Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults with a diagnosis of bipolar disorder, how effective is medication combined with focused psychotherapy or cognitive behavioural therapy (CBT), compared to medication alone, in reducing relapse?

Clarification of question using PICO structure

Patients: Adults with a diagnosis of bipolar disorder
Intervention: Medication combined with focused psychotherapy or CBT
Comparator: Medication alone
Outcome: Reducing relapse

Clinical and research implications

Evidence from three randomised controlled trials (RCTs) indicates that various psychological interventions (including cognitive behavioural therapy (CBT), family-focussed therapy (FFT) and interpersonal and social-rhythm therapy), when used in combination with pharmacotherapy to treat patients with bipolar disorder, are likely to result in fewer relapses/hospitalisations than pharmacotherapy alone. One of these RCTs, reported a reduction in hospitalisations for patients with refractory bipolar disorder who were treated with a combination of psychoeducational intervention, CBT and pharmacotherapy, compared to those who were treated with pharmacotherapy alone. All studies in this evidence summary reported results which indicated improvements in symptoms and/or function in patients with bipolar disorder who were treated with psychological interventions combined with pharmacotherapy compared to those who were treated with pharmacotherapy alone. These results are likely to be reliable, but further larger RCTs would be useful to confirm findings and to explore which psychological therapies are likely to be most effective.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified four RCTs, published in five articles, which compared psychological interventions combined with pharmacotherapy to pharmacotherapy alone and were considered relevant to this evidence summary.[1,2,3,4,5] All studies included only participants meeting DSM criteria for bipolar disorder, and one study focused specifically on patients with refractory bipolar disorder.[4] Studies assessed a variety of psychological interventions, including, where specified, group cognitive behavioural therapy (CBT),[2,3,5] family-focused therapy,[1,2,3] and interpersonal and social-rhythm therapy.[2,3] Pharmacological interventions varied, were generally at the discretion of treating clinicians and were not reported in detail. Three studies, reported in four articles, provided data relating to relapse rates,[1,2,3,4] and all studies reported data on symptoms (e.g. depression and mania scales).

Main Findings

One RCT compared family-focussed therapy (FFT) combined with mood stabilisers to mood stabilisers alone and found that the FFT group experienced significantly fewer relapses during two years of follow-up (11/31 (35%) vs. 38/70 (54%), $p < 0.05$).[1] The mean duration of remission was also longer in the FFT group (73.5±28.8 weeks) than in the CM group (53.2±39.6 weeks), HR 0.38 (95% CI: 0.20 to 0.75).[1] This trial also reported improvements in symptom scores (SADS-C) and medication adherence.[1] A second RCT, by the same group, compared psychological interventions (FFT, CBT, or interpersonal and social-rhythm therapy) combined with pharmacotherapy to pharmacotherapy alone and found that participants in the psychological intervention group had significantly higher 12 month recovery rates that those in the control group (64.4% vs. 51.5%); participants in the intensive psychotherapy groups also had shorter times to recovery, HR 1.47 (95% CI: 1.08 to 2.00).[2,3] Patients in intensive psychotherapy were 1.58 (95% CI: 1.17 to 2.13) times more likely to be clinically well during any study month than those in collaborative care.[2,3] There were no statistically significant differences in treatment effects between any of the three intensive psychotherapies.[2,3] This study also reported an improvement in functional outcomes (LIFE-RIFT), at 9 months, for patients in the psychological intervention group compared to the control group.[2,3] The third RCT assessing relapse outcomes was conducted in patients with refractory bipolar disorder and compared a psychoeducational intervention with CBT and pharmacotherapy to pharmacotherapy alone; patients in the psychological intervention group had significantly fewer hospitalisations at 12 months follow-up than those treated with pharmacotherapy alone.[4] This study also reported significantly greater improvements in anxiety (STAI-S), depression (BDI), mania (YMS) and inadaptation score in the psychological intervention group compared to the group treated with pharmacotherapy alone.[4] The final RCT compared group CBT combined with pharmacotherapy to pharmacotherapy alone over 14 weeks.[5] This trial reported significant symptom improvements in the CBT group and no significant changes in the pharmacotherapy only group, however, no between group comparison statistics were reported.[5]

Authors Conclusions

All four of the RCTs included in this evidence summary concluded that the various psychotherapy or CBT interventions assessed, in combination with pharmacotherapy, were more effective than pharmacotherapy alone in treating patients with bipolar disorder.

