BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In adults with depression, how effective is cognitive behavioural therapy (CBT) alone or combined with pharmacotherapy, compared with pharmacotherapy alone, in improving patient outcomes?

Clarification of question using PICO structure

Patients:	Adults with depression
Intervention:	Cognitive behavioural therapy (CBT) alone or in combination with pharmacotherapy
Comparator:	Pharmacotherapy alone
Outcome:	Improving patient outcomes

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Clinical and research implications

Evidence from one systematic review and two additional randomised controlled trials indicates that cognitive therapies may be similarly effective to pharmacotherapy in reducing depressive symptoms and preventing remission. Evidence from one further randomised controlled trial indicated that the addition of cognitive behavioural therapy to usual care (including pharmacotherapy) may reduce symptoms of depression, panic and anxiety and improve quality of life in people with treatment-resistant depression.

The evidence base was limited and studies included in the systematic review, as well as individual randomised controlled trials, had significant methodological weaknesses. Further, high quality research is needed to confirm the findings of these studies. Given the nature of the intervention, investigators should particularly consider the use of independent, blinded outcome assessment.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews[1,2] and three additional randomised controlled trials (RCTs)[3,4,5], which were considered relevant to this evidence summary. The first systematic review included nine RCTs that compared acute CBT to pharmacotherapy, which was either discontinued after the acute phase or continued during follow-up; the outcome measure was defined as the number of patients who responded to treatment and remained well during follow-up.[1] The second systematic review included five RCTs, all of which were included in the first systematic review, hence this study provided no additional information.[2] One RCT compared CBT to paroxetine or placebo and reported response in terms of depressive symptoms on the Hamilton Depression Rating Scale (HDRS) at 8 and 16 weeks.[3] The second RCT included patients who were classified as in remission for at least seven months following an open-label acute treatment phase.[4] This study assessed risk of relapse in people who received mindfulness-based cognitive therapy (MBCT) following discontinuation of antidepressants, compared to continuation of antidepressants or placebo and clinical management.[4] The final RCT assessed the effectiveness of adding CBT to usual care (including pharmacotherapy) in patients whose depression was resistant to pharmacotherapy.[5] This study reported measures of depressive symptoms, panic and anxiety, and quality of life, at 12 months follow-up.[5]

Main Findings

The results of the main systematic review indicated that acute CBT significantly increased positive outcomes compared to pharmacotherapy, where pharmacotherapy was discontinued after the acute phase; OR 2.61 (95% CI: 1.58 to 4.31), based on 8 studies.[1] However, where pharmacotherapy was continued during follow-up, there was no significant difference between the treatment groups.[1] The RCT that compared CBT to paroxetine or placebo found that both CBT and paroxetine were more effective than placebo in reducing depressive symptoms and achieving response at 8 and 16 weeks, but there were no significant differences between the two active treatments.[3] The second RCT, found that, in patients whose remission was classified as unstable both MBCT after discontinuation of antidepressants and maintenance of antidepressants significantly reduced the risk of relapse, during 18 months follow-up, compared to placebo; HRs were 0.26 (95% CI: 0.09 to 0.79) and 0.24 (95% CI: 0.07 to 0.89), respectively.[4] However, there was no significant difference in

effectiveness between MBCT and continuation of antidepressants and, for patients in stable remission, neither treatment was significantly more effective than placebo.[4] The final RCT found that addition of CBT to usual care (including pharmacotherapy) significantly improved depressive symptoms, rates of response and remission, symptoms of anxiety and panic, and quality of life, in patients with treatment-resistant depression.[5]

Authors Conclusions

One systematic review concluded that CBT has an enduring effect following termination of the acute treatment. This review also found no significant difference in relapse after the acute phase CBT versus continuation of pharmacotherapy after remission, but cautioned that further research is needed. A second systematic review concluded that the evidence favours a longer-term effect for cognitive therapy over tricyclic antidepressants alone; all studies included in this review were also included in the first systematic review. One additional RCT concluded that cognitive therapy can be as effective as medications for the initial treatment of moderate to severe major depression. A further RCT found that mindfulness-based cognitive therapy offers similar log-term protection from relapse to pharmacotherapy. A third RCT found that adding CBT to usual care that includes pharmacotherapy is effective in reducing depressive symptoms in patients whose depression has not responded to pharmacotherapy.

