium effect favouring the intervention on depressive symptoms and no effect on manic symptoms.

Family-focused therapy

The search identified four RCTs (n=357) on family focused therapy compared with psychoeducation, collaborative therapy or treatment as usual. Participants who were either euthymic, (84) in an episode or euthymic, (55) only depressed (41), or in any type of episode. (48)

Post-treatment data were of low quality. One study (n=79) found no effect of family focused therapy compared with treatment as usual on manic symptoms and a medium effect on depressive symptoms (although the confidence interval was also compatible with no effect). (55) A small effect was found on relapse in a study (n=53) comparing family focused therapy with psychoeducation, but the confidence interval was compatible with both a reduction and increase in the effect. (84) The confidence in the follow-up results were very low.

Cognitive behavioural therapy versus supportive therapy

The search identified one RCT (n=76) comparing individual cognitive behavioural therapy with supportive therapy, the quality of the evidence was low. (85) At post-treatment a medium effect was found of supportive therapy on depressive symptoms. Also a small effect was found of supportive therapy on manic symptoms, but cognitive behavioural therapy reduced the risk of relapses. However, the confidence intervals for the mania and relapse outcomes were compatible with either a reduction or increase in the true effect.

Interpersonal and social rhythm therapy (IPSRT) versus (active) control

The search identified three RCTs (n=299) of interpersonal and social rhythm therapy (IPSRT) compared with quetiapine, intensive clinical management or treatment as usual. Participants in all three trials were in a depressive episode at baseline.(41, 43, 46)

One study reported a small effect of quetiapine compared to interpersonal and social rhythm therapy on symptoms of depression at post treatment, but the confidence interval was compatible with both a reduction and increase in the effect. (43) A trial (n=41) of 123 weeks found effects that were in favour of intensive clinical management compared to interpersonal and social rhythm therapy on a reduction in relapses, but the confidence interval was compatible with both a reduction and increase in the effect. (46) All results were of very low quality.

Integrated group therapy versus group drug counselling

The search identified one RCT (n=61) including people with both bipolar disorder and a comorbid substance abuse disorder who were either euthymic or acutely depressed at baseline. It compared integrated group therapy with group drug counselling. (57) At post-treatment there was very low quality evidence of a small effect on depressive and manic symptoms, but confidence intervals were compatible with either reductions or increases in

symptoms. There was very low quality evidence of a moderate effect on manic symptoms at follow-up.

DISCUSSION

This is the first comprehensive systematic review and meta-analysis of the full range of psychological interventions that have been evaluated for the treatment of people with bipolar disorder. The evidence suggests that some, but not all, psychological treatments reduce relapse rates and hospitalisation, and they may improve depressive symptoms. In particular, we found moderate quality evidence that individual psychological interventions are associated with a 34% reduction in the risk of relapse at the end of treatment, sustained at 26% reduction in risk at follow-up. There was also low quality evidence that individual psychological treatment reduced symptoms of depression, but the reduction may be small. Although the evidence is not as robust, group psycho-education also shows beneficial effects for reducing risk of relapse, and perhaps for some symptomatic improvement. We also found a substantial reduction in relapse rates for people who received family psycho-education, although the quality of the evidence for this finding was also low. In addition, our analysis of collaborative care shows moderate quality evidence for a 32% reduction in hospitalisation. We found little impact on symptoms of mania, quality of life, psychological functioning or other treatment outcomes, although in most cases the underpinning evidence was very low quality and therefore inconclusive. Moreover, we found no evidence of benefit for other types of psychological interventions such as interpersonal and social rhythm therapy.

These results confirm and extend the findings of previous, smaller and narrower reviews of specific psychological treatments for bipolar disorder; (14, 15, 17-19) and suggest that, as the size of the evidence base has increased, the beneficial effects of some psychological interventions have become more apparent. Previous reviews included 10 or fewer trials and fewer than 1000 participants; by contrast, this review analysed 55 trials including data from 6010 participants. Overall, on the basis of this review, we would recommend the use of psychological interventions in the treatment of people with bipolar disorder to reduce relapse rates and to reduce depressive symptoms. Although there is not sufficient evidence to recommend a specific treatment over the others, the best evidence is for individual structured psychological interventions, and there is weaker, but still promising, evidence for group and family interventions, and for collaborative care.

These results are consistent with other recent reviews showing that psychological approaches may reduce transition to psychosis, including for people with bipolar disorder,

(86) and that family psychological interventions reduce relapse rates in people with early (87) and established schizophrenia. (88) Additionally, psychological interventions are the most effective interventions for people with major depression. (89) The effectiveness of psychological interventions in these closely related conditions is promising for the psychological treatment of bipolar disorder, and effective psychological strategies for people with bipolar disorder could be clinically and economically important.

Strengths and limitations

Participants in our review are similar to those in 'real world' practice in several ways. For example, the proportion of men and women, and of people with bipolar type 1 and bipolar type 2 in the included studies were comparable to epidemiological samples. (4, 5) Most studies recruited participants from outpatient or community type setting, where these psychological interventions could be carried out. Few studies were undertaken outside of Europe and North America, and the effects of psychological interventions might differ in places with different healthcare systems and different levels community support.

Although the evidence provides support for the use of psychological interventions in the treatment of people with bipolar disorder, our meta-analysis includes a number of trials with participants in different phases, sometimes euthymic, sometimes depressive, sometimes a mixture of both, and sometimes a mixture of depressive and manic. Most of the trials with participants in different phases of the illness did not report disaggregated data for people in the euthymic and the depressive phases, or for people who were depressed and people who were manic at the start of the trial. This is likely to lead to underestimating the effects on symptoms; people who are euthymic are without symptoms, thereby diluting the mean impact of psychological intervention on depressive and manic symptoms in these mixed populations. Similarly, where data on relapse includes trials in which participants were manic, this may have led to underestimating the impact on relapse rates; people who are manic are often difficult to engage in any psychological treatment, thereby diluting the effects of psychological therapy on relapse rates for those who are euthymic or depressed. In addition, the lack of disaggregated data on outcomes for people with mania makes it impossible to identify any possible harms or benefits of psychological therapies for this group. Finally, a limitation of including participants at different phases of illness is that we are not comparing like with like. Although statistical heterogeneity was minimal, summary effects should be interpreted with some caution in light of the clinical differences among participants across trials and also for therapeutic variations between interventions.

A further potential limitation of this analysis is the quality of the data. In some comparisons, evidence for different outcomes was not consistent. For example, a psychological intervention may appear to reduce symptoms but have no effect on treatment response. Some trials were not registered, and there was evidence of selective reporting of outcomes, which could lead us to overestimate the benefits of psychological treatments in much the same way as selective publishing of drug studies has led to overestimating their true effectiveness. (90) Using GRADE to evaluate the quality of evidence underpinning each outcome, we incorporated these limitations in our evaluation of the results and restricted our conclusions to outcomes based on low and moderate quality evidence; importantly, evidence for key outcomes—relapse rates and symptoms—was better than evidence for most secondary outcomes.

Almost all reviewed psychotherapies were given as adjuncts to pharmacotherapy (monotherapy or combinations of various medications), and they were delivered in a variety of different treatment modalities and service settings. Co-interventions and details about service settings were incompletely described in many trials and could contribute to unobserved heterogeneity. In addition, while there is a consensus that psychological treatments for bipolar disorder share many common elements and strategies (e.g. coping strategies for mood changes), they nevertheless differ in complexity, the skill and training required, content and duration, even when they bear the same name (e.g. cognitive behavioural therapy or psycho-education). These problems may be addressed in further research in this rapidly expanding field.

Implications for practice

On the basis of this review, individual psychological interventions should be offered (in addition to whatever pharmacological interventions people already receive) with the aim of reducing relapse rates for people with bipolar disorder who are depressed or euthymic and for improving symptoms in people who are depressed. Although the evidence was limited for many outcomes in this review, there is strong evidence for the effectiveness of psychological interventions for unipolar depression (89) adding some support to the view that bipolar depression may be treated effectively with psychological treatment. It is also worth considering family psychological interventions, not just because the trials show some promise, but also because the benefits of family interventions for psychosis (including schizophrenia and bipolar disorder) suggest that relapse rates can be reduced for early psychosis (87) and later psychosis. (88) It seems likely, on the basis of this broader evidence

as well as the evidence in this review, that family interventions could be beneficial for people with bipolar disorder and should be made available routinely to help reduce relapse rates.

People with bipolar disorder may also benefit from group psycho-education and from collaborative care. It is important to keep in mind that people with bipolar disorder are often only partially adherent to pharmacotherapy, which may contribute to the recurrence of symptoms and to relapse. (91) Group or family psycho-educational interventions and collaborative care could help the people develop skills related to medication use, stress management, recognising early symptoms, and coping with symptoms. Such skills could reduce risk of relapse and improve response.

Worldwide there are few people with training and experience of delivering specific psychological interventions for people with bipolar depression. However, there are many therapists providing evidence-based treatments for unipolar depression in primary care. Because the rationale and process of delivering CBT for unipolar and bipolar depression is very similar, it might be sensible for CBT therapists in primary care to provide individual CBT for people with bipolar depression if they have experience in managing people with bipolar disorder or are supervised by clinicians with that experience. Many of the skills learned through CBT for depression could also help people with bipolar disorder who are euthymic avoid relapse. In the long-term, service providers and educational institutions should endeavour to increase the number of therapists trained specifically in the treatment of bipolar depression and the prevention of bipolar relapse.

Directions for future research

While this review supports the use of individual psychological intervention for relapse reduction and symptom improvement, we do not have sufficient information to know the impact on functioning and quality of life, both key concerns for people with bipolar disorder. Further research should include sufficiently large populations to address these critical outcomes. The same is true for family interventions. Longer follow-up is needed to establish how well the effects of all of these interventions endure. Further research is needed to understand how psychological interventions compare with each other at each phase of the illness.

Future studies could be improved by reporting results separately for people in different phases of the disorder (who are at risk of different outcomes), better describing treatments and comparators, pre-registering trials, completely and transparently reporting all outcomes measured, and standardising the use of outcome measurement. Moreover, including an

economic (cost-benefit) analysis in trials, especially when there is a possible reduction in relapse, would add greatly to our understanding of what we can do to help people with bipolar disorder; comparing the cost-effectiveness of individual and group approaches would address common concerns about method of delivery.

There is very little, if any, evidence about which psychological treatments could be beneficial for people with more severe forms of bipolar disorder. More research could address the treatment of people who have very frequent episodes, people who are most severely functionally disabled, and people with persisting inter-episode symptoms. People who are hospitalized because of manic symptoms usually receive pharmacotherapy and we have identified no trial that examines whether a psychological intervention would be beneficial during this phase of the illness. Following this review, further research can be developed on the basis of much stronger evidence than was available only a few years ago. It is clear that psychological interventions now have an important place alongside medication treatments in the treatment of people with bipolar disorder, and future research will elucidate the most effective ways to deliver psychotherapy.

Contributors / Funding:

Contributors: All authors contributed to the development of the review questions. EMW drafted the protocol, which was agreed by all authors. Sarah Stockton of the National Collaborating Centre for Mental Health designed and implemented the searches. MO, RB and EMW assessed the eligibility of the studies for inclusion. MO, PC and EMW extracted data and assessed risk of bias. MO and EMW judged the quality of the evidence using GRADE criteria. MO and EMW conducted the meta-analysis. MO and EMW drafted the manuscript, to which all authors contributed. MO had full access to the data and takes responsibility for the integrity of the data and accuracy of the analysis.

