

Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In adults with type 2 diabetes and comorbid depressive and/or anxiety disorder, how effective is CBT, mindfulness or solution focussed therapy, compared to no psychological therapy, in improving patient outcomes?

Clarification of question using PICO structure

Patients: Adults with type 2 diabetes and comorbid depression and/or anxiety disorder

Intervention: CBT, Mindfulness or Solution focused therapy

Comparator: No psychological therapy

Outcome: Improvement in patient outcomes

Clinical and research implications

Limited evidence, from one systematic review and one additional randomised controlled trial (RCT), indicates that psychological interventions, particularly those based on CBT techniques, may be effective in reducing depressive symptoms and improving remission rates in people with diabetes and co-morbid depression. Evidence of the effects of psychological interventions on symptoms of anxiety and measures of health-related quality of life and function is inconsistent. Current evidence suggests that psychological interventions have no significant effect on glycaemic control in people with diabetes and depression. Overall, available data are sparse and further, high quality RCTs are needed to confirm the observed treatment effects and to further investigate areas of uncertainty.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one systematic review,¹ and one additional RCT,² which reported data relevant to this evidence summary. The systematic review included eight RCTs which compared a variety of different psychological interventions (minimal psychological intervention (MPI), health education and psychosocial intervention, psychological therapy (un-specified) and CBT (delivered in person, by telephone and using a web interface)) to usual care or waiting list control.¹ The included studies were conducted in people with type 1 and/or type 2 diabetes and depressive illness varying from mild to major; only one study included people with co-morbid anxiety.¹ The additional RCT compared a CBT-based intervention, the Study of Women's Emotions and Evaluation of a Psychoeducational (SWEEP), to usual care, in women with type 2 diabetes and a Center of Epidemiologic Studies Depression Scale score >16.²

Main Findings

The results of the systematic review suggested that psychological interventions were associated with improvements in depression score, e.g. medium term (1 to 6 months) weighted mean difference was -0.42 (95% CI: -0.70 to -0.14), based on three studies, and increased medium term remission of depression, OR 2.49 (95% CI: 1.44 to 4.32), compared to usual care.¹ The majority of the data were derived from studies of CBT interventions.¹ There was no evidence of any consistent, statistically significant effect on health-related quality of life or glycaemic control.¹ The results of the SWEEP study indicated that this CBT-based intervention was associated with significantly greater rates of decline in depressive symptoms over six months (SE = 1.43, $p < .01$) compared to usual care; at the end of the six month study period 35% of women in the SWEEP group remained depressed, cf. 80% of women in the control group ($p < 0.001$).² A significant treatment effect was also observed on some measures of anxiety, anger, and health-related quality of life and function, however, results were inconsistent across different measures.² The SWEEP intervention had no significant effect on glycaemic control.²

Authors Conclusions

The systematic review concluded that psychological interventions have a moderate and clinically significant effect on depression outcomes in diabetes patients and that glycaemic control and health-related quality of life outcomes had been insufficiently investigated. The review authors noted that, overall, the evidence was sparse and inconclusive due to several low-quality trials with substantial risk of bias and the heterogeneity of examined populations and interventions. The

additional RCT concluded that the CBT-based intervention, SWEEP, was more effective than usual care for treating depressed women with type 2 diabetes.

Reliability of conclusions/Strength of evidence

One high quality Cochrane review provided some evidence that psychological interventions, in particular CBT interventions, may be effective in reducing depressive symptoms and improving remission rates.¹ There is some concern regarding the reliability of these results since, as noted by the review authors, included studies were heterogeneous with respect to population characteristics and type of psychological intervention assessed.¹ However, it should be noted that the majority of data were derived from studies of CBT interventions.¹ The results of the RCT of the CBT-based intervention SWEEP were consistent with the systematic review; this study also found that the intervention was effective in reducing depressive symptoms and improving remission rates.² Results were inconsistent with respect to measures of anxiety,² and health-related quality of life and function.^{1,2} Both the systematic review and the RCT found that psychological interventions had no significant effect on glycaemic control.^{1,2} Overall, study findings are likely to be reliable, with respect to positive the effects of psychological interventions on depression, however, data are sparse and further confirmatory research is needed.