Reliability of conclusions/Strength of evidence

One high quality systematic review provided evidence that acute CBT may improve depressive outcomes compared to pharmacotherapy, where pharmacotherapy is discontinued after the acute phase and is similarly effective to pharmacotherapy where pharmacotherapy is continued.[1] However, as noted by the authors, this review was based on a small number of studies with some methodological weaknesses and more research is needed to confirm its findings. The second systematic review had a number of significant methodological weaknesses and provided no additional evidence.[2] Two RCTs, both with some methodological and/or reporting weaknesses also provided an indication that cognitive therapies may be similarly effective to pharmacotherapy in achieving response[3] and preventing relapse.[4] A third RCT, again with some methodological and reporting weaknesses, provided data indicating that adding CBT to pharmacotherapy may improve outcomes in people with treatment resistant depression.[5] All results require confirmation by further, high quality research.

What do guidelines say?

NICE guidelines for depression in adults (CG90, 2009) make the following comments regarding the use of psychotherapy compared with combined psychotherapy and pharmacotherapy:

“For people with moderate or severe depression, provide a combination of antidepressant medication and a high-intensity psychological intervention (CBT or IPT).” (pp.22)

“For a person whose depression has not responded to either pharmacological or psychological interventions, consider combining antidepressant medication with CBT.” (pp.32)

“For a person whose depression has failed to respond to various strategies for augmentation and combination treatments, consider referral to a practitioner with a specialist interest in treating depression, or to a specialist service.” (pp.32)

The evidence included in this summary is consistent with current guidelines

Date question received: 17/10/2006
Date searches conducted: 12/08/2014**,** updated from 03/11/2006
Date answer completed: 22/09/2014

References

SRs

1. Cuijpers, Pim., Hollon, S. D., Straten, A. V., Bockting, C., Berking, M., Andersson, G. (2013). Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open,* 3, pp. 1-8.

2. Hensley, P.L., Nadiga, D., Uhlenhuth, E.H. (2004) Long-term effectiveness of cognitive therapy in major depressive disorder. *Depression and Anxiety, 20* pp. 1-7

RCTs

3. DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, RM., et al. (2005) Cognitive Therapy vs Medications in the Treatment of Moderate to Severe Depression. *Arch Gen Psychiatry 62*(4):409-16.

4. Segal, Z. V., Bieling, P., Young, T., MacQueen, G., Cooke, R., Martin, L., Levitan, R. D. (2010). Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. *Archives of General Psychiatry*, *67*(12), 1256-1264.

5. Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., Lewis, G. (2013). Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. *The Lancet*, *381*(9864), 375-384.

Guidelines

National Institute of Health and Care Excellence. (2009). *Depression in Adults: The Treatment and Management of depression in Adults. CG90*. London: National Institute of Health and Care Excellence.
http://www.nice.org.uk/guidance/cg90/resources/guidance-depression-in-adults-pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Cuijpers et al. (2013)	22/07/2014	*Participants*: Adults with depressive disorders. Exclusion criteria: studies where depression was not diagnosed with a standardised diagnostic interview; studies in in-patients and adolescents. *Intervention*: Acute cognitive behaviour therapy (CBT) according to the Beck manual, without subsequent continuation (a maximum of five irregular booster sessions were allowed during follow-up. *Comparator*: Pharmacotherapy that was either continued or withdrawn. *Outcomes*: Relapse rates at long-term follow-up (6-18 months). *Study design:* Randomised controlled trials (RCTs).	9 Studies Total 506 participants (n=271 CBT, n=235 pharmacotherapy)	This systematic review aimed to compare the effects of acute phase CBT without any subsequent treatment with the effects of pharmacotherapy that either were continued or discontinued across 6–18 months of follow-up. Seven of the nine included studies were conducted in people with major depressive disorder (MDD). The number of CBT sessions in included studies ranged from 18-24. The pharmacotherapy comparator varied between studies; five studies used a tricyclic antidepressant (TCA), three studies used a selective serotonin re-uptake inhibitor, and one study used phenelzine. Study designs also varied; in four studies only patients who initially responded to pharmacotherapy were randomised to continuation or withdrawal, in three further studies pharmacotherapy was withdrawn from all patients after the initial treatment period, one trial withdrew pharmacotherapy after the first six months	The review reported a clear research question(s) and defined appropriate inclusion criteria. Literature searches used a regularly up-dated database that included material from four bibliographic databases. The reference lists of systematic reviews were also screened. No language restrictions were applied. No details of the

