Appendix Hoofdstuk 6 Psychologische en psychosociale interventies

6.4 Clinical review protocol

The review protocol summary, including the review questions, can be found in Table 1 (a complete list of review questions can be found in Appendix #; further information about the search strategy can be found in Appendix #; the full review protocols can be found in Appendix #).

Table 3: Clinical review protocol summary for the review of psychological interventions

Topic	Interventions
Review question(s)	*Mania* RQ 4.1: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for mania, hypomania, and mixed episodes; RQ 4.2: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for mania, hypomania, and mixed episodes; *Depression* RQ 4.3: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for depression; RQ 4.4: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for depression; *Long-term management* RQ 4.5: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management; RQ 4.6: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for long-term management; What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender?
Sub-question(s)	Does the effectiveness of treatment vary:

	1. For RQ 6.4 to RQ 6.11: For people taking a mood stabiliser (e.g. lithium or valproate) and people not taking a mood stabiliser; 2. For RQ 6.12 to RQ 6.15: For people whose most-recent episode was depressive and people whose most-recent episode was manic; 3. For people with Bipolar I and Bipolar II; 4. For adults (18 to 64) and older adults (65+).
Objectives	To estimate the efficacy of interventions to treat depression.
Criteria for considering studies for the review	
• Intervention	RQ 4.1 to RQ 4.6: All psychological and psychosocial interventions (e.g. cognitive behavioural therapy), all combined psychological with (licensed) pharmacological interventions.
• Comparator	Wait-list, placebo, and other interventions.
• Types of participants	Adults (18+) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	FOR PEOPLE IN AN ACUTE EPISODE 1) Change in symptoms of depression 2) Change in symptoms of mania 3) Response (50% reduction or greater) 4) Discontinuation 5) Quality of life 6) Psychosocial functioning FOR PEOPLE WHO ARE EUTHYMIC AT BASELINE 1) Relapse 2) Discontinuation 3) Hospitalisation 4) Quality of life 5) Psychosocial functioning
• Time	The main analysis will include outcomes at the end of treatment. For interventions the GDG considers recommending based on post-treatment results, additional analyses will be conducted for further follow-up data.
• Study design	RCTs and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Study setting	Primary, secondary, tertiary, health and social care

Note. RCT = Randomised controlled trial.

6.4.1 Studies considered[2]

Fifty-five trials of psychological and psychosocial interventions met the inclusion criteria for this review: BALL2006 (Ball et al., 2006), BARROS2012 (De Barros Pellegrinelli et al., 2012; De Barros Pellegrinelli et al., 2013), BAUER2006a (Bauer et al., 2006a; Bauer et al., 2006b), BERNHARD2009 (Bernhard, 2009), BORDBAR2009 (Bordbar, 2009), CASTLE2010 (Castle et al., 2007; Castle et al., 2010), CLARKIN1998 (Clarkin et al., 1998), COCHRAN1984 (Cochran, 1984), COLOM2003a (Colom et al., 2003b), COLOM2003b (Colom et al., 2003a; Colom et al., 2009; Miklowitz, 2009), COSTA2012 (Costa et al., 2012), DIJK2013 (Van Dijk et al., 2013), DOGAN2003 (Dogan & Sabanciogullari, 2003), DSOUZA2010 (D'Souza et al., 2010), EKER2012 (Eker & Harkin, 2012), FAGIOLINI2009 (Fagiolini et al., 2009; Kupfer et al., 2009),

FRANK1999a (Frank et al., 2005; Frank et al., 1999), GENT1991 (van Gent & Zwart, 1991), GLICK1993 (Clarkin et al., 1990; Glick et al., 1991; Glick et al., 1993; Glick et al., 1985; Glick et al., 1990; Haas et al., 1988; Spencer et al., 1988), GOMES2011 (Gomes et al., 2011), JAVADPOUR2013 (Javadpour et al., 2013), JONES2013 (Jones et al., 2013),

