BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

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Question

"For adults with bipolar disorder who are either in a manic or depressive episode, how effective is Cognitive Behavioural Therapy, compared to any other intervention, for improving patient outcomes?"

Clarification of question using PICO structure

Patients:	Adults with bipolar disorder
Intervention:	Cognitive Behavioural Therapy (CBT)
Comparator:	Any other intervention
Outcome:	Any patient outcomes

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Clinical and research implications

There was evidence from one high quality systematic review that CBT reduced the number of relapses compared to treatment as usual. However this was based on a small number of studies (up to five) and none of them reported other outcomes such as suicide or adverse events of treatment. Another, lower quality review also found significant benefits across various outcomes for CBT, but this evidence was less reliable. In terms of clinical trial evidence, one poor quality trial found a longer time to the first episode of depression with CBT, but no differences when compared to treatment as usual for relapses or the number of depressive episodes. Two other trials (one poor and one moderate quality) did not find any evidence of a difference between CBT and supportive care or psychoeducation.

There was a small amount of evidence favouring CBT, however as stated by some of the authors, more research is needed. Ideally this should involve high quality randomised controlled trials with a sufficiently large sample size to capture clinically relevant treatment differences and a long period of follow-up.

What does the evidence say?

Number of included studies/reviews (number of participants)

Two systematic reviews containing 5 relevant studies (451 participants) and 12 studies (1212 participants) and three randomised controlled trials (60, 76 and 204 participants) provided evidence for this question. One review compared CBT to treatment as usual (TAU) or a waiting list control, both in addition to usual medication, in mixed type I and II bipolar disorder adults (1). The other review was more recent and included more studies, most compared individual CBT to standard care, but it did not report any participant details (2).

There was one trial of group CBT given in addition to pharmacological treatment and compared with pharmacological treatment alone (TAU) in a group of 60 participants (76% type I) with an average age of 38 years (3). Two trials assessed individual CBT. One compared individual CBT with supportive therapy in 76 participants (79% type I) with an average age of 44 years (4). The other trial compared individual CBT with psychoeducation, in addition to mood-stabilising medication, in 204 participants (72% type I) with an average age of 41 years (5).

Main Findings

One systematic review (1) found that CBT significantly reduced the chance of a relapse compared with TAU (OR 0.24, 95% CI 0.12 to 0.51) based on a pooled analysis of three studies. One study reported manic and depressive relapses separately but a significant benefit for CBT was only seen for depressive relapses. None of the studies reported on suicide or adverse events of treatment. The other review (2) found a significant benefit for CBT on post-treatment outcomes with a low to moderate effect size (-0.42) which indicates a reduction in overall symptoms. Significant moderate reductions were also seen for clinical symptoms, cognitive behavioural etiopathogenetic mechanisms, quality of life scores, and treatment adherence. Significant low to medium benefits of CBT were also seen for outcomes measured at follow-up times of up to 6, 6 to 12, and over 12 months.

For group CBT, the time to the first depressive episode was significantly longer with CBT compared to TAU (median 31 vs. 11.5 weeks) but no differences were seen for relapses or the number of depressive episodes (3). Neither of the individual CBT trials found any significant differences between CBT and supportive therapy or psychoeduation. In one trial (4) depression symptoms reduced significantly over time in both treatment groups and the proportion of patients with a recurrence within 9 months was lower with CBT (31.6% vs. 52.6%). The other trial also showed significant reductions over 18 months for both groups in the reduction of mood burden, but similar times to recurrence and medication use (5).

Authors Conclusions

The systematic reviews concluded that: (1) there is evidence that CBT in addition to usual treatment is effective for the prevention of relapses in bipolar disorder and it may be more effective for preventing depressive rather than manic relapses; and (2) CBT can be used in addition to medication for patients with bipolar disorder, but new CBT strategies are needed to increase and enrich the impact of CBT at post-treatment and to maintain its benefits during follow-up.

The three trials concluded that: (3) group CBT is feasible in euthymic patients with bipolar disorder and further research is needed: (4) no difference in relapse rates between individual CBT and supportive therapy were observed which suggests that certain shared characteristics (information, systemic mood monitoring) might explain the effects of psychological treatment for bipolar disorder; and (5) despite longer treatment duration, individual CBT did not show a significantly greater clinical benefit compared to group psychoeducation.