				of follow-up and the final trial continued pharmacotherapy throughout. Definitions of outcome measures varied between included studies. The systematic review defined a positive outcome as "the number of patients who responded to treatment and remained well." Meta-analysis indicated that participants who received acute CBT were significantly more likely to have a positive outcome during follow-up than those who received pharmacotherapy, discontinued after the acute phase (OR 2.61 (95% CI: 1.58 to 4.31), 8 studies). This effect remained when studies were sub-grouped by type of pharmacotherapy (TCA or SSRI). A sub-group analysis of studies where all participants (not just those who responded to initial pharmacotherapy) were included in the analysis found no significant difference between acute CBT and pharmacotherapy that was discontinued after the acute phase. When acute CBT was compared to continued pharmacotherapy, there was a trend towards a positive effect for CBT, but this did not reach statistical significance (OR 1.62 (95% CI: 0.97 to 2.72),	review process (numbers of reviewers involved, checking procedures, etc.) were reported. The methodological quality of included studies was assessed using a modified version of the Cochrane risk of bias tool. The synthesis was broadly appropriate and possible sources of heterogeneity were explored using sub-group analyses.

				5 studies).	
Hensley et al. (2004)	Unknown, search date between 1966 - 2003	*Participants:* Adults with major depressive disorder. Studies with selective participant samples (e.g. people with no or partial response to initial pharmacotherapy) were excluded. *Intervention:* Cognitive behavioural therapy (CBT). Studies evaluating specific components of CBT were excluded. *Comparator:* "Credible control," defined as medication groups (in which patients are expected to relapse after treatment is withdrawn) and groups in which patients received a clearly inferior treatment, such as placebo. *Outcomes:* Outcomes were not specified in the inclusion criteria. *Study design:* Not specified. Studies with <6 months follow-up and follow-up studies limited to cross-sectional evaluations at long intervals without interim history were excluded.	5 Studies Total 536 participants	This systematic review aimed to assess the long-term effectiveness of CBT compared to a control treatment. All five of the studies included in this review were RCTs comparing cognitive therapy to TCAs, with treatment periods ranging from 12 to 20 weeks. Follow-up ranged from 15 to 27 months. Results were reported separately for each study. The authors presented re-analyses of data from the original studies using intention-to-treat principles and last-observation-carried-forward. Results of four of the five included studies indicated that cognitive therapy or cognitive therapy combined with TCAs was more effective than TCAs alone, in achieving longer-term remission. Remission was defined as either no treatment for depression or a Becks Depression Inventory (BDI) score <16/17 and no treatment for depression. The remaining study found no significant difference between cognitive therapy, interpersonal therapy, TCA, and placebo.	Some inclusion criteria were defined, but the report did not include a clearly stated objective and outcome measures were not pre-specified. Literature searches included five bibliographic databases and reference screening of review articles. No details of the review process (numbers of reviewers involved, checking procedures, etc.) were reported. No assessment of the methodological quality of included

				All five studies included in this review were also included in Cuijpers et al (2013), described above.	studies was reported. The article reported separate re-analyses of five individual studies. No synthesis was included.