Reliability of conclusions/Strength of evidence

One high quality RCT[1] and two further RCTs of moderate quality, with some weaknesses in reporting,[2,3,4] provided data indicating that various psychological interventions (including CBT, FFT and interpersonal and social-rhythm therapy), when used in combination with pharmacotherapy to treat patients with bipolar disorder, are likely to result in fewer relapses/hospitalisations than pharmacotherapy alone. One, moderate quality RCT, reported a reduction in hospitalisations for patients with refractory bipolar disorder who were treated with a combination of psychoeducational intervention, CBT and pharmacotherapy, compared to those who were treated with pharmacotherapy alone.[4] All studies in this evidence summary, including one additional small, poor quality RCT,[5] reported results which indicated improvements in symptoms and/or function in patients with bipolar disorder who were treated with psychological interventions combined with pharmacotherapy compared to those who were treated with pharmacotherapy alone. These results are likely to be reliable, but further larger RCts would be useful to confirm findings and to explore which psychological therapies are likely to be most effective.

What do guidelines say?

NICE (2006) Guidelines discuss combining medication with psychotherapeutic interventions only in reference to pregnant women with a bipolar diagnosis;

"For mild depressive symptoms in pregnant women with bipolar disorder the following should be considered:

- self-help approaches such as guided self-help and computerised CBT
- brief psychological interventions
- antidepressant medication.

For moderate to severe depressive symptoms in pregnant women with bipolar disorder the following should be considered:

- psychological treatment (CBT) for moderate depression
- combined medication and structured psychological interventions for severe depression."

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SIGN (2006) states the following in relation to bipolar affective disorder;

"Evidence based psychosocial interventions should be available to patients in addition to pharmacological maintenance treatment, especially if complete or continued remission cannot be achieved."
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The evidence presented in this summary does not contradict current guidance, but would appear to offer more support for the combined use of psychological interventions and pharmacotherapy than is indicated by current NICE guidance.

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Date answer completed: 02/09/2013

References

Guidelines

National Institute for Health and Care Excellence (2006)Bipolar Disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. CG38. London: National Institute for Health and Care Excellence.
http://www.nice.org.uk/nicemedia/live/10990/30193/30193.pdf

Scottish Intercollegiate Guideline Network (2005) Bipolar Affective Disorder. A National Clinical Guideline. CG82. Edinburgh: Scottish Intercollegiate Guideline Network.
http://www.sign.ac.uk/pdf/sign82.pdf

RCTs

1. Miklowitz, D. J., George, E.L., Richards, J.A., Simoneau, T.L. and Suddath, R.L. (2003). "A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder." *Archives of General Psychiatry 60*(**9**) pp. 904-912.

2. Miklowitz, D. J., Otto, M.W., Frank, E., Reilly-Harrington, N.A., Kogan, J.N., Sachs, G.S., Thase, M.E., Calabrese, J.R., Marangell, L.B., Ostacher, M.J., Patel, J., Thomas, M.R., Araga, M., Gonzalez, J.M. and Wisniewski, S.R. (2007a). "Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial." *American Journal of Psychiatry 164*(**9**) pp. 1340-1347.

3. Miklowitz, D. J., Otto, M.W., Frank, E., Reilly-Harrington, N.A., Wisniewski, S.R., Kogan, J.N., Nierenberg, A.A., Calabrese, J.R., Marangell, L.B., Gyulai, L., Araga, M., Gonzalez, J.M., Shirley, E.R., Thase, M.E., Sachs, G.S. (2007b). "Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program." *Archives of General Psychiatry 64*(**4**) pp. 419-426.

4. Isasi, A. G., Echeburua, E., Liminana, J.M. and Gonzalez-Pinto, A. (2010). "How effective is a psychological intervention program for patients with refractory bipolar disorder? A randomized controlled trial." *Journal of Affective Disorders 126*(**1-2**) pp. 80-87.

5. Costa, R. T., Cheniaux, E., Rosaes, P.A.L., de Carvalho, M.R., da Rocha Freire, R.C., Versiani, M., Range, B.P. and Nardi, A.E. (2011). "The effectiveness of cognitive behavioral group therapy in treating bipolar disorder: a randomized controlled study." *Revista Brasileira de Psiquiatria 33*(**2**) pp. 144-149.