Reliability of conclusions/Strength of evidence

One of the systematic reviews was considered to be high quality and its conclusions about CBT, although based on a small number of studies (up to 5), are likely to be reliable (1). The other review was poor quality as it was stated to be a meta-analysis (rather than a systematic review), it had a limited search, and did not state how the studies were selected or data extracted. It also did not assess the study quality, or clearly report the details and results of the individual studies (2). Therefore it may not be reliable.

The most reliable trial was one of individual CBT (4), although it did not show any benefit for CBT. This used appropriate randomisation, blinded the outcome assessors to the treatment group, used intention-to-treat analysis and reported all the outcomes. The two other trials were poor (individual CBT (3)) and moderate quality (group CBT (5)). The only trial to report a statistically significant benefit for CBT, in terms of a delay in the time to the first depressive episode, was also the most poor quality trial.

The results of the earlier systematic review (1) reflect the recommendations of the SIGN guidelines, as they are both based on 3 trials which found a significant benefit of CBT in terms of a reduction in relapses.

What do guidelines say?

Scottish Intercollegiate Guidelines Network (SIGN) guidelines, *Bipolar Affective Disorder* (CG82, 2005), make the following recommendations regarding the use of CBT for bipolar disorder in adults:

"Three good quality UK trials of CBT versus either treatment as usual or a waiting list control, show a benefit from seven to 25 sessions of CBT for both relapse prevention and improved social functioning over follow up periods of up to 18 months.

The CBT interventions in these studies were adapted to use in patients with bipolar affective disorders by incorporating early warning signs monitoring. This involves training patients to identify possible prodromal features of manic or depressive relapse, ie the relapse 'signature'. Early warning signs monitoring also involves developing a list of 'at risk' situations and producing and rehearsing an action plan once prodromes have been recognised by the patient.

Two of these studies also examined cognitive and behavioural approaches to enhance self management of depressive and hypomanic symptoms and to establish regular activity patterns such as daily routines and regular sleep patterns

Preliminary indications from a small open study are that concordance therapy, an abbreviated model of cognitive therapy, may be effective in improving adherence with lithium prophylaxis.

Another small open study of patients initially responsive to lithium who were treated with CBT after a relapse found that time to relapse after CBT was longer than time to relapse before CBT." (p.16)

National Institute for Health and Care Excellence (NICE) guidelines do not comment upon the use of CBT for adults with bipolar disorder.

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Date searches conducted: 01/10/2014
Date answer completed: 06/11/2014

References

SRs

1. Soares-Weiser, K., Vergel, Y. B., Beynon, S., Dunn, G., Barbieri, M., Duffy, S., ... & Woolacott, N. (2007). A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technology Assessment, 11*(39).

2. Szentagotai, A., & David, D. (2010). The efficacy of cognitive-behavioral therapy in bipolar disorder: a quantitative meta-analysis. *The Journal of Clinical Psychiatry*, *71*(1), 66-72.

RCTs

3. Gomes, B. C., Abreu, L. N., Brietzke, E., Caetano, S. C., Kleinman, A., Nery, F. G., & Lafer, B. (2011). A randomized controlled trial of cognitive behavioral group therapy for bipolar disorder. *Psychotherapy and Psychosomatics*, *80*(3), 144-150.

4. Meyer, T. D., & Hautzinger, M. (2012). Cognitive behaviour therapy and supportive therapy for bipolar disorders: relapse rates for treatment period and 2-year follow-up. *Psychological medicine*, *42*(07), 1429-1439.

5. Parikh, S. V., Zaretsky, A., Beaulieu, S., Yatham, L. N., Young, L. T., Patelis-Siotis, I., ... & Streiner, D. L. (2012). A randomized controlled trial of psychoeducation or cognitive-behavioral therapy in bipolar disorder: a Canadian Network for Mood and Anxiety treatments (CANMAT) study. *Journal of Clinical Psychiatry*, *73*(6), 803-810.