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Matthijs Oud, MSc
Researcher
Trimbos-institute, Department of Care Innovation, Da Costakade 45, 3521 VS, Utrecht, The Netherlands
Correspondence to: moud@trimbos.nl

Evan Mayo-Wilson, MPA, DPhil
Assistant Scientist
Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E6610, Baltimore, MD 21205, USA.

Ruth Braidwood, MSc
Trainee Clinical Psychologist
Department of Clinical, Educational and Health Psychology, University College London, 1-19 Torrington Place, WC1E 7HB.
Peter Schulte, MD, PhD
Psychiatrist
Treatment Centre for Bipolar Disorders, Mental Health Service Noord-Holland-Noord, Oude Hoeverweg 10, 1816 BT, Alkmaar, The Netherlands.

Steve H Jones, PhD
Professor of Clinical Psychology
Spectrum Centre for Mental Health Research, School of Health and Medicine, Lancaster University, Lancaster LA1 4YT.

Richard Morriss, MD, FRCPsych
Professor of Psychiatry & Community Mental Health
Institute of Mental Health, Jubilee Campus, Faculty of Medicine & Health Sciences, Triumph Road, Nottingham, NG8 1BB.

Ralph Kupka, MD, PhD
Professor of Psychiatry
VU University Medical Center, dept. of Psychiatry, A.J. Ernststraat 1187, 1081 HL, Amsterdam, The Netherlands.

Pim Cuijpers, Ph.D.
Professor of Clinical Psychology
Faculty of Psychology and Education, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.

Tim Kendall, FRCPsych
Director of National Collaborating Centre for Mental Health
National Collaborating Centre for Mental Health, The Royal College of Psychiatrists, Standon House, 21 Mansell Street, London E1 8AA.

Appendix 1 Systematic search

The search was constructed using the groups of terms set out in Text Box 1. The full set of search terms is documented in sections 1 and 2. The selection of search terms was kept broad to maximise retrieval of evidence.

Box 1 Summary of systematic search strategie: search strategy construction

Box 1 Summary of systematic search strategie: search strategy construction

Review area	Search type	Search construction	Study design	Databases searched and date range searched
Psychosocial interventions for adults	Generic search	General medical databases: [(1 population terms) AND (RCT terms/ SR terms)] Topic specific databases: [(population terms)]	Qualitative systematic reviews, Randomised controlled studies	General medical databases: (From inception to 20th of January 2014) CINAHL (1961-2014), Embase (1947-2014), MEDLINE (1966-2014), PreMEDLINE (1966-2014) and PsycINFO (1880-2014) Topic specific databases (From inception to 20th of January 2015): CDSR (1992-2014), DARE (1968-2014), HMIC (1980-2014), HTA (1995-2014) and CENTRAL (1898-2014)

1 Population search terms – all databases

1.1 STEM – General medical databases

Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

1 exp bipolar disorder/ or mania/
2 1 use emez
3 exp bipolar disorder/
4 3 use mesz, prem
5 exp bipolar disorder/ or exp mania/

6 5 use psyh
7 ((bi?polar adj5 (disorder$ or depress$)) or ((cyclothymi$ or rapid or ultradian) adj5 cycl$) or hypomani$ or mania$ or manic$ or mixed episode$ or rcbd).ti,ab.
8 or/2,4,6-7

1.2 STEM – topic specific databases
HTA, CDSR, DARE, CENTRAL – Wiley
#1
mesh descriptor bipolar disorder explode all trees
#2
(((bipolar or "bi polar") near/5 (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) near/5 cycl*) or hypomani* or mania* or manic* or "mixed episode*" or rcbd):ti,ab,kw
#3
(#1 or #2)

1.3 STEM – topic specific databases
CENTRAL – Wiley #1 mesh descriptor bipolar disorder explode all trees

#2 (((bipolar or "bi polar") near/5 (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) near/5 cycl*) or hypomani* or mania* or manic* or "mixed episode*" or rcbd):ti,ab,kw

#3 (#1 or #2)

1.4 STEM – topic specific databases
CINAHL – Ebsco

s3 s1 or s2

s2 ti ((((bipolar or "bi polar") n5 (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) n5 cycl*) or hypomani* or mania* or manic* or "mixed episode*" or rcbd)) or ab ((((bipolar or "bi polar") n5 (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) n5 cycl*) or hypomani* or mania* or manic* or "mixed episode*" or rcbd))

s1 (mh "bipolar disorder")

1.5 STEM – topic specific databases

HMIC – HDAS

1 hmic bipolar disorder/

2 hmic (((bipolar or "bi polar") and (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) and cycl*) or hypomani* or mania* or manic* or "mixed episode*" or rcbd).ti,ab

3 hmic 1 or 2

2. Study design filters – all databases

2.1 Quantitative systematic review study design filters

2.1.1 Quantitative systematic review study design filter, general medical databases

Embase, MEDLINE, MEDLINE In-Process, PsycINFO – OVID SP

1 meta analysis/ or systematic review/

2 1 use emez

3 meta analysis.sh,pt. or "meta-analysis as topic"/ or "review literature as topic"/

4 3 use mesz, prem

5 (literature review or meta analysis).sh,id,md. or systematic review.id,md.

6 5 use psyh

7 (exp bibliographic database/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.)

8 7 use emez

9 (exp databases, bibliographic/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.)

10 9 use mesz, prem

11 (computer searching.sh,id. or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,pt. or systematic$.ti,ab.)

12 11 use psyh

13 ((analy$ or assessment$ or evidence$ or methodol$ or quantitativ$ or systematic$) adj2 (overview$ or review$)).tw. or ((analy$ or assessment$ or evidence$ or methodol$ or quantitativ$ or systematic$).ti. and review$.ti,pt.) or (systematic$ adj2 search$).ti,ab.

14 (metaanal$ or meta anal$).ti,ab.

15 (research adj (review$ or integration)).ti,ab.

16 reference list$.ab.

17 bibliograph$.ab.

18 published studies.ab.

19 relevant journals.ab.

20 selection criteria.ab.

21 (data adj (extraction or synthesis)).ab.

22 (handsearch$ or ((hand or manual) adj search$)).ti,ab.

23 (mantel haenszel or peto or dersimonian or der simonian).ti,ab.

24 (fixed effect$ or random effect$).ti,ab.

25 ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.

26 or/2,4,6,8,10,12-25

2.1.2 Qualitative systematic review study design filter, topic specific databases

CINAHL – EBSCO HOST

s33 s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s22 or s23 or s26 or s27 or s28 or s29 or s30 or s31 or s32

s32 ti (analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or quantativ* n5 review* or systematic* n5 review*) or ab (analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or quantativ* n5 review* or systematic* n5 review*)

s31 ti (analy* n5 overview* or assessment* n5 overview* or evidence* n5 overview* or methodol* n5 overview* or quantativ* n5 overview* or systematic* n5 overview*) or ab (analy* n5 overview* or assessment* n5 overview* or evidence* n5 overview* or methodol* n5 overview* or quantativ* n5 overview* or systematic* n5 overview*)

s30 ti (pool* n2 results or combined n2 results or combining n2 results) or ab (pool* n2 results or combined n2 results or combining n2 results)

s29 ti (pool* n2 studies or combined n2 studies or combining n2 studies) or ab (pool* n2 studies or combined n2 studies or combining n2 studies)

s28 ti (pool* n2 trials or combined n2 trials or combining n2 trials) or ab (pool* n2 trials or combined n2 trials or combining n2 trials)

s27 ti (pool* n2 data or combined n2 data or combining n2 data) or ab (pool* n2 data or combined n2 data or combining n2 data)

s26 s24 and s25

s25 ti review* or pt review*

s24 ti analy* or assessment* or evidence* or methodol* or quantativ* or systematic*

s23 ti “systematic* n5 search*” or ab “systematic* n5 search*”

s22 (s17 or s18 or s19) and (s20 or s21)

s21 ti systematic* or ab systematic*

s20 tx review* or mw review* or pt review*

s19 (mh "cochrane library")

s18 ti (bids or cochrane or index medicus or “isi citation” or psyclit or psychlit or scisearch or “science citation” or web n2 science) or ab (bids or cochrane or index medicus or “isi citation” or psyclit or psychlit or scisearch or “science citation” or web n2 science)

s17 ti (“electronic database*” or “bibliographic database*” or “computeri?ed database*” or “online database*”) or ab (“electronic database*” or “bibliographic database*” or “computeri?ed database*” or “online database*”)

s16 (mh "literature review")

s15 pt systematic* or pt meta*

s14 ti (“fixed effect*” or “random effect*”) or ab (“fixed effect*” or “random effect*”)

s13 ti (“mantel haenszel” or peto or dersimonian or “der simonian”) or ab (“mantel haenszel” or peto or dersimonian or “der simonian”)

s12 ti (handsearch* or "hand search*" or "manual search*") or ab (handsearch* or "hand search*" or "manual search*")

s11 ab "data extraction" or "data synthesis"

s10 ab "selection criteria"

s9 ab "relevant journals"

s8 ab "published studies"

s7 ab bibliograph*

s6 ab "reference list*"

s5 ti (“research review*” or “research integration”) or ab (“research review*”or “research integration”)

s4 ti (metaanal* or “meta anal*”) or ab (metaanal* or “meta anal*”)

s3 (mh "meta analysis")

s2 (mh "systematic review")

s1 (mh "literature searching+")

2.2 Randomised controlled trial filters

2.2.1 Randomized controlled trial study design filter, general medical databases

Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP 1 exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/

2 1 use emez

3 exp clinical trial/ or exp “clinical trials as topic”/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/

4 3 use mesz, prem

5 (clinical trials or placebo or random sampling).sh,id.

6 5 use psyh

7 (clinical adj2 trial$).ti,ab.

8 (crossover or cross over).ti,ab.

9 (((single$ or doubl$ or trebl$ or tripl$) adj2 blind$) or mask$ or dummy or doubleblind$ or singleblind$ or trebleblind$ or tripleblind$).ti,ab.

10 (placebo$ or random$).ti,ab.