Results

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Miklowitz et al. (2003)	*Participants*: Adults (18-65 years) recruited from consecutively screened inpatients and outpatients whose medical recorders indicated a working diagnosis of bipolar disorder; DSM-II-R criteria for bipolar disorder (manic, mixed or depressed episode) within the past three months; no evidence of developmental disability or neurologic disorder; no alcohol or substance use disorders within previous six months; living with, or minimum 4 hrs per week contact with , a care giving family member; English speaking; willingness to take mood-stabilising or anti-psychotic medications. *Intervention*: Family-focussed, home-based therapy (FFT); involved all available family members (spouses, parents, siblings). Administered in 21 one-hour sessions (12 weeks, 6 bi-weekly then 3 monthly) in 3 modules; psychoeducation, communication enhancement training, problem solving skills training.) Duration of intervention 9 months. *Comparator*: Crisis management; CM was	N = 101 (FFT + medication n=31, CM + medication n=70).	This study aimed to compare the effects of family-focused therapy (FFT), in addition to mood stabilisers, with a less intensive psychoeducational crisis management intervention (CM) plus mood stabilisers, for achieving sustained remission and reduced mood symptoms. Eighty two participants were recruited in hospital and 19 were outpatients. The mean age of study participants was 35.6±10.2 years, and 63% were female. There were no significant differences between the FFT and CM groups with respect to ethnicity, family composition, education, socioeconomic status, age at onset of illness, duration and nature (e.g. previous episodes and hospitalisations), or mean affective symptom score at baseline. Pharmacotherapy dosage and frequency of clinic visits could be adjusted, for all participants, at the discretion of clinicians. Relapse: Significantly fewer participants in the FFT group than in the CM group experienced relapse during the two year follow-up (11/31 (35%) vs. 38/70 (54%), $p < 0.05$). The mean duration of remission was also longer in the FFT group (73.5±28.8	Randomisation was via a random number table, using a 1:2 allocation (determined a priori because it was estimated that more participants would be eligible than could be accommodated in the FFT programme). The randomisation sequence was concealed until group assignments

	designed to emulate standard community care. A “treatment as usual” condition with the addition of a limited amount of family education (two home-based sessions of one hour, within the first two months). Over the 9-month treatment interval, project clinicians offered CM patients emergency counselling sessions as needed, typically when suicidal crises or severe family conflicts erupted. At minimum, clinicians telephoned each CM patient monthly to monitor his or her status. *Outcomes*: Expressed emotion (Camberwell Family Interview, Vaughn and Leff 1976), symptomatic outcome and medication compliance (Schedule for Affective Disorders and Schizophrenia, change version, SADS-C Spitzer and Endicott 1978). Outcomes were assessed at 3, 6 and 9 months (during the study) and post-treatment, at 12, 18 and 24 months.		weeks) than in the CM group (53.2±39.6 weeks), HR 0.38 (95% CI: 0.20 to 0.75). Other outcomes: The article also reported that patients in the FT group had better medication adherence and, though symptom scores improved significantly in both groups over 24 months, patients in the FFT group stabilised at lower levels of symptom severity after six months.	had been made. The nature of the intervention precludes blinding of participants and therapists, but outcome assessments were carries out by independent researchers. Data were reported for all specified outcomes. Time to relapse was calculated from study entry and all patients who did not relapse were included in the at-risk