Guidelines

Scottish Intercollegiate Guidelines Network (2005) *Bipolar Affective Disorder*, *CG82*. Edinburgh: Scottish Intercollegiate Guidelines Network. http://www.sign.ac.uk/pdf/sign82.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
1. Soares-Weiser (2007)	Inception to Aug/Sept 2005	*Participants*: bipolar I disorder or bipolar II disorder diagnosed according to diagnostic criteria (e.g. DSM-IV or ICD-10). *Intervention*: CBT, either individual or group. *Comparator*: Any other intervention, placebo, or no intervention. *Outcome*: Relapse of a bipolar episode, either manic or depressive (number of hospitalisations, those with an additional treatment, or as defined by the study authors); drop-outs before the end of study; adverse events leading to discontinuation; suicide or suicide attempts. *Study design:* randomised or quasi-randomised controlled trials with at least 3 months of follow-up.	5 relevant to this question (n=451)	Of the 45 studies included in the review, 5 evaluated CBT. Four compared CBT to treatment as usual (TAU) and one to a waiting list control. CBT sessions ranged from one hour per week for 6 weeks to a maximum of 25 sessions of 45 minutes each. Two studies were in participants with bipolar I and the other three were in mixed type I and II. All participants were adults and the proportion of females ranged from 52 to 65%. Two studies were excluded from the analysis of all relapses as they randomised participants during an acute phase, but neither showed a significant result. CBT significantly reduced the chance of a relapse compared to TAU (OR 0.24, 95% CI 0.12 to 0.51). One study reported manic and	Low. The search covered a wide range of databases as well as unpublished material and was not restricted by language. Study selection, data extraction and quality assessment were performed by one reviewer and checked by a second to reduce the risk of errors. The quality assessment used recommended criteria for RCTs. The synthesis used appropriate

				depressive relapses separately but only found a significant reduction for depressive relapses with CBT (OR 0.32, 95% CI 0.13 to 0.74). Drop-out rates were similar between groups in the one study which reported this outcome. None of the studies reported suicide or adverse events.	meta-analysis methods.
2. Szentagotai (2010)	Jan 1980 to Mar 2008	*Participants*: diagnosed with bipolar disorder, in a manic or depressive episode, or between episodes. *Intervention*: CBT, either individual or group, with standard care. *Comparator*: Standard care (e.g., medication plus clinical management). *Outcome*: Clinical symptoms (depressive and/or manic), including intensity and duration; coping skills; quality of life/social adjustment; relapse (e.g., number of relapses); treatment adherence; treatment costs. *Study design:* Randomised clinical trials.	12 (n=1212)	Of the 12 included studies, 10 reported post-treatment outcomes and 2 only reported follow-up outcomes. The timing of outcome measures varied and included 6, 12 or 18 months. Eleven studies were of individual CBT and one was of group CBT. Most control groups received standard care with two including collaborative care and one a waiting list control. Cohens' d effect sizes (ES) were calculated and averaged across different studies and timepoints. Post-treatment: CBT had a significant overall benefit for those with bipolar disorder (ES -0.42, 95% CI -0.51 to -0.34). Significant effects were seen for clinical symptoms (-0.44), cognitive behavioural etiopathogenetic mechanisms (-0.49), quality of life (-	Low Inclusion criteria were clearly specified. The literature search was limited as it only covered one database for published studies in English. No details were given of how studies were selected or data extracted. The study was described as a meta-analysis rather than a systematic review and it seems systematic review methods were not

				0.38) and treatment adherence (-0.53). Follow-up: CBT had low to medium significant ES for follow-ups between 6 and 18 months, ranging from -0.27 to -0.41. Significant effects were seen for clinical symptoms and cognitive behavioural etiopathogenetic mechanisms at all timepoints.	used. Study quality was not assessed. Although meta-analyses were performed these did not use the correct methods and were based on simple, rather than weighted means.

RCTs

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
3. Gomes et al. (2011)	*Participants*: Inclusion criteria: DSM-IV diagnosis of BD type I or II; age between	*n* = 60 were randomised	The trial was conducted between March and December 2008 in Brazil. There were 5 CBT groups	High