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
DeRubeis et al. (2005)	*Particpants:* Adults (age 18 -70 years) with moderate to severe major depressive disorder, according to *DSM-IV.* *Intervention:* 16 weeks of cognitive therapy (50-minute sessions to be held twice weekly for the first 4 weeks of treatment, once or twice weekly for the middle 8 weeks, and once weekly for the final 4 weeks) or 8 weeks of pill placebo. *Comparator:* 16 weeks of antidepressant medication	n = 240, Medication (n = 120), Cognitive therapy (n = 120), Pill placebo (n = 60)	This study aimed to compare the effectiveness of cognitive therapy to pharmacotherapy for the treatment of moderate to severe depression. Baseline HDRS scores did not differ significantly between treatment groups. Other baseline demographic, social and clinical characteristics were reported overall and by study centre. The rates of substance abuse, Axis I comorbidity, melancholic depression, and atypical depression differed significantly between treatment groups. Over the 16 week treatment period, 16% of participants in	No details of the randomisation procedure or allocation concealment were reported. The nature of the intervention

	(variable dose paroxetine) or placebo. *Outcomes:* Change in depressive symptoms on the Hamilton Depression Rating Scale (HDRS).		the antidepressant medication group and 15% of participants in the CT group dropped out or were lost to follow-up. The mean daily dose of paroxetine increased from 14.0 ± 4.9 mg to 38.8 ± 11.0 mg over the first eight week treatment period; the mean daily dose over the second eight week treatment period was 37.3 ± 12.4 mg. Response was defined as a HDRS score ≤12. At eight weeks, 50% of participants in the antidepressant medication group, 43% of participants in the CT group and 25% of participants in the placebo group were classified as responders. Pairwise comparisons indicated that both CT and antidepressant medication were significantly more effective than placebo, but there was no statistically significant difference between the two active treatments; this remained the case at 16 weeks. Results were similar when HDRS was analysed as a continuous outcome.	precluded blinding of participants and study personnel, but outcomes were assessed blind to treatment group. It was unclear whether all randomised participants were included in the analyses. Results were reported for all specified outcomes.
Segal et al. (2010)	*Participants:* Adults (aged 18 to 65 years) meeting DSM-IV for major depressive disorder with a minimum of 2 past episodes and achieved remission. *Intervention:* Mindfulness Based Cognitive Therapy	Open label acute treatment phase (n = 160) Remitted patients	This study aimed to compare rates of relapse in remitted depressed patients receiving MBCT to rates of relapse in those receiving maintenance antidepressant pharmacotherapy. Participants who had achieved a minimum of seven months	Computerised randomisation was performed by an independent

	(MBCT) for 8 weeks after discontinuing antidepressant medication. *Comparator:* Continuation on their therapeutic dose of antidepressant medication or discontinued active medication (switch to placebo). *Outcome:* Relapse (SCID) and depressive symptoms (HDRS-17), during the 18 month maintenance phase.	randomised (n = 84), Maintenance of medication (n = 28), discontinuation of medication + MBCT (n = 26), discontinuation of medication + placebo and clinical management (n = 30)	remission, following an open-label acute treatment phase, were eligible for randomisation. Baseline demographic characteristics, clinical history and HDRS and Quick Inventory of Depressive Symptoms (QIDS) scores were similar across treatment groups; HDRS and QIDS scores were also similar at randomisation (i.e. when remission had been achieved. The only statistically significant difference between groups was greater percentage of Axis II comorbidity in the MBCT group. 75% of randomised participants completed the study. The numbers of drop outs were: 7 in the maintenance of medication group; 5 in the discontinuation + MBCT group; 6 in the discontinuation + placebo and clinical management group. For unstable remitters, defined as people with one or more HDRS scores >7 during remission, both MBCT and maintenance of medication significantly reduced the risk of relapse, during the 18 month maintenance period, compared to placebo; the hazard ratios were 0.26 (95% CI: 0.09 to 0.79) and 0.24 (95% CI: 0.07 to 0.89), respectively. However there was no difference in the effectiveness of MBCT and continued medication (hazard ratio 1.07 (95% CI: 0.25 to 4.49). For stable remitters, there was no significant difference in the risk of relapse between any of the treatment groups	statistician. Group allocations were contained in sealed envelopes, opened by the statistician and communicated to study personnel once a participant had been included. For continuation of medication and placebo, clinicians and participants were blind to group allocation.