11 treatment outcome$.md. use psyh

12 animals/ not human$.mp. use emez

13 animal$/ not human$/ use mesz, prem

14 (animal not human).po. use psyh

15 (or/2,4,6-11) not (or/12-14)

2.2.2 Randomized controlled trial study design filter, topic specific databases

CINAHL– EBSCO Host

s10 s9 not s8

s9 s1 or s2 or s3 or s4 or s5 or s6 or s7

s8 (mh "animals") not (mh "human")

s7 (pt "clinical trial") or (pt "randomized controlled trial")

s6 ti (placebo* or random*) or ab (placebo* or random*)

s5 ti (single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind*) or ab (single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind*)

s4 ti (crossover or cross over) or ab (crossover or cross over)

s3 ti clinical n2 trial* or ab clinical n2 trial*

s2 (mh "crossover design") or (mh "placebos") or (mh "random assignment") or (mh "random sample")

s1 (mh "clinical trials+")

Figure 1 PRISMA Flow Diagram (21)

Table 1 Characteristics of the included studies

STUDY	**Country**	**Mean Age**	**% Female**	**% Bipolar I**	**Mood at baseline**	**Intervention**	**N** Total or per arm	**Drop-out** Total or per arm	**Hours of contact**	**Duration** (weeks)	**Follow-up** (weeks)
Individual Cognitive therapy (CT) / Cognitive Behavioural therapy (CBT)											
BALL2006 (64)	AUS	42	58%	NR	M	CT v TAU	25, 27	16%	20	26	52 / 78
JONES2014 (33)	GB	39	70%	79%	M	CBT v TAU	33, 34	3%	18	26	52
LAM2000 (66)	GB	39	52%	100%	M	CBT v TAU	13, 12	8%	NR	26	52
LAM2003 (67)	GB	44	56%	100%	M	CT v TAU	51, 52	16%	16	26	52
MEYER2012 (85)	DE	44	50%	79%	M	CBT v Supportive therapy	38, 38	13%, 16%	18, 18	39	143
MIKLOWITZ2007 (41)	US	40	59%	67%	Ad	CBT v Collaborative therapy	75, 130	41%, 30%	11, 2	39, 6	52
SCHMITZ2002 (44)	US	34	52%	NR	Ad	CBT v TAU	25, 21	36%, 67%	20	12	-
SCOTT2001 (50)	GB	39	60%	81%	A and M	CT v TAU	21, 21	14%	11	26	-
SCOTT2006 (51)	GB	41	65%	94%	A and M	CBT v TAU	127, 126	17%	NR	26	72
ZARETSKY2008 (65)	CA	41	NR	66%	M	CBT v TAU	40, 39	28%	NR	13	52
Psychological therapy for medication adherence (PTM)											
COCHRAN1984 (68)	US	33	61%	75%	M	PTM v TAU	14, 14	14%	6	6	32
EKER2012 (40)	TR	36	54%	NR	M	PTM vs Attention control	35, 36	17%	12	6	-
Individual Psychoeducation (PE)											
JAVADPOUR2013 (61)	IR	NR	51%	NR	M	PE v TAU	54, 54	17%, 24%	7	8	26 / 52 / 78
LOBBAN2010 (62)	GB	45	68%	98%	M	PE v TAU	56, 40	5%	6	6	48
PERRY1999 (63)	GB	45	68%	91%	M	PE v TAU	34, 36	21%	9	NR	52
DOGAN2003 (60)	TR	37	35%	NR	M	PE v TAU	14, 12	NR	14	6	-
Individual PE vs Group Cognitive Behavioural therapy (CBT)											
PARIKH2012 (37)	CA	41	58%	72%	M	PE vs CBT	95, 109	34%, 36%	17, 9	20, 6	72
Online Psychoeducation (PE)											
PROUDFOOT2012 (58)	AUS	NR	70%	NR	Ad and M	PE vs Attention control	139, 141	32%, 29%	0	8	26
SMITH2011 (59)	GB	44	62%	86%	M	PE vs TAU	24, 26	33%	NR	17	43
TODD 2014 (49)	GB	43	72%	NR	A and M	PE vs TAU	61, 61	66%	0	26	-
Group Cognitive Behavioural therapy (CBT)											

STUDY	**Country**	**Mean Age**	**% Female**	**% Bipolar I**	**Mood at baseline**	**Intervention**	**N** Total or per arm	**Drop-out** Total or per arm	**Hours of contact**	**Duration** (weeks)	**Follow-up** (weeks)
DEBARROS2013 (34)	BR	44	69%	NR	M	CBT v Attention control	32, 23	NR	24	8	34 / 60
BERNHARD2009 (31)	DE	39	73%	63%	M	CBT v TAU	32, 36	22%	18	12	52
GOMES2011 (73)	BR	38	76%	76%	M	CBT v TAU	23, 27	0%	27	26	78
COSTA2012 (74)	BR	40	62%	84%	M	CBT v TAU	27, 14	0%	28	14	40
Group Social cognition and interaction training											
LAHERA2013 (77)	ES	39	65%	76%	M	CBT v TAU	21, 16	19%	18	18	-
Group Mindfulness based cognitive therapy											
WILLIAMS2008 (76)	GB	NR	NR	NR	M	Mindfulness v Wait list	9, 8	NR	23	8	-
PERICH2013 (75)	AUS	NR	65%	62%	M	Mindfulness v TAU	48, 47	21%, 38%	18	8	22/ 35/48/61
Group Dialectical Behaviour Therapy (DBT)											
VAN DIJK2013 (42)	CA	42	75%	42%	Ad	DBT v TAU	13, 13	8%, 8%	18	12	-
Functional remediation											
TORRENT2013 (71)	ES	40	NR	NR	M	Functional remediation v TAU	77, 80	29%, 18%	32	21	47
Group Psychoeducation (PE)											
SAJATOVIC2009 (47)	US	41	68%	NR	A	PE v TAU	84, 80	51%	NR	52	-
CASTLE2010 (72)	AUS	42	77%	74%	M	PE v TAU	42, 42	24%	23	13	52
TORRENT2013 (71)	ES	40	NR	NR	M	PE v TAU	82, 80	24%, 18%	32	21	47
COLOM2003 (69)	ES	35	62%	100%	M	PE v Attention control	25, 25	NR	32	20	124
COLOM2003 ((70)	ES	34	63%	83%	M	PE v Attention control	60, 60	27%	32	21	124
Family psychoeducation (Service users and carers)											
CLARKIN1998 (36)	US	48	46%	100%	A	Family PE v TAU	19, 23	5%, 35%	NR	48	-
D'SOUZA2010 (78)	AUS	40	52%	86%	M	Family PE v TAU	27, 31	NR	18	12	60
GLICK1993 (35)	US	32	67%	NR	A	Family PE v TAU	15, 11	20%, 19%	8	7	33
MILLER2004 (48)	US	39	56%	100%	A	Family PE v TAU	33, 29	36%	10	NR	121
Family psychoeducation (Carers)											
BORDBAR2009 (79)	IR	30	22%	100%	M	Family PE v TAU	29, 28	0%	2	1	52
VAN GENT1991 (82)	NL	49	NR	NR	M	Family PE v Waitlist	14, 12	0%	NR	5	31
MADIGAN2012 (80)	IE	42	65%	NP	M	Family PE v Short carer focused intervention v TAU	18, 19, 10	28%, 21%	NR	5	57 / 109
PERLICK2010 (56)	US	35	62%	87%	A and M	Short carer focused intervention v TAU	25, 21	4%, 10%	11	14	-

STUDY	**Country**	**Mean Age**	**% Female**	**% Bipolar I**	**Mood at baseline**	**Intervention**	**N** Total or per arm	**Drop-out** Total or per arm	**Hours of contact**	**Duration** (weeks)	**Follow-up** (weeks)
REINARES2008 (81)	ES	34	54**%**	83**%**	M	Family PE v TAU	57, 56	5%	18	12	65
Family Focused Therapy (FFT)											
MIKLOWITZ2000 (55)	US	36	63**%**	100**%**	A and M	FFT v TAU	31, 70	10%	21	39	52 / 104
MIKLOWITZ2007 (41)	US	40	59%	67%	Ad	FFT v Collaborative therapy	26, 130	27%, 30%	11, 2	39, 6	52
MILLER2004 (48)	US	39	56**%**	100**%**	A	FFT vTAU	30, 29	36%, 33%	10, 9	NR	121
REA2003 (84)	US	26	NR	100**%**	M	FFT v PE (Individual)	28, 25	21%, 2%	21, 11	39, 39	-
Interpersonal and social rhythm therapy (IPSRT)											
SWARTZ2012 (43)	US	37	60**%**	0**%**	Ad	IPRST v Quetiapine	14, 11	21%, 38%	6	12	-
FRANK1999 (46)	US	35	56	100%	A	IPRST v Intensive clinical management	39 43	43% 37%	38 15	123	-
MIKLOWITZ2007 (41)	US	40	59%	67%	Ad	IPRST vs TAU	62, 130	32%, 30%	14, 2	39, 6	52
Collaborative care (Psychiatric focus)											
BAUER2006 (45)	US	47	9%	87%	A	Collaborative care v TAU	166, 164	25%, 15%	NR	156	-
SIMON2005 (54)	US	44	69**%**	76**%**	A and M	Systematic care management program v TAU	212 229	NR	NR	52	-
KESSING2013 (83)	DK	36	54%	NR	M	Specialized outpatient mood disorder clinic v TAU	72, 86	0%, 0%	NR NR	104/130 104/130	-
Collaborative care (Physical health focus)											
FAGIOLINI2009 (38)	US	41	61%	67%	A and M	Enhanced Clinical Intervention vs TAU	235, 228	NR	NR	85	-
KILBOURNE2008 (52)	US	55	9%	76%	A and M	Collaborative care v TAU	61	NR	NR	26	-
KILBOURNE2012 (53)	US	45	61%	NR	A and M	Collaborative care v TAU	34, 34	NR	NR	30	52
Integrated group therapy (IGT)											
WEISS2007 (39)	US	42	52%	81%	Ad and M	IGT v Drug counselling	31,31	23%, 45%	20, 20	20, 20	35
WEISS2009 (57)	US	38	41%	79%	Ad and M	IGT v Drug counselling	31, 30	19%, 20%	12, 12	12, 12	26
Integrated Cognitive and Interpersonal Therapy (IC&IT)											
SCHWANNAUER2007	GB	37	48%	95%	NR	IC&IT v TAU	212	23%, 17%	25	20	46, 98

STUDY	**Country**	**Mean Age**	**% Female**	**% Bipolar I**	**Mood at baseline**	**Intervention**	**N** Total or per arm	**Drop-out** Total or per arm	**Hours of contact**	**Duration** (weeks)	**Follow-up** (weeks)
(32)											

Definitions of abbreviations
TAU = Treatment as usual; PE = Psychoeducation; NR = Not reported;
M = maintenance (participants euthymic at baseline); Ad = participants in an acute depression at baseline; A = participants in an acute episode of mania or depression;
AUS = Australia; BR = Brazil; CA = Canada; DE = Germany; DK = Denmark; ES = Spain; GB = United Kingdom; IE = Ireland; IR = Islamic Republic of Iran;
NL = Netherlands; TR = Turkey; US = United States;

Table 2 Defining characteristics of psychological interventions* and collaborative care

Intervention	Mean/range contact (hours)	Mean/range group size	Mean/range duration (weeks)	Key elements
First comparison				
Individual Cognitive therapy (CT) / Cognitive Behavioural therapy (CBT)	16 (11-20)	N/A	28 (12-39)	Psychoeducation, identifying and modifying dysfunctional and negative thoughts, underlying maladaptive assumptions and beliefs, problem-solving training and strategies for early detection of mood episodes.
Psychological therapy for medication adherence (PTM)	9 (6-12)	N/A	6	Modified cognitive-behavioural intervention aimed at altering cognitions and behaviours that interfere with compliance. Psychoeducation, monitoring, and then instructions to alter compliance behaviour.
Individual Psychoeducation (PE)	9 (6-11)	N/A	17 (6-39)	Education on bipolar disorder, causative factors, clinical symptoms and early warning signs, medication side effects, and coping strategies for mood changes. Most PE interventions include the creation of a (relapse prevention) action plan.
Online Psychoeducation (PE)	0	N/A	15 (8-26)	Online interactive program addressing topics such as the causes of bipolar disorder, diagnosis, treatments, role of lifestyle (changes) and the importance of support.
Functional remediation	32	NR	21	Psychoeducation on cognitive deficits and their impact on daily life, strategies to manage them , especially attention, memory and executive function, with a special focus on enhancement of functioning in daily routine
Second comparison				
Group Cognitive Behavioural therapy (CBT)	24 (18-28)	6	17 (12-26)	Psychoeducation, identifying and modifying dysfunctional and negative thoughts, underlying maladaptive assumptions and beliefs, problem-solving training and strategies for early detection of mood episodes.
Group Social cognition and interaction training	18	12	18	Emotional training (definition of emotions, facial expression training, understanding of paranoid symptoms as an emotion); role-play social situations (distinguishing facts from guesses, jumping to conclusions, understanding bad events); and integration of learning.
Group Mindfulness based cognitive therapy	21 (18-23)	10 (6-14)	8	Psychoeducation, mindfulness meditation (observations of thoughts, feelings and bodily reactions) practice and cognitive therapy regarding depression.
Group Dialectical Behaviour Therapy (DBT)	18	N/A	12	Psychoeducation about bipolar disorder and treatment. Training of skills: states of mind, reducing vulnerability to emotions, non judgmental stance, acceptance, distracting, self-soothing, pro's and con's, urge management, self-validation opposite to emotion action and balancing enjoyable activities with responsibilities.
Group Psychoeducation (PE)	25 (9-32)	9 (7-10)	22 (8-26)	Interactive group sessions covering illness and treatment education, symptom monitoring and early detection, treatment adherence, illness management skills, coping strategies and problem solving.
Third comparison				