				sample up to their final study assessment. Survival curves fro relapse were calculated using an intension-to-treat sample and compared using Kaplan-Meier product-limit formula.
Miklowitz et al. (2007a and 2007b)	*Participants*: Inclusion criteria: age ≥18 years; DSM-IV criteria for bipolar I or II disorder with a current major depressive episode; concurrently treated with a mood stabilizer or willing to initiate mood stabilizer treatment; not being treated with psychotherapy, or willing to discontinue psychotherapy or taper sessions to ≤1 per month; English speaking. Exclusion criteria: DSM-IV substance misuse disorders (excluding nicotine), which required immediate treatment; pregnancy or planning pregnancy in the next year (randomized acute depression	N = 293 randomised (N = 152 with baseline LIFE-RIFT score were included in the article reporting 9 month data functional outcomes (Miklowitz 2007a) and	This study aimed to assess the effects of intensive psychosocial treatment plus pharmacotherapy on the functional outcomes, time to recovery and likelihood of remaining well of patients with bipolar disorder, following a depressive episode. Study participants included participants in a pharmacotherapy trial (n=236) who had been randomised to bupropion or paroxetine and were willing to be further randomised to psychosocial treatment. A further 57 participants, not eligible for the pharmacotherapy trial, were included in this study; these participants continued to receive pharmacotherapy treatment in accordance with clinician-patient agreement and best practice guidelines.	A stratified randomisation procedure was used; participants were allocated 60:40 to intensive psychosocial intervention or collaborative care with each stratum. No details of

	study only); history of intolerance, non-response or contraindication to paroxetine or bupropion; requiring initiating or changing the dose of an antipsychotic medication (randomized acute depression study only). *Intervention*: Psychosocial intervention - 30 one hour sessions over 9 months (interpersonal and social rhythm therapy, CBT or family-focussed therapy). *Comparator*: Collaborative care; Patients received a self-care workbook and an educational videotape, which included information about the diagnosis, course, treatment, and self-management of bipolar disorder. The three, one hour, collaborative care sessions, conducted over six weeks, focused on implementing self-management tools (e.g., mood and sleep monitoring) and developing an individualized relapse prevention plan. *Outcomes*: Level of depression (Montgonery-Asberg Depression Rating Scale and LIFE-RIFT), time to recovery and number of participants classified as well during each of 12 months.	all 293 were included in the article reporting 12 data on time to recovery and likelihood of remaining well (Miklowitz 2007b))	There were no significant differences between the intensive psychosocial treatment and collaborative care groups, on any demographic, diagnostic, illness history, or current clinical state characteristic, or on the proportion of patients being treated with lithium, divalproex sodium, carbamazepine, lamotrigine, atypical/typical antipsychotics, antidepressants, or anxiolytics. There were also no differences the groups on baseline LIFE-RIFT total scores and scores on relationship, satisfaction, work, or recreation. Each of the study sites chose to administer one type of intensive psychotherapy (e.g., CBT) based on its preferences and clinical expertise. A second modality (e.g., interpersonal and social rhythm therapy) was randomly assigned to the site. Of the 15 sites, 10 offered CBT, nine offered family-focused therapy, and 11 offered interpersonal and social rhythm therapy. Relapse (follow-up 12 month recovery outcomes): Participants in the intensive psychotherapy group had significantly higher 12 month recovery rates that those in the collaborative care group (64.4% vs. 51.5%); participants in the intensive psychotherapy groups also had shorter times to recovery, HR 1.47 (95% CI: 1.08 to 2.00), p=0.01. Patients in intensive psychotherapy were 1.58 (95% CI: 1.17 to 2.13) times more likely to be clinically well during any study month than those in collaborative care (p=003). There were no statistically significant differences in treatment effects between any of the three intensive psychotherapies. Other outcomes (on study 9 month functional outcomes): Participants in intensive psychotherapy had significantly better LIFE-RIFT total score (F=4.32, df=1, 135, p=0.04),	allocation concealment were reported. The nature of the intervention precludes blinding of participants and therapists, but outcome assessments were carries out by independent researchers. Data were reported for all specified outcomes. Anlyses were intention-to-treat.