			(MBCT, continuation of medication, or placebo).	For all treatment groups, outcomes were assessed blind to allocation. Intention-to-treat analyses were reported. Results were reported for all specified outcome measures.
Wiles et al. (2013)	*Participants:* Adults (aged 18 to 75 years) with treatment resistant depression (on antidepressants for ≥6 weeks, with a BDI score ≥14 and meeting criteria for depression according to ICD-10). *Intervention:* CBT in addition to usual care (including pharmacotherapy). CBT comprised 12 sessions of individual CBT (each lasting 50–60 min), with (up to) a further six sessions when judged to be clinically appropriate	n = 469, Usual care + CBT (n = 234), Usual care (n = 235)	This study aimed to assess the effectiveness of cognitive behavioural therapy (CBT) as an adjunct to usual care (including pharmacotherapy) for primary care patients with treatment resistant depression compared with usual care alone. There were no significant differences in demographic, socio-economic, or clinical characteristics between the treatment groups. Baseline BDI and SF-12 scores were also similar. 84% of participants completed the study. The numbers of	Randomisation was by means of a computer-generated code from a remote automated telephone randomisation service.

	by the therapist. *Comparator:* Usual care (including pharmacotherapy) *Outcome:* Primary outcome: Response (50% reduction from baseline in depressive symptoms, as measured by BDI. Secondary outcomes: Depressive symptoms (BDI continuous measure); remission (BDI score <10); quality of life (Short Form health survey 12 (SF-12)); panic; anxiety (Generalised Anxiety Disorder assessment (GAD-7)); Patient Health Questionnaire (PHQ).		dropouts were 36 from the CBT + usual care group and 37 from the usual care group. Depressive symptoms: Significantly more patients in the CBT + usual care group (55%) were classified as responders at 12 months than in the usual care alone group (31%); OR 2.89 (95% CI: 2.03 to 4.10). Similarly, more patients in the CBT + usual care group (40%) than in the usual care alone group (18%) achieved remission; OR 2.74 (95% CI: 1.82 to 4.13). The mean BDI score at 12 months was also lower in the CBT + usual care group (17.0 ± 14.0) than in the usual care alone group (21.7 ± 12.9); adjusted mean difference -5.1 (95% CI: -7.1 to -3.1). The mean PHQ-9 score, at 12 months was also lower in the CBT + usual care group (9.0 ± 7.0) than in the usual care alone group (10.9 ± 6.4); adjusted mean difference -2.8 (95% CI: -3.7 to -1.8). Anxiety and panic: Anxiety and panic were both reduced in the CBT + usual care group compared to the usual care alone group. The mean GAD-7 score, at 12 months, was lower in the CBT + usual care group (6.7 ± 6.2) than in the usual care alone group (8.5 ± 5.8); adjusted mean difference -2.2 (95% CI: -3.0 to -1.3). The mean panic score, at 12 months, was lower in the CBT + usual care group (1.5 ± 2.1) than in the usual care alone group (1.7 ± 2.2); adjusted mean difference -0.5 (95% CI: -0.8 to -0.2). Quality of life:	No details of allocation concealment were reported. The nature of the intervention precluded blinding of participants and study personnel, and it was not clear whether outcome assessors were blinded to treatment group. Intention-to-treat analyses were reported. Results were reported for

			At 12 months, the mean score of the mental subscale of the SF-12 was higher in the CBT + usual care group (39.1 ± 14.6) than in the usual care alone group (35.4 ± 12.8); adjusted mean difference 4.8 (95% CI: 2.7 to 6.9). There was no significant difference between the groups on the physical subscale.	all specified outcomes.