Family psychoeducation (Service user and carers)	12 (9-18)	N/A	22 (7-48)	Intervention for family and the service user. Psychoeducation on bipolar and treatment, enhancing relationships (spouse, family, clinician), problem focused coping strategies.
Family psychoeducation (Carers)	10 (2-18)	N/A	6 (1-12)	Intervention for the family only. Psychoeducation on bipolar and treatment, dealing with one's own functioning (stress and other health risks) and practical advice.
Fourth comparison				
Collaborative care (Psychiatric focus)	N/A	N/A	N/A	Psychoeducation and a review of symptoms and side effects, medical and behavioural management of side effects, discussion of early-warning signs of impending episodes, and a (24-hour on-call) coordinating team of health professionals.
Collaborative care (Physical health focus)	N/A	N/A	N/A	Self-management, psychoeducation, disease (cardiovascular) prevention strategies and a care manager/team who advocates the service users interests.
Fifth comparison				
Integrated Cognitive and Interpersonal Therapy	25	8	20	Individuals could choose the group or individual intervention. Psychoeducation, identification of early warning signs, behavioural strategies for coping with symptoms, cognitive strategies, affect regulation techniques, social network analysis, and identification of interpersonal patterns and strategies.
Sixth comparison				
Family Focused Therapy (FFT)	15 (10-21)	N/A	39	An intervention with the service user and his/her family. Psychoeducation about bipolar disorder, communication enhancement training, and problem-solving skills training.
Seventh comparison (See Individual Cognitive Behavioural therapy (CBT) for characteristics)				
Eight comparison				
Interpersonal and social rhythm therapy (IPSRT)	16 (6-38)	N/A	12 (19-39)	Based on interpersonal therapy, but focussing on stabilizing social rhythms (social routines, daily activities and sleep/wake cycles) trough monitoring and anticipating on disruptive events.
Ninth comparison				
Integrated group therapy (IGT)	16 (12-20)	5	16 (12-20)	Cognitive behavioural relapse prevention model focusing on similarities between recovery/relapse processes in bipolar disorder and substance use disorder.
Drug counselling	16 (12-20)	5	16 (12-20)	A treatment group to facilitate abstinence from drug misuse, encourage mutual support, and teach new ways to cope with substance-related problems.

* Psychological interventions are structured interventions based on psychological models (linking thoughts, feelings and behaviour) of mood disorders. Main goals are to establish stable, normal mood and restore (social) functioning.
N/A = not applicable

Table 3 Continuous measures used in included trials

Outcome type	Scales
Symptoms of depression	Bech–Rafaelsen Melancholia Scale (BRMS), Beck Depression Inventory (BDI), Center for Epidemiological Studies Depression Scale (CES-D), Goldberg Anxiety and Depression Scale (GADS), Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Bipolar Longitudinal Investigation of Problems (BLIP), Internal State Scale (ISS), Depression and Schedule for Affective Disorders and Schizophrenia, change version (SADS-C).
Symptoms of mania symptoms	Altman Self-Rating-Mania-Scale, Bech-Rafaelsen Mania Scale (BRMS), Bipolar Longitudinal Investigation of Problems (BLIP), Mania Rating Scale (MAS), Schedule for Affective Disorders and Schizophrenia, change version (SADS-C), Self-Rating Mania Inventory (SRMI) and Young Mania Rating Scale (YMRS).
Psychosocial functioning	Global Assessment of Functioning (GAF), MRC Social Performance Schedule (SPS), Social Adaptation Self Evaluation Scale (SASS), different versions of Social Adjustment Scale (SAS), Social and Occupational Functioning Assessment Scale (SOFAS), Social Functioning Interview, Social Performance Schedule (SPS), UCLA Social Attainment Scale, Work and Social Adjustment Scale (WSAS) and World Health Organization Disability Assessment Scale (WHODAS).
Quality of life	Medical Outcomes Study 36-item Short Form Health Survey (MOS-SF-36), Satisfaction with Life Scale (SWLS), Quality of Life in BD scale (QoL.BD), World Health Organisation Quality of Life Instrument.

Table 4 Risk of Bias graph

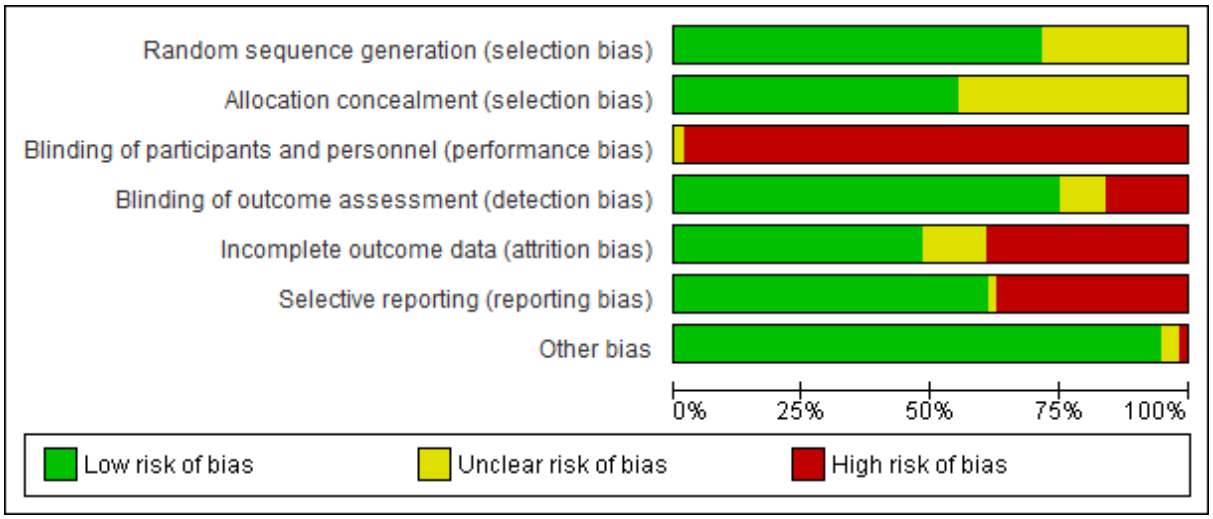


Table 5 Risk of Bias summary

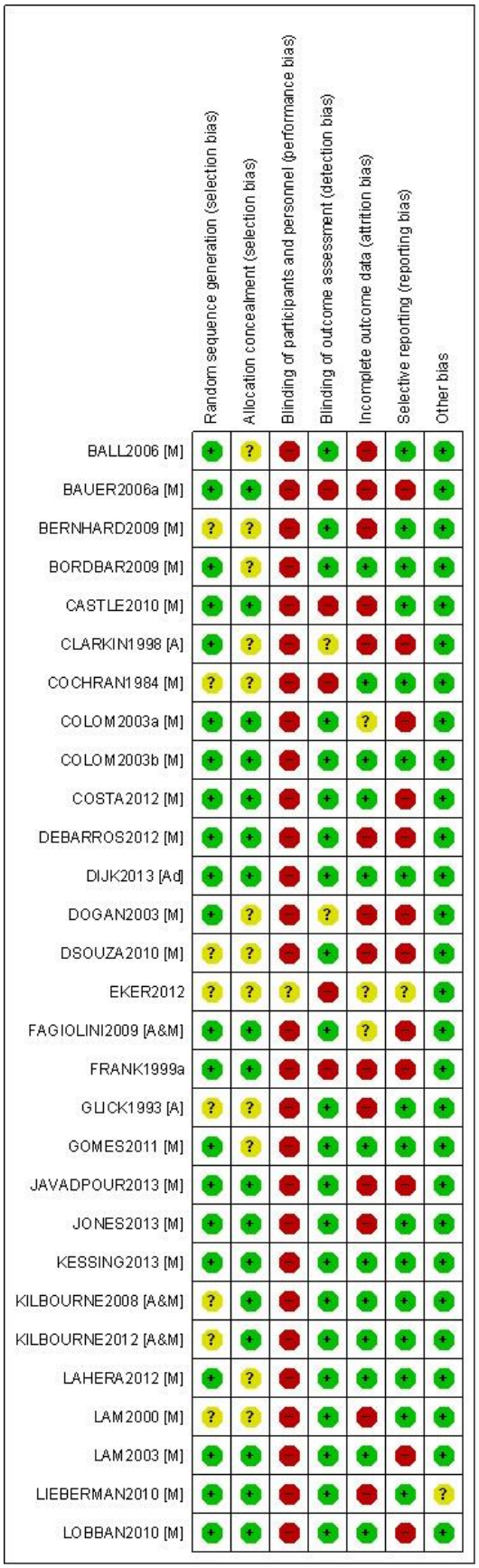
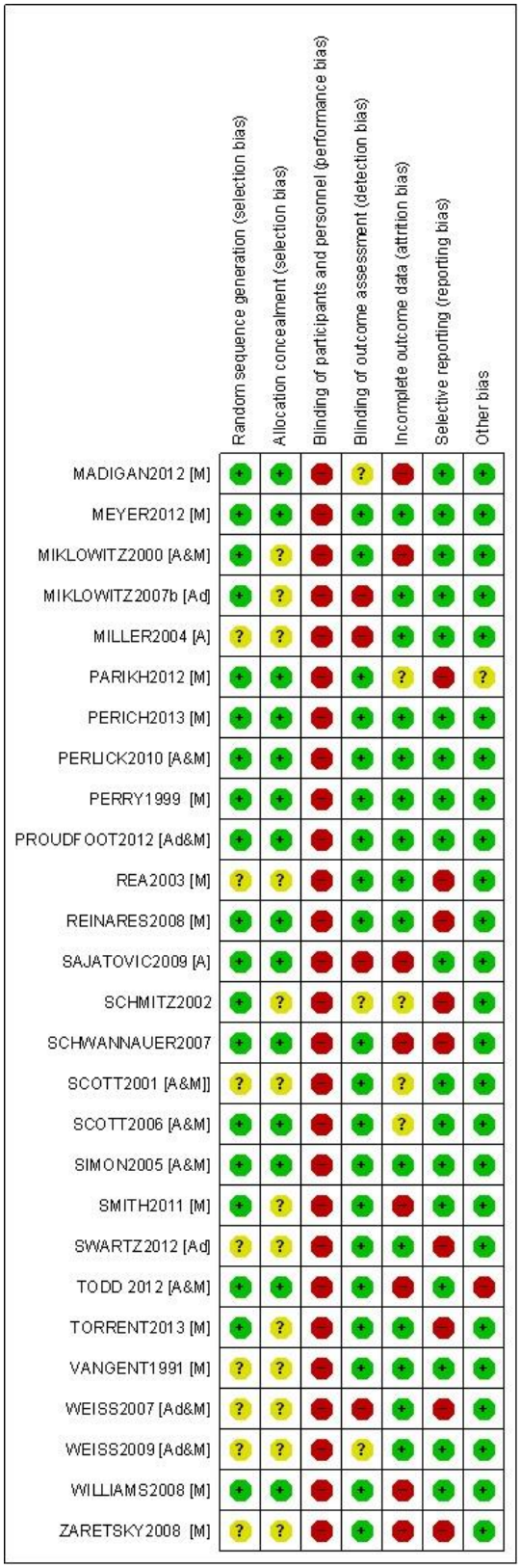