What do guidelines say?

NICE guidelines for preventing type 2 diabetes (2012, CG38) makes the following statement regarding depression;

“Depression may be a barrier to participation in an intensive lifestyle-change programme. However, physical activity (a major component of lifestyle interventions to prevent type 2 diabetes) can help manage mild to moderate depression” (pp.57)

SIGN guidelines for the management of diabetes (2010, CG116) make the following recommendations regarding the treatment of depression;

“Antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) is a useful treatment in depressed patients with diabetes and may improve glycaemic control, however tricyclic antidepressants may adversely affect metabolic control. Continued antidepressant treatment for one year after recovery may prevent recurrence of depression in some patients with diabetes.

Cognitive behavioural therapy is a psychological treatment which attempts to find links between the person’s feelings and the patterns of thinking which underpin their distress. CBT, psychotherapy programmes and coping skills training are useful in treating depression in patients with diabetes. However, cognitive behavioural therapy may be less effective in patients with complications.

In view of the limited evidence, the most sensible approach is for healthcare professionals who are involved in the treatment of significant psychological problems in children and adults with diabetes to refer to standard guidelines for those specific disorders.” (pp.28)

No recommendations could be found regarding comorbid anxiety.

The evidence included in this summary provides some additional information to, but does not contradict, the recommendations contained in current guidelines.

Date question received: 27/01/2014

Date searches conducted: 05/02/2014

Date answer completed: 10/02/2014

References

SRs

1. Baumeister, H, Hutter, N, Bengel, J. (2012). Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *Cochrane Database of Systematic Reviews*.

RCTS

2. Penckofer, S. M., Ferrans, C., Mumby, P., Byrn, M., Emanuele, M. A., Harrison, P. R., Durazo-Arvizu, R. A., Lustman, P., (2012). "A psychoeducational intervention (SWEEP) for depressed women with diabetes." *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 44(2): 192-206.

Guidelines

Scottish Intercollegiate Guidelines Network (2010) Management of Diabetes. A National Clinical Guideline. CG116. Edinburgh: Scottish Intercollegiate Guidelines Network.

National Institute for Health and Care Excellence (2012) Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. CG38. London: National Institute for Health and Care Excellence.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Baumeister 2012	11/2011	<p><i>Population:</i> Studies of adults with a diagnosis of diabetes mellitus were included. Depressive disorders should have been assessed by standardised interviews, self-reports, medical records or physicians' diagnosis.</p> <p><i>Intervention:</i> Studies comprised of psychological interventions such as CBT, Psychodynamic psychotherapy, interpersonal therapy and other approaches such as non-directive or supportive therapy and counselling were included. Studies not explicitly describing the intervention were only included if techniques used could be assigned to one of the above categories.</p> <p><i>Comparator:</i> 'No intervention' or 'usual care.' Trials with a control group receiving pharmacological or psychological treatment were considered if treatment approaches had differential or incremental effects.</p> <p><i>Outcomes:</i></p>	Total n=18 studies, n = 8 studies of psychological interventions (total number of participants unclear)	<p>The objective of this systematic review was to determine the effects of psychological and pharmacological interventions for depression in patients with diabetes and depression.</p> <p>Only the assessment of psychological interventions is included in this evidence summary.</p> <p>Reporting of participant characteristics was limited, but it was clear that the review included both studies which included people with type 2 diabetes only and studies which included people with either type 1 or type 2. Additionally the type of depressive illness specified by included studies varied from mild to major and only one study included people with co-morbid anxiety.</p> <p>Included studies assessed a range of psychological interventions: minimal psychological intervention (MPI); health</p>	<p>The review reported a clear research objective and fully defined inclusion criteria.</p> <p>Four bibliographic databases were searched without language restriction. Electronic searches were supplemented by screening the references of included studies and relevant systematic reviews and meta-analyses.</p> <p>All stages of the review process</p>