KESSING2013 (Kessing et al., 2013), KILBOURNE2008 (Kilbourne et al., 2008), KILBOURNE2012 (Kilbourne et al., 2012), LAHERA2013 (Lahera et al., 2013), LAM2000 (Lam et al., 2000), LAM2003 (Lam et al., 2005; Lam et al., 2003), LOBBAN2010 (Lobban et al., 2010), MADIGAN2012 (Madigan et al., 2012), MEYER2012 (Meyer & Hautzinger, 2012), MIKLOWITZ2000 (Miklowitz et al., 2003; Miklowitz et al., 2000; Richards & Miklowitz, 2002), MIKLOWITZ2007b (Miklowitz et al., 2007a; Miklowitz et al., 2007b), MILLER2004 (Miller et al., 2004; Solomon et al., 2008; Uebelacker et al., 2006), PARIKH2012 (Parikh et al., 2012), PERICH2013 (Perich et al., 2013), PERLICK2010 (Perlick et al., 2010), PERRY1999 (Perry et al., 1999), PROUDFOOT2012 (Proudfoot et al., 2012), REA2003 (Rea et al., 2003), REINARES2008 (Reinares et al., 2008; Reinares et al., 2004), SAJATOVIC2009 (Sajatovic et al., 2009), SCHMITZ2002 (Schmitz et al., 2002), SCHWANNAUER2007 (Schwannauer, 2007), SCOTT2001 (Scott et al., 2001), SCOTT2006 (Lam, 2006; Scott et al., 2006), SIMON2005 (Simon et al., 2005), SMITH2011 (Smith et al., 2011), SWARTZ2012 (Swartz et al., 2012), TODD2012 (Todd et al., 2012), TORRENT2013 (Torrent et al., 2013), WEISS2007 (Weiss et al., 2007), WEISS2009 (Weiss et al., 2009), WILLIAMS2008 (Williams et al., 2008), ZARETSKY2008 (Zaretsky et al., 2008). 47 trials

[2]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

A further five trials were excluded; three because a minority of participants had bipolar disorder and it was not possible to obtain disaggregated data: JACKSON2008 (Jackson et al., 2008), PICKETTSCHENK2008 (Pickett-Schenk et al., 2008) and STARING2010 (Staring et al., 2010); one because on closer inspection it did not appear to be randomised: COSTA2011 (Costa et al., 2011); and one because the GDG determined it was not relevant to the UK: DASHTBOZORGI2009 (Dashtbozorgi et al., 2009).

Two ongoing studies were also identified: PRASKO2013 (Prasko et al., 2013) and GINDRE2009 (Gindre et al., 2009).

Of the 55 included studies, four were unpublished (BERNHARD2009, TODD2012, JONES2013, SCHWANNAUER2007) and the other 51 were published between 1984 and 2013. Seven were not included in the meta-analysis because the authors did not report useable outcomes, which remained unavailable after contacting authors: CLARKIN1998, BARROS2012, EKER2012, FAGIOLINI2009, GLICK1993, PARIKH2012, and WEISS2007.

Study characteristics

Included studies randomised 6,010 participants, ranging from 19 to 441 per study (a summary of study characteristics can be found in Appendix 18). Studies were conducted in North America (k = 22), England and Ireland (k = 12), Europe (k = 11), Australia (k = 5), Brazil (k = 3), and Iran (k = 2). Participants were recruited from an outpatient (k = 23) or inpatient setting (k = 12), GP practice (k = 2), community mental health team (k = 2), or via advertising combined with referral (k = 16). In 52 studies a diagnostic interview was used to establish the presence of a bipolar disorder, in one study participants themselves reported if they had a bipolar disorder, another confirmed the diagnosis through a mood questionnaire, while one study only reported that bipolar disorder was an inclusion criteria.