			relationship functioning scores (F=5.26, df=1, 141, p=0.02), and life satisfaction scores (F=3.98, df=1, 140, p=0.048) over 9 months than patients in collaborative care group; these treatment effects were apparent for all types of psychotherapy intervention (CBT, family-focussed therapy and interpersonal and social rhythm therapy). No effects of psychosocial intervention were observed on work/role functioning or recreation scores.	
Isasi et al. (2010)	*Participants*: Participants recruited at The Centre of Mental Health in Las Palmas. All patients were under pharmacological treatment mainly consisting of a mood stabilizer (predominantly lithium); in some cases, antipsychotics and/or benzodiazepines were also administered. Participants were required to: meet the DSM-IV-TR diagnostic criteria (American Psychiatry Association, 2000) for type I or type II bipolar disorder; have a duration of illness of at least 2 years; history of severe or unfavourable progression of the disease despite adequate pharmacological treatment (two or more relapses in the preceding year, suicide attempts, persistent affective symptoms); be aged 18 to 65 years. *Intervention*: Pharmacological treatment plus psychotherapy; objectives of the psychological intervention program were to enhance patients' understanding of their disorder, to reduce the number of hospitalizations, to reduce their anxiety levels, to improve their repertoire of social	N = 40 (intervention group n=20, control group n=20).	This study aimed to assess the short-term and long-term effectiveness psychoeducational and cognitive-behavioural therapy combined with pharmacotherapy, compared with pharmacotherapy alone in patients with refractory bipolar disorder. There were no significant differences between the intervention and control groups on gender distribution, age, prior hospitalisations, or baseline symptom scores. Participants were assessed post-treatment and at six and 12 months follow-up. Relapse: Participants in the psychoeducational and cognitive-behavioural therapy combined with pharmacotherapy group experienced significantly fewer hospitalisations than those in the control group, both during treatment (mean(se) 0.00(0.09) vs. 0.28(0.09), p=0.037) and at 12 months follow-up (mean(se) 0.00(0.09) vs. 0.39(0.10), p=0.007); the difference was non-significant at 6 months follow-up. Other outcomes:	No details of the randomisation or allocation concealment procedures were reported. The nature of the intervention precludes blinding of participants and therapists, but outcome assessments were carries out by independent researchers, who were blinded to

	skills and assertiveness control, to help them control their mood by shifting thoughts and enhancing involvement in enjoyable activities, to enhance their self-esteem and to improve their adaptation to daily life by learning problem-solving strategies. The intervention consisted of 20 weekly sessions of 1.5 hours per session. *Comparator*: Pharmacological treatment only; received individualised psychoactive drug(s) treatment (mood stabilizers, antipsychotics and/or benzodiazepines) adjusted by the psychiatrist. *Outcomes*: Symptomology; Beck's Depression Index (BDI) (Beck et al., 1979; Spanish version by Vázquez and Sanz, 1997), Young Mania Rating Scale (YMRS) (Young et al., 1978; Spanish version by Colom et al., 2002), State Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1970; Spanish version by Seisdedos) and Inadaptation Scale (IS) (Echeburúa et al., 2000), and number of hospitalisations.		This study also reported significantly greater improvements in anxiety (STAI-S) and depression (BDI) in the treatment compared to the control group, at 6 and 12 months follow-up, and significantly greater improvements the Young mania scale and the inadaptation scale in the treatment compared to the control group, at all time points.	treatment group. Outcomes were not pre-specified, but data appeared to be complete. It was not clear whether all study participants were included in the analyses.
Costa et al. (2011)	*Participants*: Subjects were recruited from the Institute of Psychiatry of the *Universidade Federal do Rio de Janeiro* (Anxiety and Depression Program Outpatient Clinic). Inclusion criteria: age 18 to 60 years; DSM-IV criteria for BD I or II; had experienced at least one hypomanic, manic or depressive episode in the previous 12 months; had been taking	N=41 (intervention group n=27, control group n=14).	This study aimed to compare the effectiveness of 14 sessions of cognitive behavioural group therapy, combined with pharmacotherapy, with that of pharmacotherapy alone for the treatment of patients with bipolar disorder. There were no significant differences in gender distribution, age, marital status, level of education, or psychiatric co-morbidities, between the CBGT and control groups.	No details of the randomisation or allocation concealment procedures were reported.