	18 and 60 years; euthymic state (e.g., Young Mania Rating Scale score < 6 and 17-item Hamilton Depression Rating Scale score < 8) when enrolled in the study; use of at least one mood stabilizer or atypical antipsychotic. Exclusion criteria: substance disorders in the last 6 months; organic brain disorders. *Intervention*: Group CBT, adjunctive to pharmacological treatment. Group CBT included 18 structured sessions, each 90 minutes long. Sessions taught information about bipolar disorder, cognitive and behavioural strategies to manage episodes, assertive and problem-solving techniques, and techniques to improve relapse prevention. *Comparator*: Treatment as usual (TAU pharmacological treatment) *Outcome*: Relapse occurrence, time to first relapse, and number of depressive episodes.	but 50 were included in the analysis	and 5 TAU groups containing on average 4 or 5 participants. Outcomes were measured 6 months after the first group therapy session (post-treatment) and then every 3 months up to Match 2010. In total there was a 22 week treatment phase and up to 2 years of follow-up. Seventy-six percent of the participants were female with a median age of 38 years. The median age at BD onset was 18 years, 76% were BD type I, 68% had psychotic symptoms and 20% had rapid cycling. Twelve percent were currently receiving psychotherapy and 78% had previously received psychotherapy. There were no significant between group differences for the proportion of participants relapsing (63.6% CBT and 56% TAU), or for time to relapse. The median time to the first depressive episode was significantly longer for the CBT group (31 weeks with a range of 66 weeks) compared to the TAU group (11.5 weeks with a range of 48 weeks). However there was no significant difference between groups in the number of depressive episodes.	Randomisation used random numbers. However the method of placing participants in groups was not concealed and could have been altered. Due to the nature of the interventions the participants and personnel could not have been blinded, but the outcome assessors were blinded. Overall 13/60 randomised participants were excluded from the analysis, and some outcomes were not reported (suicide attempts and hospitalisations).
4. Meyer et al. (2012)	*Participants*: Inclusion criteria: DSM-IV diagnosis of BD; age between 18 and 65 years; willingness to continue current or start medication. Exclusion criteria: primary diagnosis of a non-affective	*n* = 76	The trial was conducted in Germany between August 1999 and September 2004. Outcomes were assessed immediately post-treatment, then every 3 months for the first year, and then after 2 years. The total follow-up period was 33 months. Eleven participants	Low Randomisation was stratified by age, gender and type of bipolar

	disorder; current major affective episode (depressed, mixed or mania) or Bech–Rafaelsen Melancholia Scale (BRMS) score >14 or Bech–Rafaelsen Mania Rating Scale (BRMAS) score >9; current substance dependency; serious cognitive deficits. *Intervention*: Individual CBT, comprising 20 sessions (50-60 minutes) over 9 months. Topics included information and motivation, relapse prevention, cognitive and behavioural strategies, communication and problem-solving skills. *Comparator*: Supportive therapy, comprising 20 sessions (50-60 minutes) over 9 months. *Outcome*: Relapse (DSM-IV criteria using the SCID); bipolar symptoms (Center for Epidemiologic Studies Depression Scale (CESD; BRMS; BRMAS); Global Assessment Scale (GAS); Beck Depression Inventory (BDI); Self-Rating Mania Inventory (SRMI)).		(14.5%) attended less than 16 sessions and were treated as drop-outs. Fifty percent of the participants were female with a mean age of 44 years, the mean age of onset was 28 years, and 79% were bipolar I. At baseline 37% had psychotic mood-related symptoms, and 20% had a personality disorder. Symptoms of depression decreased significantly over time for both groups but there was no significant difference between them. The proportion of participants with a recurrence during the 9 month treatment phase was lower with CBT than supportive therapy (31.6% vs. 52.6%, p=0.06) but there was no difference in the mean time to recurrence of any affective episode (around 67 weeks overall). The mean time to the first recurrence of a depressive episode was 86 weeks for CBT and 89 weeks for supportive therapy.	disorder. It was unclear if there was allocation concealment. It was not possible to blind participants and personnel, but post-treatment assessments were made by raters who were blind to the treatment conditions. All participants appear to have been included in the analysis and it was by intention-to-treat. All outcomes seem to have been reported.
5. Parikh et al. (2012)	*Participants*: Inclusion criteria: DSM-IV diagnosis of BD type I or II; age between 18 and 64 years; being treated with a mood-stabilizing medication at study entry; 2 episodes within the previous 3 years; no episodes in month prior to	*n* = 204	The trial was conducted in 4 academic centres in Canada between June 2002 and September 2006. Both groups could also receive medication, as prescribed by their usual physician. Outcomes were assessed weekly but reported as combined scores every 8 weeks. The total follow-up period was 72	Moderate Randomisation used an appropriate method and allocation concealment was maintained using