Table 5 (continues) Risk of Bias



Caption: Risk of bias was rated as low (+), high (-), or unclear (?) using the Cochrane Risk of Bias Tool (22).; M = maintenance (participants euthymic at baseline); Ad = participants in an acute depression at baseline; A = participants in an acute episode of mania or depression;

Table 6: Outcomes at post-treatment

Outcome	Number of studies (k) and participants (N)	Effect size (95% CI)	Heterogeneity: Chi² (p value); I²	Intervention length (weeks)	Quality (GRADE)(26)
1. Individual psychological intervention[1] versus treatment as usual (TAU)					
Depression symptoms	k=8 ; N=683	SMD = -0.23 (-0.41, -0.05)	8.55 (P = 0.29); 18%	6-26	Low [a e]
Mania symptoms	k=3 ; N=171	SMD= -0.05 [-0.35, 0.25]	0.48 (P = 0.79); 0%	26	Very Low [a d e]
Hospitalisation	k=1 ; N=28	RR = 0.14 (0.01, 2.53)	N/A	6	Low [d e]
Relapse (any)	k=6 ; N=365	RR = 0.66 (0.48, 0.92)	2.50 (P = 0.78); 0%	6-26	Moderate [d]
Response	k=1 ; N=33	RR = 0.71 (0.46, 1.07)	N/A	26	Very Low [d e]
2. Group psychological intervention[2] versus TAU					
Depression symptoms	k=8 ; N=423	SMD = -0.24 (-0.64, 0.16)	25.65 (P = 0.0006); 73%	8-52	Very Low [a b d e]
Mania symptoms	k=6 ; N=375	SMD= -0.08 [-0.33, 0.16]	5.60 (P = 0.35); 11%	8-52	Very low [a d e]
Hospitalisation	k=3 ; N=205	RR = 0.45 (0.10, 2.09)	3.94 (P = 0.14); 49%	14-21	Low [d]
Relapse (any)	k=2 ; N=170	RR = 0.48 (0.22, 1.04)	2.42 (P = 0.12); 59%	21	Low [d]
Relapse (depression)	k=2 ; N=170	RR = 0.39 (0.19, 0.78)	0.45 (P = 0.50); 0%	21	Low [d]
Relapse (mania)	k=2 ; N=170	RR = 0.48 (0.28, 0.82)	0.80 (P = 0.37); 0%	21	Low [d]
3. Family psychoeducation versus TAU					
Depression symptoms	k=1 ; N=43	SMD = -0.73 (-1.35, -0.10)	N/A	14	Low [d e]
Mania symptoms	k=1 ; N=43	SMD= -0.66 [-1.28, -0.04]	N/A	14	Low [d e]
4. Collaborative care versus TAU					
Depression symptoms	k=2 ; N=123	SMD = -0.22 (-0.63, 0.19)	1.32 (P = 0.25); 24%	26-30	Low [a d e]
Mania symptoms	k=2 ; N=123	SMD=-0.07 [-0.47, 0.32]	1.24 (P = 0.27); 19%	26-30	Low [a d e]
Hospitalisation	k=3 ; N=572	RR = 0.68 (0.49, 0.94)	0.13 (P = 0.72); 0%	52-130	Moderate [d]
Relapse (any)	k=1 ; N=414	RR = 0.99 (0.84, 1.17)	N/A	52	Low [d e]

[1] Cognitive behaviour therapy; (online) psychoeducation; medication adherence therapy.
[2] Mindfulness based cognitive therapy; dialectical behaviour therapy; social cognition and interaction training, psychoeducation, cognitive behaviour therapy.

5. Integrated cognitive and interpersonal therapy versus TAU					
Depression symptoms	k=1 ; N=193	SMD = -0.64 (-1.19, -0.09)	N/A	20	Low [d]
Mania symptoms	k=1 ; N=193	SMD= -0.10 [-0.30, 0.10]	N/A	20	Low [d e]
6. Family -focused therapy versus active control					
Depression symptoms	k=1 ; N=79	SMD = -0.40 (-0.80, 0.00)	N/A	39	Low [a d]
Mania symptoms	k=1 ; N=79	SMD= 0.00 [-0.40, 0.40]	N/A	39	Low [a d]
Relapse (any)	k=1 ; N=53	RR = 0.89 (0.52, 1.54)	N/A	39	Low [d]
Hospitalisation	k=1 ; N=53	RR = 0.71 (0.33, 1.52)	N/A	39	Low [d]
7. CBT versus active control					
Depression symptoms	k=1 ; N=76	SMD = 0.41 (0.12, 0.70)	N/A	39	Low [d e]
Mania symptoms	k=1 ; N=76	SMD=0.20 [-0.11, 0.51]	N/A	39	Low [d e]
Relapse (any)	k=1 ; N=76	RR = 0.60 (0.34, 1.05)	N/A	39	Low [d e]
8. Interpersonal and social rhythm therapy versus active control					
Depression symptoms	k=1 ; N=25	SMD = 0.44 (-0.34, 1.22)	N/A	12	Very Low [a d]
Relapse (any)	k=1 ; N=41	RR = 1.55 (0.63, 3.84)	N/A	123	Very Low [a d]
Response (any)	k=1 ; N=25	RR = 0.98 (0.60, 1.60)	N/A	12	Very Low [a d]
9. Integrated group therapy versus active control					
Depression symptoms	k=1 ; N=61	SMD = -0.35 (-0.85, 0.16)	N/A	12	Very Low [c d e]
Mania symptoms	k=1 ; N=61	SMD= -0.17 [-0.68, 0.33]	N/A	12	Very Low [c d e]

[a] Risk of bias, [b] Inconsistency, [c] Indirectness, [d] Imprecision, [e] Publication/Reporting Bias); N/A = not applicable; SMD = Standardized Mean Difference; RR = Risk Ratio

Table 7: Outcomes at follow-up

Outcome	Number of studies (k) and participants (N)	Effect size (95% CI)	Heterogeneity: Chi^2 (p value); I^2	Follow-up period (weeks)	Quality (GRADE)(26)
1. Individual psychological intervention[3] versus TAU					
Depression symptoms	k=5 ; N=534	SMD = -0.21 (-0.43, 0.01)	6.85 (P = 0.23); 27%	26-52	Low [a d]
Mania symptoms	k=4 ; N=164	SMD=-0.38 [-0.71, -0.04]	3.40 (P = 0.33); 12%	52	Very Low [a d e]
Hospitalisation	k=3 ; N=194	RR = 0.63 (0.38, 1.02)	2.19 (P = 0.35); 9%	32-52	Low [d]
Relapse (any)	k=8 ; N=532	RR = 0.74 (0.63, 0.87)	5.78 (P = 0.57); 0%	32-78	Moderate [d]
Response	k=1 ; N=52	RR = 0.46 (0.21, 1.02)	N/A	52	Very Low [a d e]
2. Group psychological intervention versus[4] TAU					
Depression symptoms	k=3 ; N=219	SMD = 0.22 (-0.05, 0.49)	0.95 (P = 0.62); 0%	52-61	Very Low [a d e]
Mania symptoms	k=3 ; N=219	SMD= 0.16 [-0.10, 0.43]	0.76 (P = 0.68); 0%	52-61	Very Low [a d e]
Hospitalisation	k=3 ; N=200	RR = 0.48 (0.16, 1.45)	2.30 (P = 0.13); 56%	78-124	Very Low [b d e]
Relapse (any)	k=5 ; N=395	RR = 0.86 (0.61, 1.20)	21.46 (P = 0.0003); 81%	52-124	Very Low [b d e]
Relapse (depression)	k=5 ; N=333	RR = 0.62 (0.45, 0.88)	7.12 (P = 0.13); 44%	52-124	Low [b d]
Relapse (mixed episode)	k=4 ; N=274	RR = 0.48 (0.30, 0.77)	2.38 (P = 0.50); 0%	52-124	Low [b d]
3. Family psychoeducation versus TAU					
Depression symptoms	k=1 ; N=53	SMD = -0.15 (-0.69, 0.39)	N/A	60	Very Low [a d e]
Mania symptoms	k=1 ; N=53	SMD= -0.78 [-1.34, -0.22]	N/A	60	Very Low [a d e]
Hospitalisation	k=1 ; N=57	RR = 0.05 (0.00, 0.83)	N/A	60	Low [d]
Relapse (any)	k=3 ; N=228	RR = 0.52 (0.32, 0.84)	2.61 (P = 0.27); 23%	52-65	Low [d e]
Relapse (depression)	k=1 ; N=113	RR = 0.73 (0.44, 1.21)	N/A	65	Low [d e]
Relapse (mania)	k=1 ; N=113	RR = 0.35 (0.15, 0.85)	N/A	65	Low [d]
Response	k=1 ; N=59	RR = 0.67 (0.34, 1.32)	N/A	121	Very Low [a d e]
4. Collaborative care versus TAU					
Depression symptoms	k=1 ; N=65	SMD = -0.56 (-1.06, -0.07)	N/A	52	Very Low [a d]

[3] Cognitive behaviour therapy; (online) psychoeducation; medication adherence therapy.
[4] Mindfulness based cognitive therapy; psychoeducation, cognitive behaviour therapy.

Mania symptoms	k=1 ; N=65	SMD= -0.10 [-0.59, 0.38]	N/A	52	Very Low [a d]
6. Family-focused therapy versus (active) control					
Depression symptoms	k=1 ; N=79	SMD = -0.10 (-0.56, 0.36)	N/A	52	Very Low [a d e]
Mania symptoms	k=1 ; N=79	SMD= -0.30 [-0.68, 0.08]	N/A	52	Very Low [a d]
Relapse (any)	k=1 ; N=101	RR = 0.67 (0.34, 1.30)	N/A	52	Very Low [a d e]
Response (any)	k=1 ; N=62	RR = 1.15 (0.68, 1.94)	N/A	121	Very Low [a d e]
Hospitalisation	k=1 ; N=38	RR = 0.24 (0.08, 0.74)	N/A	104	Very Low [a d]
7. CBT versus active control					
Depression symptoms	k=1 ; N=76	SMD = 0.49 (0.04, 0.94)	N/A	143	Very Low [d e]
Relapse (any)	k=1 ; N=76	RR = 1.13 (0.81, 1.58)	N/A	143	Very Low [d e]
8. Interpersonal and social rhythm therapy versus active control					
Response (depression)	k=1 ; N=192	RR = 0.73 (0.50, 1.07)	N/A	52	Very Low [a d e]
9. Integrated group therapy versus drug counselling (group)					
Depression symptoms	k=1 ; N=61	SMD = 0.11 (-0.39, 0.61)	N/A	26	Very Low [c d e]
Mania symptoms	k=1 ; N=61	SMD= -0.53 [-1.05, -0.02]	N/A	26	Very Low [c d e]

[a] Risk of bias, [b] Inconsistency, [c] Indirectness, [d] Imprecision, [e] Publication/Reporting Bias)