The median of mean age of participants was 40 years (range of 26 to 55 years), 58% were female and 81% had bipolar I disorder. Four studies included participants in a depressed episode at baseline (MIKLOWITZ2007b, SCHMITZ2002, SWARTZ2012, DIJK2013), six studies had a mix of participants in depressed or manic episode (BAUER2006a, CLARKIN1998, FRANK1999a, GLICK1993, MILLER2004, SAJATOVIC2009) and 32 studies included euthymic participants. Twelve studies (FAGIOLINI2009, KILBOURNE2012, KILBOURNE2008, MIKLOWITZ2000, PERLICK2010, PROUDFOOT2012, SCOTT2001, SCOTT2006, SIMON2005, TODD2012, WEISS2009, WEISS2007) included a mix of euthymic and symptomatic participants at baseline, while two (PROUDFOOT2012, TODD2012) provided disaggregated data.

6.4.2 Clinical evidence for psychological interventions

Evidence from each important outcome and overall quality of evidence are presented in Appendices 20 and 21.

Risk of bias

No trials were at high risk of bias for sequence generation (not truly random), however, the method of randomisation was unclear (not reported) in 15 trials. Allocation concealment was unclear in 25 trials and low risk in 30 trials. All trials were at high risk of bias for blinding for participants and providers per se. Nine trials had no assessors and 31 reporting assessor-rated outcomes used a blind assessor and were at low risk of bias for blinding, but eight studies did not have blind assessors, which was a reason for a high risk of bias. For six studies, blinding of assessors remained unclear. For incomplete outcome data, almost half (k = 25) of the trials were at low risk of bias and the other half (k = 23) were at high risk of bias because of the high amount of dropouts or because dropouts were excluded from the analyses.

There was a risk of outcome reporting bias in 22 trials. 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. Risk of publication bias could not be assessed by means of funnel plots because of the small number of studies per intervention.

Overall quality of the evidence

Most evidence was of low or very low quality. Nearly all results were downgraded at least one level owing to imprecision because the analyses included few participants or events, and/or the boundaries of the confidence interval (CI) crossed the decision-making threshold. Also, risk of bias in studies and reporting bias had a negative influence on some of the outcomes. Some outcomes were also downgraded for inconsistency when there was evidence of statistical heterogeneity.

Post-treatment data were mostly of low to very low quality. Only relapse data on individual interventions, hospitalisation data on collaborative care and discontinuation on interpersonal and social rhythm therapy were of moderate quality.

Studies also reported controlled comparisons at follow-up, but most outcomes were of very low quality, except for most hospitalisation and relapse outcomes with regards to the comparisons of individual and group psychological interventions, and family psychoeducation with treatment as usual.

Effects of interventions

Across nine comparisons, results of the meta-analyses suggest that psychological interventions may be associated with symptomatic improvement, reduced relapse and hospitalisation. The majority of these moderate to low quality outcomes are summarised per comparison and presented in Table 2 (post-treatment) and

Table 3 (follow-up), and additional outcomes are presented in Appendix #. Reasons for downgrading are given per outcome in the tables.[3]

Individual psychological interventions

The search identified RCTs of face-to-face psychoeducation and interactive online psychoeducation (DOGAN2003, JAVADPOUR2013, LOBBAN2010, PERRY1999, PROUDFOOT2012, SMITH2011, TODD2012), CBT (BALL2006, JONES2013, LAM2000, LAM2003, MIKLOWITZ2007b, SCOTT2001, SCOTT2006, ZARETSKY2008) and medication adherence therapy (COCHRAN1984). Eleven trials started with euthymic participants at baseline, and four had a mix of participants in an acute episode and euthymic (PROUDFOOT2012, SCOTT2001, SCOTT2006, TODD2012).

At post-treatment, seven trials (N = 637) reported low quality evidence that individual psychological interventions when compared with treatment as usual, produced a small effect in symptoms of depression (see Table 2). Six trials (N = 365) reported moderate quality evidence that individual psychological interventions reduced the risk of relapse. One trial with few events was inconclusive regarding the risk of hospitalisation.

At follow-up, seven trials (N = 446) reported moderate quality evidence that individual psychological interventions were associated with a long-term reduction in the risk of relapse (see Table 3). In three studies (N = 214) there was a reduction in the risk of hospitalisations, but the estimate was imprecise.