Risk of Bias:
SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Cuijpers et al. (2013)	☺	☺	?	☺	☺
Hensley et al. (2004)	☹	☺	?	☹	☹

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
DeRubeis et al. (2005)	?	?	☹	☺	?	☺
Segal et al. (2010)	☺	☺	☹	☺	☺	☺
Wiles et al. (2013)	☺	?	☹	?	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	cbt combined antidepressant depression	36	1
DARE	(depress*) IN DARE FROM 2006 TO 2014 1412 Delete 2 MeSH DESCRIPTOR Depression EXPLODE ALL TREES 513 Delete 3 MeSH DESCRIPTOR Depressive Disorder EXPLODE ALL TREES 922 Delete 4 MeSH DESCRIPTOR Depressive Disorder, Major EXPLODE ALL TREES 292 Delete 5 #1 OR #2 OR #3 OR #4 2069 Delete 6 ((behaviour* or behavior* or cognitive*) adj3 therap*) IN DARE FROM 2006 TO 2014 871 Delete 7 (cbt) IN DARE FROM 2006 TO 2014 213 Delete 8 MeSH DESCRIPTOR Cognitive Therapy EXPLODE ALL TREES 687 Delete 9 #6 OR #7 OR #8 1199 Delete 10 #5 AND #9	430	1
Primary studies			
CENTRAL	#1 MeSH descriptor: [Depression] explode all trees 5420 #2 MeSH descriptor: [Depressive Disorder] explode all trees7497 #3 depress* 57434 #4 #1 or #2 or #3 57449 #5 MeSH descriptor: [Cognitive Therapy] explode all trees4999	472	2

	#6 Cognitive behav* therap* 10546 #7 CBT 2575 #8 #5 or #6 or #7 11570 #9 MeSH descriptor: [Drug Therapy] explode all trees 117215 #10 pharmacotherapy 5087 #11 medication 40336 #12 MeSH descriptor: [Antidepressive Agents] explode all trees 4896 #13 #9 or #10 or #11 or #12 153624 #14 #4 and #8 and #13 1873 #15 2006 or 2007 or 2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014 371467 #16 #14 and #15 1486 Central only 472		
PsycINFO	1. PsycINFO; exp MAJOR DEPRESSION/; 93761 results. 2. PsycINFO; "DEPRESSION (EMOTION)"/; 21670 results. 3. PsycINFO; depression.ti,ab; 171227 results. 4. PsycINFO; 1 OR 2 OR 3; 191229 results. 5. PsycINFO; CBT.ti,ab; 7807 results. 6. PsycINFO; "cognitive behav*".ti,ab; 28109 results. 7. PsycINFO; exp COGNITIVE BEHAVIOR THERAPY/; 12093 results. 8. PsycINFO; 5 OR 6 OR 7; 30263 results. 9. PsycINFO; group.ti,ab; 430281 results. 10. PsycINFO; 8 not 9; 22825 results. 11. PsycINFO; DRUG THERAPY/; 108216 results. 12. PsycINFO; pharmacotherapy.ti,ab; 9098 results. 13. PsycINFO; medication.ti,ab; 45552 results. 14. PsycINFO; exp ANTIDEPRESSANT DRUGS/; 32036	264	0

	results. 15. PsycINFO; 11 OR 12 OR 13 OR 14; 144978 results. 16. PsycINFO; 4 AND 10 AND 15; 994 results. 17. PsycINFO; CLINICAL TRIALS/; 7790 results. 18. PsycINFO; random*.ti,ab; 132117 results. 19. PsycINFO; groups.ti,ab; 371210 results. 20. PsycINFO; (double adj3 blind).ti,ab; 17995 results. 21. PsycINFO; (single adj3 blind).ti,ab; 1427 results. 22. PsycINFO; EXPERIMENTAL DESIGN/; 9229 results. 23. PsycINFO; controlled.ti,ab; 82008 results. 24. PsycINFO; (clinical adj3 study).ti,ab; 8039 results. 25. PsycINFO; trial.ti,ab; 69475 results. 26. PsycINFO; "treatment outcome clinical trial".md; 27486 results. 27. PsycINFO; 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26; 575154 results. 28. PsycINFO; 16 AND 27; 426 results. 29. PsycINFO; 28 [Limit to: Publication Year 2006-2014]; 264 results.		
Embase	1. EMBASE; exp DEPRESSION/; 309290 results. 2. EMBASE; CBT.ti,ab; 7696 results. 3. EMBASE; exp COGNITIVE THERAPY/; 34124 results. 4. EMBASE; "cognitive behav* therapy".ti,ab; 11217 results. 5. EMBASE; 2 OR 3 OR 4; 37424 results. 6. EMBASE; exp DRUG THERAPY/; 1678164 results. 7. EMBASE; exp ANTIDEPRESSANT AGENT/; 302113 results. 8. EMBASE; pharmacotherapy.ti,ab; 28495 results.	227	0