N/A = not applicable; SMD = Standardized Mean Difference; RR = Risk Ratio

Table 8 Outcomes at post-treatment

1. Individual psychological intervention vs Treatment as usual (TAU)							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**Total**	**8**	**683**	**SMD= -0.23 [-0.41, -0.05]**	**8.55 (P = 0.29); 18%**	**6-26**	**Low** [a e]
	Online Psychoeducation	(49, 58)	378	SMD= -0.18 [-0.63, 0.26]	3.88 (P = 0.05); 74%	6-26	
	CBT	(33, 64, 66, 67)	305	SMD= -0.31 [-0.53, -0.08]	2.97 (P = 0.70); 0%	26	
Mania symptoms	**CBT**	(64, 66, 67)	**171**	**SMD= -0.05 [-0.35, 0.25]**	**0.48 (P = 0.79); 0%**	**26**	**Very Low** [a d e]
Hospitalisation	**Medication adherence therapy**	**(68)**	**28**	**RR= 0.14 [0.01, 2.53]**	**N/A**	**6**	**Low** [d e]
Relapse, any type	**Total**	**6**	**365**	**RR= 0.66 [0.48, 0.92]**	**2.50 (P = 0.78); 0%**	**6-26**	**Moderate** [d]
	Psychoeducation	(63)	70	RR= 0.69 [0.41, 1.15]	N/A	6	
	Medication adherence therapy	**(68)**	28	RR= 0.40 [0.09, 1.73]	N/A	6	
	CBT	(50, 64, 65, 67)	267	RR= 0.67 [0.43, 1.04]	2.02 (P = 0.57); 0%	26	
Relapse, depression	**Total**	**2**	**122**	**RR= 0.54 [0.06, 4.70]**	**4.15 (P = 0.04); 76%**	**6-26**	**Very Low** [a b d]
	Psychoeducation	(63)	70	RR= 1.29 [0.61, 2.73]	N/A	6	
	CBT	(64)	52	RR= 0.15 [0.02, 1.17]	N/A	26	
Relapse, mania	**Psychoeducation**	(63)	**70**	**RR= 0.19 [0.05, 0.81]**	**N/A**	**6**	**Very Low** [d e]
Response, any	**CBT**	**(50)**	**33**	**RR= 0.71 [0.46, 1.07]**	**N/A**	**26**	**Very Low** [d e]
Quality of life	**Total**	**4**	**451**	**SMD= -0.46 [-1.05, 0.12]**	**20.14 (P = 0.0002); 85%**	**6-26**	**Very Low** [a b e]
	Psychoeducation	(60)	26	SMD= -0.36 [-1.30, 0.59]	N/A	6	
	Online Psychoeducation	(49, 58)	378	SMD= -0.86 [-1.26, -0.45]	16.50 (P < 0.0001); 94%	6-26	
	CBT	(33)	47	SMD= -0.35 [-0.93, 0.23]	N/A	26	
Psychosocial	**CBT**	**(64)**	**94**	**SMD= -0.49 [-0.90, -0.08]**	**0.10 (P = 0.75); 0%**	**26**	**Very Low** [a d e]

functioning GAF							
Psychosocial functioning Social and/or Work	**Total**	**7**	**606**	**SMD= -0.34 [-0.51, -0.17]**	**6.49 (P = 0.37); 8%**	**6-26**	**Low** [a e]
	Psychoeducation	(33, 63)	70	SMD= -0.17 [-0.64, 0.30]	N/A	6	
	Online Psychoeducation	(49, 58)	378	SMD= -0.31 [-0.67, 0.05]	2.55 (P = 0.11); 61%	6-26	
	CBT	(33, 50, 64, 66)	158	SMD= -0.55 [-0.87, -0.23]	1.20 (P = 0.75); 0%	26	
Study Discontinuation	**Total**	**9**	**755**	**RR= 0.74 [0.44, 1.27]**	**11.29 (P = 0.13); 38%**	**6-26**	**Low** [d e]
	Psychoeducation	(62, 63)	166	RR=3.04 [0.33, 28.16]	1.28 (P = 0.26); 22%	6	
	Online Psychoeducation	(49)	122	RR=1.13 [0.46, 2.72]	N/A	26	
	Medication adherence therapy	(68)	28	No dropout	N/A	6	
	CBT	(33, 50, 51, 64, 66)	439	RR= 0.58 [0.30, 1.13]	7.87 (P = 0.10); 49%	26	
2. Group psychological intervention vs Treatment as usual (TAU)							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**Total**	**8**	**423**	**SMD= -0.24 [-0.64, 0.16]**	**25.65 (P = 0.0006); 73%**	**8-52**	**Very Low** [a b d e]
	Psychoeducation	(47, 72)	152	SMD= 0.14 [-0.17, 0.46]	0.00 (P = 0.98); 0%	13-52	
	Mindfulness based cognitive therapy	(75, 76)	109	SMD= -0.50 [-0.89, -0.12]	0.20 (P = 0.65); 0%	8	

	Dialectical behaviour therapy	(42)	24	SMD=-1.18 [-2.06, -0.30]	N/A	12	
	CBT	(31, 74)	91	SMD= -0.55 [-1.12, 0.02]	1.68 (P = 0.20); 40%	12-14	
	Social cognition and interaction training	(77)	37	SMD= 0.92 [0.23, 1.61]	N/A	18	
Mania symptoms	**Total**	**6**	**375**	**SMD= -0.08 [-0.33, 0.16]**	**5.60 (P = 0.35); 11%**	**8-52**	**Very low** [a d e]
	Psychoeducation	(47, 72)	152	SMD=0.06 [-1.05, 1.18]	1.69 (P = 0.19); 41%	13-52	
	Mindfulness based cognitive therapy	(75)	95	SMD=-0.10 [-0.50, 0.30]	N/A	8	
	CBT	(31, 74)	91	SMD=-0.21 [-0.89, 0.47]	1.75 (P = 0.19); 43%	12-14	
	Social cognition and interaction training	(77)	37	SMD= -0.37 [-1.02, 0.28]	N/A	18	
Hospitalisation	**Total**	**3**	**205**	RR=0.45 [0.10, 2.09]	**3.94 (P = 0.14); 49%**	**14-21**	**Low** [d]
	PE vs attention control	(69, 70)	170	RR=0.52 [0.06, 4.84]	2.48 (P = 0.12); 60%	21	
	CBT	(74)	35	RR=0.20 [0.02, 1.97]	N/A	14	
Relapse, any type	**PE vs attention control**	**(69, 70)**	**170**	**RR=0.48 [0.22, 1.04]**	**2.42 (P = 0.12); 59%**	**21**	**Low** [d]
Relapse, depression	**PE vs attention control**	**(69, 70)**	**170**	**RR=0.39 [0.19, 0.78]**	**0.45 (P = 0.50); 0%**	**21**	**Low** [d]
Relapse, mania	**PE vs attention control**	**(69, 70)**	**170**	**RR=0.48 [0.28, 0.82]**	**0.80 (P = 0.37); 0%**	**21**	**Low** [d]
Relapse, mixed episode	**PE vs attention control**	**(69, 70)**	**170**	**RR=0.43 [0.18, 1.07]**	**1.11 (P = 0.29); 10%**	**21**	**Low** [d]
Quality of life	**CBT**	**(31, 74)**	**91**	**SMD=-0.38 [-1.74, 0.99]**	**9.06 (P = 0.003); 89%**	**12-14**	**Very Low** [a b d e]
Psychosocial functioning GAF	**Total**	**2**	**89**	**SMD= 0.01 [-0.40, 0.43]**	**0.01 (P = 0.92); 0%**	**12-18**	**Very Low** [a d e]
	CBT	(31)	52	SMD=0.03 [-0.51, 0.58]	N/A	12	
	Social cognition and interaction training	(77)	37	SMD=-0.01 [-0.66, 0.64]	N/A	18	
Psychosocial functioning Social and/or Work	**Social cognition and interaction training**	**(77)**	**37**	**SMD=0.43 [-0.23, 1.09]**	**N/A**	**18**	**Very Low** [a d e]
Study Discontinuation	**Total**	**9**	**703**	**RR=1.23 [0.83, 1.81]**	**6.77 (P = 0.24); 26%**	**8-52**	**Very Low** [a b e]

	Psychoeducation	(47, 71, 72)	410	RR=1.41 [0.75, 2.64]	5.61 (P = 0.06); 64%	13-52	
	PE vs attention control	(70)	120	No discontinuation	N/A	21	
	Mindfulness based cognitive therapy	(76)	19	RR=2.91 [0.40, 21.35]	N/A	8	
	Dialectical behaviour therapy	(42)	26	RR=1.00 [0.07, 14.34]	N/A	12	
	CBT	(31, 74)	91	RR= 0.88 [0.37, 2.08]	N/A (1 study no discontinuation)	14	
	Social cognition and interaction training	(77)	37	No discontinuation	N/A	18	
3. Family psychoeducation vs Treatment as usual (TAU)							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**Group Family PE (carers)**	**(56)**	**43**	**SMD= -0.73 [-1.35, -0.10]**	**N/A**	**14**	**Low** [d e]
Mania symptoms	**Group Family PE (carers)**	**(56)**	**43**	**SMD= -0.66 [-1.28, -0.04]**	**N/A**	**14**	**Low** [d e]
Study Discontinuation	**Group Family PE (carers)**	**(56)**	**46**	**RR=0.42 [0.04, 4.31]**	**N/A**	**14**	**Low** [b d]
4. Collaborative care vs TAU							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length**	*Quality (GRADE)(26)*

						h *(weeks)*	
Depression symptoms	**Physical health focus**	**(52, 53)**	**123**	**SMD=-0.22 [-0.63, 0.19]**	**1.32 (P = 0.25); 24%**	**26-30**	**Low** [a d e]
Mania symptoms	**Physical health focus**	**(52, 53)**	**123**	**SMD=-0.07 [-0.47, 0.32]**	**1.24 (P = 0.27); 19%**	**26-30**	**Low** [a d e]
Hospitalisation	**Psychiatric focus**	**(54, 83)**	**572**	**RR=0.68 [0.49, 0.94]**	**0.13 (P = 0.72); 0%**	**52-130**	**Moderate** [d]
Relapse, any type	**Psychiatric focus**	**(54)**	**414**	**RR=0.99 [0.84, 1.17]**	**N/A**	**52**	**Low** [d e]
Relapse, depression (number)	**Psychiatric focus**	**(54, 83)**	**424**	**RR= 0.96 [0.80, 1.17]**	**0.48 (P = 0.49); 0%**	**52-104**	**Low** [d e]
Relapse, mania	**Psychiatric focus**	**(54, 83)**	**505**	**RR= 0.93 [0.57, 1.52]**	**5.23 (P = 0.05); 81%**	**52-104**	**Very Low** [b d e]
Quality of life	**Total**	**2**	**379**	**SMD=-1.30 [-3.78, 1.18]**	**75.41 (P < 0.00001); 99%**	**30-156**	**Very Low** [a b d e]
	Physical health focus	(53)	65	SMD= -0.03 [-0.51, 0.46]	N/A	30	
	Psychiatric focus	(45)	314	SMD= -2.56 [-2.86, -2.26]	N/A	156	
Study Discontinuation	**Total**	**4**	**997**	**RR= 0.99 [0.47, 2.07]**	**4.48 (P = 0.21); 33%**	**30-156**	**Low** [b d]
	Physical health focus	(53)	68	RR=2.00 [0.19, 21.03]	N/A	30	
	Psychiatric focus	3(45, 54, 83)	929	RR= 0.96 [0.40, 2.30]	4.02 (P = 0.13); 50%	52-156	

5. Integrated Cognitive and Interpersonal Therapy (IC&IT) vs Treatment as usual (TAU)

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length**	*Quality (GRADE)(26)*