	randomisation. Exclusion criteria: current substance dependence; severe borderline or antisocial personality disorder; significant cognitive deficit. *Intervention*: Individual CBT, comprising 20 sessions of 50 minutes duration. Topics included psychoeducation, detailed life history, goal setting, a range of cognitive and behavioural approaches, and a relapse prevention plan. Participants were also using a mood-stabilizing medication. *Comparator*: Psychoeducation, comprising 6 therapist-led group sessions of 90 minutes duration. Topics included illness recognition, treatment approaches, coping strategies, and an action plan. Participants were also using a mood-stabilizing medication. *Outcome*: Reduction of mood burden over 72 weeks (Longitudinal Interval Follow-up Evaluation (LIFE); Modified Social Adjustment Scale (MSAS); Hamilton Rating Scale for Depression (HDRS); Clinician-Administered Rating Scale for Mania, (CARSM)).		weeks. Completers were defined as those who received 18 to 20 sessions of CBT (66% of participants), or 5 or 6 sessions of psychoeducation (64% of participants). The mean participant age was 41 years, 58% of participants were female and 72% were bipolar type I. The mean age at the first episode was 22 years, 70% had had more than 10 episodes, and 66% had previously been hospitalised. Both groups showed significant reductions in LIFE scores over time ($p<0.01$) but there was no difference between groups. There was also no difference between groups in the time to recurrence for depression or for mania. No difference between groups was seen for medication use. The use of lithium and valproate remained at baseline levels throughout the study and antidepressants were used by approximately 50% of participants.	sealed opaque envelopes kept at a co-ordinating centre. It was not possible to blind participants and personnel. However assessments were made by raters who were blind to the treatment group. It was unclear whether non-completers were included in the analysis, or if it was by intention to treat. There was selective outcome reporting as results for some outcomes (HDRS and CARSM) were not reported.

Risk of Bias:

SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Soares-Weiser (2007)	☺	☺	☺	☺	☺
Szentagotai (2010)	☺	☹	☹	☹	☹

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Gomes et al. (2011)	☺	☹	☹	☺	☹	☹
Meyer et al. (2012)	☺	?	☹	☺	☺	☺
Parikh et al. (2012)	☺	☺	☹	☺	?	☹

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	bipolar cbt adults	23	1
DARE	1 ((cognit* adj2 therap*) OR CBT) IN DARE 897 Delete 2 MeSH DESCRIPTOR Cognitive Therapy EXPLODE ALL TREES 712 Delete 3 #1 OR #2 1116 Delete 4 (bipolar OR manic OR mania) IN DARE 266 Delete 5 MeSH DESCRIPTOR Bipolar Disorder EXPLODE ALL TREES 166 Delete 6 #4 OR #5 323 Delete 7 #3 AND #6 29 Delete	29	2
Primary studies			
CENTRAL	#1 MeSH descriptor: [Bipolar Disorder] explode all trees 1581 #2 bipolar 4405 #3 "manic depress*" 197 #4 mania 1317 #5 #1 or #2 or #3 or #4 4836 #6 MeSH descriptor: [Cognitive Therapy] explode all trees 5037 #7 "cognitive behav*" 6960 #8 CBT 2615 #9 #6 or #7 or #8 9079 #10 #5 and #9 288 Central only 89	89	3
PsycINFO	1. PsycINFO; exp BIPOLAR DISORDER/; 19786 results. 2. PsycINFO; bipolar.ti,ab; 27872 results.	171	0