One study (N = 76) compared individual CBT with supportive therapy for depression (MEYER2012). At follow-up, there was very low quality evidence favouring supportive therapy for symptoms, but the effect on relapse was not conclusive (see Table 3).

Group psychological interventions

The search identified trials of group interventions including psychoeducation, (CASTLE2010, COLOM2003A, COLOM2003B, SAJATOVIC2009, TORRENT2013) CBT (BERNHARD2009, COSTA2012, GOMES2011), mindfulness (PERICH2013, WILLIAMS2008), social cognition and interaction training (LAHERA2013), and dialectical behaviour therapy (DIJK2013). Interventions were compared with treatment as usual, except for two studies that compared psychoeducation with attention control (COLOM2003A, COLOM2003B). In ten trials, participants were

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

euthymic at baseline (BERNHARD2009, CASTLE2010, COLOM2003A, COLOM2003B, COSTA2012, GOMES2011, LAHERA2013, PERICH2013, TORRENT2013, WILLIAMS2008) and two studies included participants experiencing an acute episode (SAJATOVIC2009, DIJK2013).

Eight trials (N = 423) reported very low quality evidence of a small effect on depression outcomes (see Table 2). Furthermore, the two studies comparing psychoeducation with attention control (N = 170) found a reduction in depression and mania relapses. In three trials (N = 205) the effect estimate on the number of hospitalisation was very imprecise.

Long-term results in five studies (N = 333) reported low quality evidence of a reduction in depression relapses (Table 3). Also, four studies (N = 274) reported a reduction of relapses into mixed episodes. However, the effect on depression symptoms and hospitalisation was inconclusive.

Family psychoeducation

Two trials included an intervention on psychoeducation for service users and their family members (DSOUZA2010, MILLER2004) and in five trials psychoeducation was only for family members (BORDBAR2009, MADIGAN2012, PERLICK2010, REINARES2008, GENT1991). Five trials started with euthymic participants at baseline (BORDBAR2009, DSOUZA2010, MADIGAN2012, REINARES2008, GENT1991), one trial had a mix of participants in an acute episode and euthymic (PERLICK2010) and another included only participants in an acute episode (MILLER2004).

In comparison with treatment as usual, one trial (N = 43) found low quality evidence of medium effect in depression symptoms favouring family psychoeducation at post-treatment (see Table 2).

At follow-up, three trials (N = 228) reported low quality evidence of a reduction in the risk of relapse (see Table 3). One trial (N = 113) reported a reduction in the risk of mania relapses, but the effect on depression relapses was inconclusive. One study (N = 57) reported a very large effect on reduction of the number of hospitalisations, but effect estimates were imprecise with only nine events in the study.

Family-focused therapy

Trials of family-focused therapy included participants who were euthymic (REA2003), either in an acute episode and euthymic (MIKLOWITZ2000), only depressed (MIKLOWITZ2007b) or in any type of episode (MILLER2004).

Post-treatment data were of low quality. One study (N = 79) found a medium effect favouring family-focused therapy when compared with treatment as usual on depression symptoms (see Table 2). Furthermore, a study (N = 53)

comparing family-focused therapy with psychoeducation found little difference with regard to relapse, but the estimate was imprecise.

The follow-up evidence was of very low quality and found little difference in effects on depression symptoms, relapse and response, but the estimates were imprecise (see Table 3). The evidence suggested family-focused therapy reduced the risk of hospitalisation.

Interpersonal and social rhythm therapy

There were three trials of interpersonal and social rhythm therapy with participants in an acute episode at baseline (FRANK1999a, MIKLOWITZ2007b, SWARTZ2012). At post-treatment, very low quality from one study was inconclusive with regard to symptoms of depression, relapse and response (see Table 2). At follow-up, one trial (N = 41) reported that interpersonal and social rhythm therapy reduced the risk of relapse, but the results were imprecise (see Table 3).

Collaborative care

Two trials of collaborative care started with euthymic participants (BAUER2006a, KESSING2013) and three trials recruited participants in an acute episode (KILBOURNE2012, KILBOURNE2008, SIMON2005).