	mood stabilizing medication for a minimum of one month before the therapy was initiated; were euthymic, mildly depressed or mildly hypomanic at the time of the initial assessment. Exclusion criteria: Beck Depression Inventory (BDI) score ≥35; Young Mania Rating Scale (YMS) score ≥20; comorbid personality disorder and/or any other axis I severe psychiatric disorder; severe physical illness and/or using alcohol or illicit drugs; required the administration of a new mood stabiliser and/or a new antidepressant during the course of treatment. *Intervention*: Cognitive behavioural group therapy; consisted of 14 two-hour CBGT sessions which were divided into two stages: the first consisted of three sessions during which the therapist provided psychoeducation on BD, symptoms and medications to the patients and their families. In the second stage, patients learned CBT skills by means of specific behavioural and cognitive interventions. *Comparator*: Treatment as usual; attended sessions as prescribed by their respective psychiatrists, and did not attend any psychotherapy session. *Outcomes*: Mood and anxiety symptoms were assessed in all subjects using the Beck Depression Inventory (BDI), the		Participants were assessed at baseline and post-treatment (at 14 weeks). The control group showed no statistically significant changes, between the baseline and 14 week assessments, on any of the outcome measures assessed. The group receiving CBGT + pharmacotherapy showed significant improvements in mean BDI, BAI, YMRS and BHS scores, between the baseline and 14 week assessments. No between-group statistical comparisons were reported. No data were reported for the six month follow-up assessment. This study did not report any data specifically describing relapse rates.	The nature of the intervention precludes blinding of participants and therapists; it was not clear whether outcomes were independently assessed blind to treatment group. Data were reported for all specified outcomes. However, the methods section suggests that a six-month follow-up examination was conducted; no data are reported for

	Young Mania Rating Scale (YMRS) and the Beck Anxiety Inventory (BAI). The Beck Hopelessness Scale (BHS) was used for predicting suicidal ideation.			this time point. It was not clear whether all study participants were included in the analyses.

Risk of Bias:

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Miklowitz et al. (2003)	☺	☺	☹	☺	☺	☺
Miklowitz et al. (2007 + follow up)	?	?	☹	☺	☺	☺
Isasi et al. (2010)	?	?	☹	☺	?	☺
Costa et al. (2011)	?	?	☹	?	?	?

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Bipolar Disorder	95	2
DARE	(Lithium*) IN DARE 111 Delete 2 (valproate* or valproic*) IN DARE 105 Delete 3 (carbamazepine or carbatrol or equetro or tegretol or epitol or teril*) IN DARE 122 Delete 4 (lamotrigine*) IN DARE 56 Delete 5 (quetiapine or seroquel) IN DARE 110 Delete 6 (olanzapine or zyprexa) IN DARE 161 Delete 7 (risperidone or risperdal) IN DARE 181 Delete 8 (aripiprazole or abilify) IN DARE 71 Delete 9 (haloperidol or haldol) IN DARE 174 Delete 10 MeSH DESCRIPTOR Lithium EXPLODE ALL TREES 28 Delete 11 MeSH DESCRIPTOR Lithium Carbonate EXPLODE ALL TREES 11 Delete 12 MeSH DESCRIPTOR Valproic Acid EXPLODE ALL TREES 51 Delete 13 MeSH DESCRIPTOR Carbamazepine EXPLODE ALL TREES 42 Delete 14 MeSH DESCRIPTOR Risperidone EXPLODE ALL TREES 103 Delete 15 MeSH DESCRIPTOR Haloperidol EXPLODE ALL TREES 55 Delete 16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #11 OR #12 OR #13 OR #14 OR #15 608 Delete 17 (CBT or cognitive* or behaviour* or behavior*) IN DARE 3452 Delete 18 MeSH DESCRIPTOR Cognitive Therapy EXPLODE ALL TREES 599 Delete 19 #17 OR #18 3638 Delete 20 #16 AND #19 144 Delete 21 (bipolar*) IN DARE 230 Delete 22 MeSH DESCRIPTOR Bipolar Disorder EXPLODE ALL TREES 146 Delete	144	