	3. PsycINFO; 1 OR 2; 30303 results. 4. PsycINFO; exp COGNITIVE BEHAVIOR THERAPY/; 12292 results. 5. PsycINFO; "cognitive behav*".ti,ab; 28405 results. 6. PsycINFO; CBT.ti,ab; 7948 results. 7. PsycINFO; 4 OR 5 OR 6; 30612 results. 8. PsycINFO; 3 AND 7; 471 results. 22. PsycINFO; mania.ti,ab; 8304 results. 24. PsycINFO; "manic depress*".ti,ab; 4562 results. 25. PsycINFO; 1 OR 2 OR 22 OR 24; 36042 results. 26. PsycINFO; 8 AND 25; 471 results. 27. PsycINFO; CLINICAL TRIALS/; 7925 results. 28. PsycINFO; random*.ti,ab; 133602 results. 29. PsycINFO; groups.ti,ab; 374352 results. 30. PsycINFO; (double adj3 blind).ti,ab; 18131 results. 31. PsycINFO; (single adj3 blind).ti,ab; 1441 results. 32. PsycINFO; EXPERIMENTAL DESIGN/; 9281 results. 33. PsycINFO; controlled.ti,ab; 82874 results. 34. PsycINFO; (clinical adj3 study).ti,ab; 8115 results. 35. PsycINFO; trial.ti,ab; 70303 results. 36. PsycINFO; "treatment outcome clinical trial".md; 27839 results. 37. PsycINFO; 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36; 580366 results. 38. PsycINFO; 26 AND 37; 171 results.		
Embase	24. EMBASE; exp BIPOLAR DISORDER/; 40432 results. 25. EMBASE; bipolar.ti,ab; 57231 results. 26. EMBASE; 24 OR 25; 72168 results. 27. EMBASE; exp COGNITIVE BEHAVIOR THERAPY/; 34483 results. 28. EMBASE; "cognitive behav*".ti,ab; 22107 results. 29. EMBASE; CBT.ti,ab; 7789 results.	278	0

	30. EMBASE; 27 OR 28 OR 29; 43771 results. 31. EMBASE; 26 AND 30; 1408 results. 32. EMBASE; mania.ti,ab; 10330 results. 33. EMBASE; "manic depress*".ti,ab; 3304 results. 34. EMBASE; 24 OR 25 OR 32 OR 33; 77210 results. 35. EMBASE; 30 AND 34; 1435 results. 36. EMBASE; random*.ti,ab; 901764 results. 37. EMBASE; factorial*.ti,ab; 23344 results. 38. EMBASE; (crossover* OR cross-over*).ti,ab; 69903 results. 39. EMBASE; placebo*.ti,ab; 202258 results. 40. EMBASE; (doubl* ADJ blind*).ti,ab; 143607 results. 41. EMBASE; (singl* ADJ blind*).ti,ab; 14657 results. 42. EMBASE; assign*.ti,ab; 242394 results. 43. EMBASE; allocat*.ti,ab; 85358 results. 44. EMBASE; volunteer*.ti,ab; 177975 results. 45. EMBASE; CROSSOVER PROCEDURE/; 40265 results. 46. EMBASE; DOUBLE BLIND PROCEDURE/; 115501 results. 47. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 350374 results. 48. EMBASE; SINGLE BLIND PROCEDURE/; 18844 results. 49. EMBASE; 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48; 1434407 results. 50. EMBASE; 35 AND 49; 278 results.		
Cinahl		6	0
Medline	23. MEDLINE; "manic depress*".ti,ab; 3253 results. 24. MEDLINE; exp BIPOLAR DISORDER/; 32191 results. 25. MEDLINE; bipolar.ti,ab; 44481 results. 26. MEDLINE; 24 OR 25; 59477 results. 27. MEDLINE; exp COGNITIVE BEHAVIOR THERAPY/; 16638 results. 28. MEDLINE; "cognitive behav*".ti,ab; 16069 results. 29. MEDLINE; CBT.ti,ab; 5394 results.	206	0

	30. MEDLINE; 27 OR 28 OR 29; 25609 results. 32. MEDLINE; mania.ti,ab; 7844 results. 33. MEDLINE; 23 OR 24 OR 25 OR 32; 61674 results. 34. MEDLINE; 30 AND 33; 443 results. 35. MEDLINE; "randomized controlled trial".pt; 389180 results. 36. MEDLINE; "controlled clinical trial".pt; 89873 results. 37. MEDLINE; randomized.ab; 309343 results. 38. MEDLINE; placebo.ab; 159886 results. 39. MEDLINE; "drug therapy".fs; 1746500 results. 40. MEDLINE; randomly.ab; 223287 results. 41. MEDLINE; trial.ab; 322124 results. 42. MEDLINE; groups.ab; 1407657 results. 43. MEDLINE; 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42; 3451670 results. 44. MEDLINE; 34 AND 43; 206 results.		
Summary	**NA**	**NA**	

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