In comparison with treatment as usual, two trials (N = 123) reported low quality evidence of a small effect favouring collaborative care in depression and mania symptoms at post-treatment, but the effect estimate was imprecise (see Table 2). One trial (N = 234) found no difference in the risk of relapse. However, two trials (N = 572) reported moderate quality evidence suggesting collaborative care reduced the risk of hospitalisation at post-treatment. At follow-up, there was very low quality evidence from one trial suggesting a medium effect favouring collaborative care on symptoms of depression (see Table 3).

Integrated group therapy and group drug counselling

One study (N = 61) included euthymic or depressed participants and compared integrated group therapy with group drug counselling (WEISS2009). Based on very low quality evidence, there was no conclusive evidence of difference between groups at post-treatment (see Table 2) or follow-up (see Table 3).

Integrated cognitive and interpersonal therapy

One trial compared a group of participants that were randomised to integrated cognitive and interpersonal therapy or treatment as usual (SCHWANNAUER2007). 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 of a medium effect favouring the intervention on depression symptoms at post-treatment (see Table 2).

Table 4: Outcomes at post-treatment

Outcome	Effect size (95% CI)	Heterogeneity: Chi² (p value); I²	Time (weeks)	Quality (GRADE)
1. Individual psychological intervention versus treatment as usual (TAU)				
Depression symptoms	SMD = -0.23 (-0.41, -0.05)	8.55 (P = 0.29); 18%	6-26	Low a e
Hospitalisation	RR = 0.14 (0.01, 2.53)	N/A	6	Low d e
Relapse	RR = 0.66 (0.48, 0.92)	2.50 (P = 0.78); 0%	6-26	Moderate d
Response	RR = 0.71 (0.46, 1.07)	N/A	26	Very Low d e
2. Group psychological intervention versus TAU				
Depression symptoms	SMD = -0.24 (-0.64, 0.16)	25.65 (P = 0.0006); 73%	8-52	Very Low a b d e
Hospitalisation	RR = 0.45 (0.10, 2.09)	3.94 (P = 0.14); 49%	14-21	Low d
Relapse (any)	RR = 0.48 (0.22, 1.04)	2.42 (P = 0.12); 59%	21	Low d
Relapse (depression)	RR = 0.39 (0.19, 0.78)	0.45 (P = 0.50); 0%	21	Low d
Relapse (mania)	RR = 0.48 (0.28, 0.82)	0.80 (P = 0.37); 0%	21	Low d
3. Family psychoeducation versus TAU				
Depression symptoms	SMD = -0.73 (-1.35, -0.10)	N/A	14	Low d e

4. Family -focused therapy versus control				
Depression symptoms	SMD = -0.40 (-0.80, 0.00)	N/A	39	Low a d
Relapse	RR = 0.89 (0.52, 1.54)	N/A	39	Low d
Hospitalisation	RR = 0.71 (0.33, 1.52)	N/A	39	Low d
5. CBT versus active control				
Depression symptoms	SMD = 0.41 (0.12, 0.70)	N/A	39	Low d e
Relapse	RR = 0.60 (0.34, 1.05)	N/A	39	Low d e
6. Interpersonal and social rhythm therapy versus active control				
Depression symptoms	SMD = 0.44 (-0.34, 1.22)	N/A	12	Very Low a d
Relapse	RR = 1.55 (0.63, 3.84)	N/A	123	Very Low a d
Response	RR = 0.98 (0.60, 1.60)	N/A	12	Very Low a d
7. Collaborative care versus TAU				
Depression symptoms	SMD = -0.22 (-0.63, 0.19)	1.32 (P = 0.25); 24%	26-30	Low a d e
Hospitalisation	RR = 0.68 (0.49, 0.94)	0.13 (P = 0.72); 0%	52-130	Moderate d
Relapse	RR = 0.99 (0.84, 1.17)	N/A	52	Lowd e
8. Integrated group therapy versus drug counselling (group)				
Depression symptoms	SMD = -0.35 (-0.85, 0.16)	N/A	12	Very Low c d e