	23 #21 OR #22 283 Delete 24 #19 AND #22		
Primary studies			
CENTRAL	2 MeSH descriptor: [Bipolar Disorder] explode all trees 1446 #3 MeSH descriptor: [Psychotherapy] explode all trees 13737 #4 MeSH descriptor: [Drug Therapy] explode all trees 109819 #5 Enter terms for search mood stabilizersmood stabilizers 354 #6 MeSH descriptor: [Central Nervous System Depressants] explode all trees 21839 #7 MeSH descriptor: [Central Nervous System Agents] explode all trees 37717 #8Enter terms for searc#6 or #737717 #9Enter terms for searc#5 or #837865 #10Enter terms for searc#4 or #9135228 #11Enter terms for searc#2 and #3 and #1056	52	
PsycINFO	1. PsycINFO; BIPOLAR DISORDER/; 18102 results. 3. PsycINFO; exp DRUGS/; 231395 results. 4. PsycINFO; DRUG THERAPY/; 101724 results. 5. PsycINFO; exp PSYCHOTHERAPY/; 168090 results. 6. PsycINFO; 3 OR 4; 263705 results. 7. PsycINFO; 1 AND 5 AND 6; 207 results. 8. PsycINFO; CLINICAL TRIALS/; 6909 results. 9. PsycINFO; random*.ti,ab; 121028 results. 10. PsycINFO; groups*.ti,ab; 348861 results. 11. PsycINFO; (doubl* adj3 blind*).ti,ab; 17502 results. 12. PsycINFO; (singl* adj3 blind*).ti,ab; 1514 results. 13. PsycINFO; EXPERIMENTAL DESIGN/; 8713 results. 14. PsycINFO; controlled.ti,ab; 75446 results. 15. PsycINFO; (clinical adj3 study).ti,ab; 7459 results. 16. PsycINFO; trial.ti,ab; 63734 results. 17. PsycINFO; "treatment outcome clinical trial".md; 24473 results. 18. PsycINFO; RCT.ti,ab; 1633 results.	64	

	19. PsycINFO; 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18; 538458 results. 20. PsycINFO; 7 AND 19; 64 results.		
Embase	21. EMBASE; BIPOLAR DISORDER/; 31893 results. 22. EMBASE; DRUG THERAPY/; 268232 results. 23. EMBASE; exp PSYCHOTROPIC AGENT [+NT]/; 643677 results. 24. EMBASE; exp CENTRAL NERVOUS SYSTEM AGENTS/; 1256397 results. 25. EMBASE; 22 OR 23 OR 24; 1469007 results. 26. EMBASE; exp PSYCHOTHERAPY/; 176804 results. 27. EMBASE; 21 AND 25 AND 26; 1537 results. 28. EMBASE; RCT.ti,ab; 12318 results. 29. EMBASE; random*.tw; 835949 results. 30. EMBASE; factorial*.tw; 21480 results. 31. EMBASE; placebo*.tw; 193467 results. 32. EMBASE; (crossover* OR cross-over*).tw; 67284 results. 33. EMBASE; (doubl* adj3 blind*).tw; 139501 results. 34. EMBASE; (singl* adj3 blind*).tw; 15944 results. 35. EMBASE; assign*.tw; 229054 results. 36. EMBASE; allocat*.tw; 78645 results. 37. EMBASE; volunteer*.tw; 171643 results. 38. EMBASE; CROSSOVER PROCEDURE/; 38092 results. 39. EMBASE; DOUBLE-BLIND PROCEDURE/; 116998 results. 40. EMBASE; SINGLE-BLIND PROCEDURE/; 18070 results. 41. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 353771 results. 42. EMBASE; 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 1355439 results. 43. EMBASE; 27 AND 42; 212 results.	212	
Medline	1. MEDLINE; BIPOLAR DISORDER/; 31425 results. 2. MEDLINE; DRUG THERAPY/; 34104 results. 3. MEDLINE; exp CENTRAL NERVOUS SYSTEM DEPRESSANTS/; 566424 results. 4. MEDLINE; LITHIUM CARBONATE/; 2736 results.	309	

	5. MEDLINE; VALPROIC ACID/; 10316 results. 6. MEDLINE; 2 OR 3 OR 4 OR 5; 598429 results. 8. MEDLINE; exp PSYCHOTHERAPY/; 149512 results. 9. MEDLINE; 1 AND 6 AND 8; 488 results. 10. MEDLINE; RCT.ti,ab; 9166 results. 11. MEDLINE; "randomized controlled trial".pt; 382606 results. 12. MEDLINE; "controlled clinical trial".pt; 88896 results. 13. MEDLINE; randomi?ed.ab; 362515 results. 14. MEDLINE; placebo.ab; 160354 results. 15. MEDLINE; "drug therapy".fs; 1738769 results. 16. MEDLINE; randomly.ab; 211259 results. 17. MEDLINE; trial.ab; 313911 results. 18. MEDLINE; groups.ab; 1345201 results. 19. MEDLINE; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18; 3373129 results. 20. MEDLINE; 10 OR 19; 3374330 results. 21. MEDLINE; 9 AND 20; 309 results.		
Summary	**NA**	**NA**	

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