						(weeks)	
Depression symptoms	**(IC&IT) vs TAU**	**(92)**	**193**	**SMD= -0.64 [-1.19, -0.09]**	**N/A**	**20**	**Low** [d]
Mania symptoms	**(IC&IT) vs TAU**	**(92)**	**193**	**SMD= -0.10 [-0.30, 0.10]**	**N/A**	**20**	**Low** [d e]
Quality of life	**(IC&IT) vs TAU**	**(92)**	**193**	**SMD= -0.37 [-0.65, -0.08]**	**N/A**	**20**	**Low** [d]
Study Discontinuation	**(IC&IT) vs TAU**	**(92)**	**193**	**RR= 1.13 [0.47, 2.68]**	**N/A**	**20**	**Low** [d]

6. Family Focused therapy (FFT) vs Active control

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**FFT vs TAU**	**(55)**	**79**	**SMD= -0.40 [-0.80, 0.00]**	**N/A**	**39**	Low [a d]
Mania symptoms	**FFT vs TAU**	**(55)**	**79**	**SMD= 0.00 [-0.40, 0.40]**	**N/A**	**39**	Low [a d]
Relapse, any type	**FFT vs PE**	**(84)**	**53**	**RR= 0.89 [0.52, 1.54]**	**N/A**	**39**	Low [d]
Hospitalisation	**FFT vs PE**	**(84)**	**53**	RR= 0.71 [0.33, 1.52]	**N/A**	**39**	**Low** [d]
Study Discontinuation	**Total**	**2**	**154**	**RR= 0.63 [0.21, 1.89]**	**1.99 (P = 0.16); 50%**	**39**	Low [b d]
	FFT vs TAU	**(55)**	101	RR= 0.36 [0.11, 1.12]	N/A		
	FFT vs PE	**(84)**	53	RR= 1.07 [0.37, 3.08]	N/A		

7. Cognitive behaviour therapy (CBT) vs Active Control

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Interventi**	*Quality (GRADE)(26)*

						on length *(weeks)*	
Depression symptoms	**CBT individual vs Supportive Therapy (ST)**	**(85)**	**76**	**SMD= 0.41 [0.12, 0.70]**	**N/A**	**39**	Low [d e]
Mania symptoms	**CBT individual vs Supportive Therapy (ST)**	**(85)**	**76**	**SMD=0.20 [-0.11, 0.51]**	**N/A**	**39**	Low [d e]
Relapse, any type	**CBT individual vs Supportive Therapy (ST)**	**(85)**	**76**	**RR=0.60 [0.34, 1.05]**	**N/A**	**39**	Low [d e]
Study Discontinuation	**CBT individual vs Supportive Therapy (ST)**	**(85)**	**76**	**RR=0.80 [0.56, 1.14]**	**N/A**	**39**	Low [d]
8. Interpersonal and social rhythm therapy (IPSRT) vs Active control							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**IPSRT vs Quetiapine**	**(43)**	**25**	**SMD= 0.44 [-0.34, 1.22]**	**N/A**	**12**	**Very Low [a d]**
Relapse, any type	**IPSRT vs Intensive**	**(46)**	**41**	**RR= 1.55 [0.63, 3.84]**	**N/A**	**123**	**Very Low [a d]**

	clinical management						
Response, any type (number)	**IPSRT vs Quetiapine**	**(43)**	**25**	**RR= 0.98 [0.60, 1.60]**	**N/A**	**12**	**Very Low** [a d]
Psychosocial functioning GAF	**IPSRT vs Quetiapine**	**(43)**	**25**	**SMD= 0.55 [-0.26, 1.36]**	**N/A**	**12**	**Very Low** [a d]
Psychosocial functioning Social and/or Work	**IPSRT vs Intensive clinical management**	**(46)**	**82**	**SMD= -0.36 [-0.72, 0.00]**	**N/A**	**123**	**Very Low** [a d]
Study Discontinuation	**Total**	**2**	**107**	**RR= 0.94 [0.55, 1.59]**	**0.07 (P = 0.79); 0%**	**12-123**	**Moderate** [d]
	IPSRT vs Quetiapine	**(43)**	25	RR= 0.79 [0.20, 3.16]	N/A	12	
	IPSRT vs Intensive clinical management	**(46)**	82	RR= 0.96 [0.54, 1.71]	N/A	123	

9. Integrated group therapy (IGT) vs Active control

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Intervention length** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**IGT vs group drug counselling**	**(57)**	**61**	**SMD= -0.35 [-0.85, 0.16]**	**N/A**	**12**	Very Low [c d e]
Mania symptoms	**IGT vs group drug counselling**	**(57)**	**61**	**SMD= -0.17 [-0.68, 0.33]**	**N/A**	**12**	Very Low [c d e]

a Risk of bias, b Inconsistency, c Indirectness, d Imprecision, e Publication/Reporting Bias
TAU = Treatment as usual; CBT = Cognitive behaviour therapy; PE= Psychoeducation
N/A = not applicable; SMD = Standardised mean difference ; RR = Risk Ratio;

Table 9 Outcomes at follow-up

1. Individual psychological intervention vs Treatment as usual (TAU)							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**Total**	**5**	**534**	**SMD= -0.21 [-0.43, 0.01]**	**6.85 (P = 0.23); 27%**	**26-52**	**Low** [a]
	Online Psychoeducation	(58, 59)	326	SMD= -0.36 [-1.09, 0.37]	5.82 (P = 0.02); 83%	26-43	

	CBT	(33, 64, 66, 67)	208	SMD= -0.19 [-0.46, 0.08]	0.64 (P = 0.73); 0%	52	
Mania symptoms	**Total**	**4**	**164**	**SMD=-0.38 [-0.71, -0.04]**	**3.40 (P = 0.33); 12%**	**52**	**Very Low** [a d e]
	Online Psychoeducation	(59)	37	SMD=-0.24 [-0.89, 0.40]	N/A	43	
	CBT	(64, 66, 67)	127	SMD=-0.45 [-0.92, 0.01]	3.21 (P = 0.34); 38%	52	
Hospitalisation	**Total**	**3**	**194**	**RR= 0.63 [0.38, 1.02]**	**2.19 (P = 0.35); 9%**	**32-52**	**Low** [d]
	Psychoeducation	(63)	70	RR= 0.85 [0.47, 1.54]	N/A	52	
	Medication adherence therapy	(68)	28	RR= 0.40 [0.09, 1.73]	N/A	32	
	CBT	(67)	96	RR= 0.44 [0.20, 0.97]	N/A	52	
Relapse, any type	**Total**	**8**	**532**	**RR= 0.74 [0.63, 0.87]**	**5.78 (P = 0.57); 0%**	**32-78**	**Moderate** [d]
	Psychoeducation	(61-63)	252	RR= 0.81 [0.64, 1.02]	1.96 (P = 0.37); 0%	48-78	
	Medication adherence therapy	(68)	28	RR= 0.73 [0.43, 1.24]	N/A	32	
	CBT	(33, 64, 65, 67)	252	RR= 0.67 [0.53, 0.86]	2.84 (P = 0.42); 0%	52	
Relapse, depression	**Total**	**7**	**616**	**RR= 0.82 [0.59, 1.15]**	**14.84, (P = 0.02); 60%**	**43-72**	**Low** [b d]
	Psychoeducation	(62, 63)	166	RR=1.07 [0.53, 2.14]	2.87 (P = 0.09); 65%	48-52	
	Online Psychoeducation	(59)	37	RR=1.31 [0.70, 2.45]	N/A	43	
	CBT	(33, 51, 64, 67)	413	RR=0.65 [0.41, 1.02]	7.95 (P = 0.05); 62%	52-72	
Relapse, mania	**Total**	**6**	**564**	**RR= 0.74 [0.50, 1.08]**	**7.92 (P = 0.16); 37%**	**43-72**	**Low** [b d]
	Psychoeducation	(62, 63)	166	RR=0.56 [0.28, 1.11]	1.36 (P = 0.24); 27%	48-52	
	Online Psychoeducation	(59)	37	RR=0.94 [0.30, 2.96]	N/A	43	
	CBT	(33, 51, 67)	361	RR= 0.78 [0.45, 1.38]	4.65 (P = 0.10); 57%	52-72	
Response, any	**CBT**	(64)	**52**	**RR=0.46 [0.21, 1.02]**	**N/A**	**52**	**Very Low** [a d]
Response, depression	**CBT**	**(41, 64)**	**257**	**RR= 0.69 [0.40, 1.13]**	**2.23 (P = 0.14); 55%**	**52**	**Very Low** [a b d]

Response, mania	**CBT**	**(64)**	**52**	**RR= 1.53 [0.93, 2.52]**	**N/A**	**52**	**Very Low [a d]**
Quality of life	**Total**	**3**	**347**	**SMD= 0.04 [-0.17, 0.25]**	**1.44 (P = 0.49); I^2 = 0%**	**26-52**	**Very Low [a d e]**
	Online Psychoeducation	(58, 59)	310	SMD= 0.08 [-0.14, 0.31]	0.02 (P = 0.90); I^2 = 0%	26-43	
	CBT	(33)	37	SMD= -0.34 [-1.00, 0.32]	N/A	52	
Psychosocial functioning GAF	**Total**	**2**	**89**	**SMD=-0.25 [-0.66, 0.17]**	**0.00 (P = 0.98); 0%**	**43-52**	**Low [a d]**
	Online Psychoeducation	(59)	37	SMD=-0.25 [-0.90, 0.40]	N/A	43	
	CBT	(64)	52	SMD=-0.24 [-0.79, 0.31]	N/A	52	
Psychosocial functioning Social and/or Work	**Total**	**8**	**585**	**SMD= -0.27 [-0.60, 0.05]**	**18.39 (P = 0.005); 67%**	**26-52**	**Very Low [a b d e]**
	Psychoeducation	(62, 63)	70	SMD= -0.74 [-1.23, -0.26]	N/A	52	
	Online Psychoeducation	(58, 59)	310	SMD= 0.08 [-0.14, 0.30]	0.32 (P = 0.57); 0%	26-43	
	CBT	(33, 64, 66, 67)	205	SMD= -0.39 [-0.78, 0.01]	5.36 (P = 0.15); 44%	52	
Study Discontinuation	**Total**	**12**	**1163**	**RR= 0.97 [0.77, 1.23]**	**10.21 (P = 0.42); 2%**	**32-78**	**Low [d]**
	Psychoeducation	(61-63)	274	RR= 1.26 [0.29, 5.58]	3.46 (P = 0.18); 42%	48-78	
	Online Psychoeducation	(58, 59)	330	RR= 0.85 [0.28, 2.56]	1.54 (P = 0.22); 35%	26-43	
	Medication adherence therapy	(68)	28	No discontinuation	N/A	32	
	CBT	(33, 41, 64-67)	531	RR= 0.98 [0.74, 1.30]	5.47 (P = 0.36); 9%	52	

2. Group psychological intervention vs Treatment as usual (TAU)

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period**	*Quality (GRADE) (26)*