9. Integrated cognitive and interpersonal therapy versus TAU				
Depression symptoms	SMD = -0.64 (-1.19, -0.09)	N/A	20	Low d
a Risk of bias, b Inconsistency, c Indirectness, d Imprecision, e Publication/Reporting Bias)				

Table 5: Outcomes at follow-up

Outcome	Effect size (95% CI)	Heterogeneity: Chi² (p value); I²	Time (weeks)	Quality (GRADE)
1. Individual psychological intervention versus TAU				
Depression symptoms	SMD = -0.21 (-0.43, 0.01)	6.85 (P = 0.23); 27%	26-52	Low a d
Hospitalisation	RR = 0.63 (0.38, 1.02)	2.19 (P = 0.35); 9%	32-52	Low d
Relapse	RR = 0.74 (0.63, 0.87)	5.78 (P = 0.57); 0%	32-78	Moderate d
Response	RR = 0.46 (0.21, 1.02)	N/A	52	Very Low a d e
2. Group psychological intervention versus TAU				
Depression symptoms	SMD = 0.22 (-0.05, 0.49)	0.95 (P = 0.62); 0%	52-61	Very Low a d e
Hospitalisation	RR = 0.48 (0.16, 1.45)	2.30 (P = 0.13); 56%	78-124	Very Low b d e
Relapse (any)	RR = 0.86 (0.61, 1.20)	21.46 (P = 0.0003); 81%	52-124	Very Low b d e
Relapse (depression)	RR = 0.62 (0.45, 0.88)	7.12 (P = 0.13); 44%	52-124	Low b d
Relapse (mixed episode)	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	SMD = -0.15 (-0.69, 0.39)	N/A	60	Very Low a d e
Hospitalisation	RR = 0.05 (0.00, 0.83)	N/A	60	Low d
Relapse (any)	RR = 0.52 (0.32, 0.84)	2.61 (P = 0.27); 23%	52-65	Low d e
Relapse (depression)	RR = 0.73 (0.44, 1.21)	N/A	65	Low d e
Relapse (mania)	RR = 0.35 (0.15, 0.85)	N/A	65	Low d
Response	RR = 0.67 (0.34, 1.32)	N/A	121	Very Low a d e
4. Family-focused therapy versus (active) control				
Depression symptoms	SMD = -0.10 (-0.56, 0.36)	N/A	52	Very Low a d e
Relapse	RR = 0.67 (0.34, 1.30)	N/A	52	Very Low a d e
Response	RR = 1.15 (0.68, 1.94)	N/A	121	Very Low a d e
Hospitalisation	RR = 0.24 (0.08, 0.74)	N/A	104	Very Low a d
5. CBT versus supportive therapy				
Depression symptoms	SMD = 0.49 (0.04, 0.94)	N/A	143	Very Low d e
Relapse	RR = 1.13 (0.81, 1.58)	N/A	143	Very Low d e
6. Interpersonal and social rhythm therapy versus active control				
Response (depression)	RR = 0.73 (0.50, 1.07)	N/A	52	Very Low a d e

7. Collaborative care versus TAU				
Depression symptoms	SMD = -0.56 (-1.06, -0.07)	N/A	52	Very Low a d
8. Integrated group therapy versus drug counselling (group)				
Depression symptoms	SMD = 0.11 (-0.39, 0.61)	N/A	26	Very Low c d e
a Risk of bias, b Inconsistency, c Indirectness, d Imprecision, e Publication/Reporting Bias)				

6.4.3 Clinical evidence summary

Evidence suggests that psychological interventions may improve symptoms and reduce the risk of relapse and hospitalisation for people with bipolar depression, though the evidence for particular psychological interventions varies in quality. There is better evidence that individual psychological interventions and collaborative care may be effective. Group interventions, integrated cognitive and interpersonal therapy and psychoeducation for families showed promising results. There is no evidence that interpersonal and social rhythm therapy was superior to no intervention or to other interventions. Interventions appeared to be well tolerated, and there was no evidence of harm.