	9. EMBASE; medication.ti,ab; 193078 results. 10. EMBASE; adult*.ti,ab; 961658 results. 11. EMBASE; 6 OR 7 OR 8 OR 9; 2015152 results. 12. EMBASE; 1 AND 5 AND 10 AND 11; 688 results. 13. EMBASE; random*.ti,ab; 890028 results. 14. EMBASE; factorial*.ti,ab; 23115 results. 15. EMBASE; (crossover* OR cross-over*).ti,ab; 69264 results. 16. EMBASE; placebo*.ti,ab; 200148 results. 17. EMBASE; (doubl* ADJ blind*).ti,ab; 142310 results. 18. EMBASE; (singl* ADJ blind*).ti,ab; 14472 results. 19. EMBASE; assign*.ti,ab; 239701 results. 20. EMBASE; allocat*.ti,ab; 84228 results. 21. EMBASE; volunteer*.ti,ab; 176506 results. 22. EMBASE; CROSSOVER PROCEDURE/; 39769 results. 23. EMBASE; DOUBLE BLIND PROCEDURE/; 114758 results. 24. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 347300 results. 25. EMBASE; SINGLE BLIND PROCEDURE/; 18650 results. 26. EMBASE; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25; 1418211 results. 27. EMBASE; 12 AND 26; 227 results.		
Medline	17. MEDLINE; exp MAJOR DEPRESSION/; 0 results. 18. MEDLINE; "DEPRESSION (EMOTION)"/; 77827 results. 19. MEDLINE; depression.ti,ab; 222896 results.	484	

	20. MEDLINE; 17 OR 18 OR 19; 252208 results. 21. MEDLINE; CBT.ti,ab; 5285 results. 22. MEDLINE; "cognitive behav*".ti,ab; 15832 results. 23. MEDLINE; exp COGNITIVE BEHAVIOR THERAPY/; 16402 results. 24. MEDLINE; 21 OR 22 OR 23; 25235 results. 25. MEDLINE; group.ti,ab; 1791637 results. 26. MEDLINE; 24 not 25; 18288 results. 27. MEDLINE; DRUG THERAPY/; 28233 results. 28. MEDLINE; pharmacotherapy.ti,ab; 19811 results. 29. MEDLINE; medication.ti,ab; 137431 results. 30. MEDLINE; exp ANTIDEPRESSANT DRUGS/; 122569 results. 31. MEDLINE; 27 OR 28 OR 29 OR 30; 293556 results. 32. MEDLINE; 20 AND 26 AND 31; 1133 results. 33. MEDLINE; exp DEPRESSIVE DISORDER/; 82053 results. 34. MEDLINE; 20 OR 33; 278964 results. 35. MEDLINE; 26 AND 31 AND 34; 1283 results. 36. MEDLINE; "randomized controlled trial".pt; 385321 results. 37. MEDLINE; "controlled clinical trial".pt; 89633 results. 38. MEDLINE; randomized.ab; 305424 results. 39. MEDLINE; placebo.ab; 158473 results. 40. MEDLINE; "drug therapy".fs; 1731283 results. 41. MEDLINE; randomly.ab; 219958 results. 42. MEDLINE; trial.ab; 317284 results. 43. MEDLINE; groups.ab; 1392065 results. 44. MEDLINE; 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43; 3417076 results. 45. MEDLINE; 35 AND 44; 796 results.		

	46. MEDLINE; 45 [Limit to: Publication Year 2006-2014]; 484 results.		
Summary	**NA**	**NA**	

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