						(weeks)	
Depression symptoms	**Total**	**3**	**219**	**SMD= 0.22 [-0.05, 0.49]**	**0.95 (P = 0.62); 0%**	**52-61**	**Very Low** [a d e]
	Psychoeducation	(72)	72	SMD=0.40 [-0.07, 0.87]	N/A	52	
	CBT	(31)	52	SMD=0.06 [-0.48, 0.60]	N/A	52	
	Mindfulness based cognitive therapy	(75)	95	SMD=0.18 [-0.22, 0.58]	N/A	61	
Mania symptoms	**Total**	**3**	**219**	**SMD= 0.16 [-0.10, 0.43]**	**0.76 (P = 0.68); 0%**	**52-61**	**Very Low** [a d e]
	Psychoeducation	(72)	72	SMD= 0.33 [-0.14, 0.80]	N/A	52	
	CBT	(31)	52	SMD= 0.12 [-0.42, 0.66]	N/A	52	
	Mindfulness based cognitive therapy	(75)	95	SMD= 0.06 [-0.34, 0.46]	N/A	61	
Hospitalisation	**Total**	**3**	**200**	**RR= 0.48 [0.16, 1.45]**	**2.30 (P = 0.13); 56%**	**78-124**	**Very Low** [b d e]
	PE vs attention control	(69, 70)	166	RR=0.48 [0.16, 1.45]	2.30 (P = 0.13; 56%	124	
	CBT	(73)	34	No hospitalisations	N/A	78	
Relapse, any type	**Total**	**5**	**395**	**RR= 0.86 [0.61, 1.20]**	**21.46 (P = 0.0003); 81%**	**52-124**	**Very Low** [b d e]
	Psychoeducation	(72)	84	RR= 0.52 [0.32, 0.84]	N/A	52	
	PE vs attention control	(69, 70)	166	RR= 0.75 [0.64, 0.88]	0.83 (P = 0.36); 0%	124	
	Mindfulness based cognitive therapy	(75)	95	RR=1.41 [1.07, 1.87]	N/A	61	
	CBT	(73)	50	RR= 1.17 [0.72, 1.91]	N/A	78	
Relapse, depression	**Total**	**5**	**333**	**RR= 0.62 [0.45, 0.88]**	**7.12 (P = 0.13); 44%**	**52-124**	**Low** [b d]
	Psychoeducation	(72)	72	RR=0.33 [0.12, 0.91]	N/A	52	
	PE vs attention control	(69, 70)	166	RR=0.54 [0.36, 0.79]	1.25 (P = 0.26); 20%	124	
	Mindfulness based cognitive therapy	(75)	59	RR= 0.87 [0.59, 1.28]	N/A	61	

	CBT	(73)	36	RR=0.87 [0.41, 1.82]	N/A	78	
Relapse, mania	**Total**	**5**	**328**	**RR= 0.97 [0.60, 1.57]**	**13.04 (P = 0.01); 69%**	**52-124**	**Very Low** [a b d]
	Psychoeducation	(72)	72	RR= 1.02 [0.48, 2.16]	N/A	52	
	PE vs attention control	(69, 70)	166	RR= 0.64 [0.54, 0.76]	0.59 (P = 0.44); 0%	124	
	Mindfulness based cognitive therapy	(75)	54	RR= 1.21 [0.71, 2.07]	N/A	61	
	CBT	(73)	36	RR= 2.61 [0.80, 8.52]	N/A	78	
Relapse, mixed episode	**Total**	**4**	**274**	**RR= 0.48 [0.30, 0.77]**	**2.38 (P = 0.50); 0%**	**52-124**	**Low** [b d]
	Psychoeducation	(72)	72	RR= 1.25 [0.08, 19.22]	N/A	52	
	PE vs attention control	(69, 70)	166	RR= 0.43 [0.26, 0.71]	0.01 (P = 0.93); 0%	124	
	CBT	(73)	36	RR= 2.24 [0.22, 22.51]	N/A	78	
Quality of life	**CBT**	(31)	**52**	**SMD= 0.30 [-0.25, 0.84]**	**N/A**	**52**	**Very Low** [a d]
Psychosocial functioning GAF	**CBT**	(31)	**52**	**SMD= 0.67 [0.11, 1.23]**	**N/A**	**52**	**Very Low** [a d]
Study Discontinuation	**Total**	**3**	**322**	**RR= 1.85 [0.53, 6.43]**	**1.85 (P = 0.09); 55%**	**52-124**	**Very Low** [b d e]
	Psychoeducation	(72)	84	RR= 5.00 [1.17, 21.46]	N/A	52	
	PE vs attention control	(70)	120	RR= 9.00 [0.50, 163.58]	N/A	124	
	CBT	(31, 73)	118	RR= 0.83[0.37, 1..81]	0.10 (P = 0.66); 0%	52-78	

3. Family psychoeducation (PE) vs Treatment as usual (TAU)

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(weeks)*	*Quality (GRADE)(26)*

Depression symptoms	**PE (Service user and carers)**	**(78)**	**53**	**SMD= -0.15 [-0.69, 0.39]**	**N/A**	**60**	**Very Low** [a d e]
Mania symptoms	**PE (Service user and carers)**	**(78)**	**53**	**SMD= -0.78 [-1.34, -0.22]**	**N/A**	**60**	**Very Low** [a d e]
Hospitalisation	**PE (Service user and carers)**	**(79)**	**57**	**RR= 0.05 [0.00, 0.83]**	**N/A**	**60**	**Low** [d]
Relapse, any type	**Total**	**3**	**228**	**RR=0.52 [0.32, 0.84]**	**2.61 (P = 0.27); 23%**	**52-65**	**Low** [d e]
	PE (Service user and carers)	(78)	58	RR=0.26 [0.08, 0.83]	N/A	60	
	Group Family PE (carers)	(79, 81)	170	RR=0.61 [0.44, 0.86]	0.50 (P = 0.48); 0%	52-65	
Relapse, depression	**Group Family PE (carers)**	**(81)**	**113**	**RR= 0.73 [0.44, 1.21]**	**N/A**	**65**	**Low** [d e]
Relapse, mania	**Group Family PE (carers)**	**(81)**	**113**	**RR= 0.35 [0.15, 0.85]**	**N/A**	**65**	**Low** [d]
Relapse, mixed episode	**Group Family PE (carers)**	**(81)**	**113**	**RR= 0.20 [0.01, 4.00]**	**N/A**	**65**	**Very Low** [d e]
Response, any	**PE (Service user and carers)**	**(48)**	**59**	**RR= 0.67 [0.34, 1.32]**	**N/A**	**121**	**Very Low** [a d]
Response, mania	**PE (Service user and carers)**	**(48)**	**59**	**RR= 0.79 [0.46, 1.33]**	**N/A**	**121**	**Very Low** [a d]
Quality of life	**Group Family PE (carers)**	**2 arms of (80)**	**35**	**SMD= -0.63 [-1.44, 0.18]**	**0.22 (P = 0.64); I^2 = 0%**	**57**	**Very Low** [a d]
Psychosocial functioning GAF	**Group Family PE (carers)**	**2 arms of (80)**	**35**	**SMD= -1.03 [-1.86, -0.19]**	**0.01 (P = 0.93); I^2 = 0%**	**57**	**Very Low** [a d]
Study Discontinuation	**Group Family PE (carers)**	**(79-81)**	**217**	**RR= 1.02 [0.38, 2.74]**	**0.37 (P = 0.95); I^2 = 0%**	**31-65**	**Very Low** [d e]
4. Collaborative care vs TAU							

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**Physical health focus**	**(53)**	**65**	**SMD= -0.56 [-1.06, -0.07]**	**N/A**	**52**	**Very Low** [a d]
Mania symptoms	**Physical health focus**	**(53)**	**65**	**SMD= -0.10 [-0.59, 0.38]**	**N/A**	**52**	**Very Low** [a d]
Quality of life	**Physical health focus**	**(53)**	**65**	**SMD= -0.38 [-0.87, 0.11]**	**N/A**	**52**	**Very Low** [a d]
Study Discontinuation	**Physical health focus**	**(53)**	**68**	**RR=2.00 [0.19, 21.03]**	**N/A**	**52**	**Low** [a d]

6. Family Focused therapy (FFT) vs (active) control

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**FFT vs TAU**	**(55)**	**79**	**SMD= -0.10 [-0.56, 0.36]**	**N/A**	**52**	**Very Low** [a d]
Mania symptoms	**FFT vs TAU**	**(55)**	**79**	**SMD= -0.30 [-0.68, 0.08]**	**N/A**	**52**	**Very Low** [a d]
Relapse, any type	**FFT vs TAU**	**(55)**	**101**	**RR= 0.67 [0.34, 1.30]**	**N/A**	**52**	**Very Low** [a d]
Response, any	**FFT vs TAU**	**(48)**	**62**	**RR= 1.15 [0.68, 1.94]**	**N/A**	**121**	**Very Low** [a d]
Response, depression	**FFT vs TAU**	**(41)**	**156**	**RR= 0.48 [0.23, 0.98]**	**N/A**	**52**	**Very Low** [a d]
Response, mania	**FFT vs TAU**	**(48)**	**62**	**RR=1.15 [0.76, 1.75]**	**N/A**	**121**	**Very Low** [a d]
Hospitalisation	**FFT vs PE**	**(84)**	**38**	**RR= 0.24 [0.08, 0.74]**	**N/A**	**104**	**Very Low** [a d]
Study Discontinuation	**FFT vs TAU**	**(41, 48, 55)**	**144**	**RR= 0.63 [0.26, 1.50]**	**1.83 (P = 0.18); 45%**	**52-121**	**Low** [d]

7. Cognitive behaviour therapy (CBT) vs Active Control

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**CBT individual vs Supportive Therapy**	**(85)**	**76**	**SMD= 0.49 [0.04, 0.94]**	**N/A**	**143**	**Very Low** [d e]
Relapse, any type	**CBT individual vs Supportive Therapy**	**(85)**	**76**	**RR= 1.13 [0.81, 1.58]**	**N/A**	**143**	**Very Low** [d e]
Relapse, depression	**CBT individual vs Supportive Therapy**	**(85)**	**76**	**RR= 1.12 [0.69, 1.80]**	**N/A**	**143**	**Very Low** [d e]
Relapse, mania	**CBT individual vs Supportive Therapy**	**(85)**	**76**	**RR= 1.67 [0.96, 2.91]**	**N/A**	**143**	**Very Low** [d e]
Relapse, mixed episode	**CBT individual vs Supportive Therapy**	**(85)**	**76**	**RR= 0.33 [0.01, 7.93]**	**N/A**	**143**	**Very Low** [d e]
Study Discontinuation	**CBT individual vs Supportive Therapy**	**(85)**	**76**	**No discontinuation**	**N/A**	**143**	**-**

8. Interpersonal and social rhythm therapy (IPSRT) vs Active control

Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(week*	*Quality (GRADE)(26)*

						s)	
Response, depression	**IPRST vs TAU**	**(41)**	**192**	**RR= 0.73 [0.50, 1.07]**	**N/A**	**52**	**Very Low** [a d]
Study Discontinuation	**IPRST vs TAU**	**(41)**	**193**	**RR= 1.05 [0.67, 1.63]**	**N/A**	**52**	**Low** [d]
9. Integrated group therapy vs Active control							
Outcome	*(Sub-)analysis*	*Trials (reference)*	*N*	*ES [95% CI]*	*Heterogeneity: Chi² (p value); I²*	**Follow-up period** *(weeks)*	*Quality (GRADE)(26)*
Depression symptoms	**IGT vs group drug counselling**	**(57)**	**61**	**SMD= 0.11 [-0.39, 0.61]**	**N/A**	**26**	**Very Low** [c d e]
Mania symptoms	**IGT vs group drug counselling**	**(57)**	**61**	**SMD= -0.53 [-1.05, -0.02]**	**N/A**	**26**	**Very Low** [c d e]

a Risk of bias, b Inconsistency, c Indirectness, d Imprecision, e Publication/Reporting Bias
TAU = Treatment as usual; CBT = Cognitive behaviour therapy; PE= Psychoeducation
N/A = not applicable; SMD = Standardised mean difference ; RR = Risk Ratio;

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