		<p>Primary outcome: the reduction of depressive symptoms or remission of clinically significant depression. This was assessed by validated self-report questionnaires or standardised interviews. Glycaemic control (HbA1c or gHb) were also primary outcomes for studies. Other measures were HRQoL, Healthcare costs, Adherence to diabetic treatment regimen, Diabetes complications and Death. Studies with any length of follow-up were included.</p> <p><i>Study design:</i> Randomised controlled trials (RCTs)</p>		<p>education and psychosocial intervention; psychological therapy (un-specified); CBT (delivered in person, by telephone and using a web interface).</p> <p>Studies of psychological interventions all has 'usual care' or waiting 'list control' as the comparator, however, no description of what constituted 'usual care' was provided.</p> <p>Analyses, for each outcome were stratified by follow-up duration: short term (immediately after treatment); medium term (1 to 6 months after treatment); long term (>6 months after treatment).</p> <p>Depression score: Seven studies reported a short term outcome; no meta-analysis was conducted and effect sizes (standard mean difference) ranged from -0.14 (95% CI: -0.41 to 0.13) to -1.47 (95% CI: -2.04 to -0.90), in favour of the psychological intervention; three studies of CBT interventions all reported a statistically significant treatment effect. The pooled estimate of medium term treatment effect, weighted mean difference (WMD) was -0.42 (95% CI: -0.70 to -0.14), based on three studies two of which were on CBT</p>	<p>included measures to minimise error and/or bias (involvement of at least two reviewers).</p> <p>The methodological quality of included studies was assessed and a summary of the risk of bias was provided.</p> <p>Although the authors stated that they did not conduct meta-analyses where there was substantial statistical between study heterogeneity, those meta-analyses which were reported included studies</p>
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			<p>interventions. One study, of MPI, reported a borderline significant long-term treatment effect on depression score (-0.31 (95% CI: -0.58 to -0.04)).</p> <p>Remission of depression: The results of meta-analyses indicated that psychological therapies were associated with increase depression remission rates. The estimated summary effect measures for remission of depression were odds ratio (OR) 2.88 (95% CI: 1.58 to 5.25) for the short term, based on four studies three of which were on CBT interventions, and OR 2.49 (95% CI: 1.44 to 4.32) for the medium term, based on two studies of CBT interventions.</p> <p>There was no consistent evidence to suggest that psychological therapies were associated with an improvement in glycaemic control (HbA1c), health-related quality of life, or medication adherence.</p>	<p>with a variety of very different psychological interventions, conducted in clinically heterogeneous populations and using different tools to assess outcome.</p>
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RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Penckofer 2012	<i>Participants:</i> The study included adults females (aged	n=74 (SWEEP	The study aimed to assess the effectiveness of the Study of Women's Emotions and Evaluation of a Psychoeducational	Four randomisation

	<p>18 or over), who have had type 2 diabetes for over 6 months and had an average score of 16 or over on the Center of Epidemiologic Studies Depression Scale from 2 screenings (phone and baseline) within 4 weeks of one another.</p> <p><i>Intervention:</i> Women assigned to the SWEEP program were educated about type 2 diabetes this included; recognition of signs and symptoms of depression, anxiety and anger, the relationship between moods, metabolic control and self-care behaviours and the management of depression, anxiety and anger using CBT. The program was delivered over eight, weekly, one hour sessions. Two additional booster sessions were delivered during the six month study period.</p> <p><i>Comparator:</i> 'No study-related intervention' but were allowed treatment for diabetes and depression outside of the study if required.</p> <p><i>Outcomes:</i> For depression the Center of Epidemiologic Studies Depression Tool was used. For anxiety the State-Trait Anxiety Inventory was used and for anger the</p>	<p>n=38, usual care n=36)</p>	<p>(SWEEP), a group therapy for depression treatment based on CBT principles, in women with type 2 diabetes. There were no significant differences between the treatment and control groups, at baseline, with respect to demographic characteristics, duration of diabetes and measures of glycaemic control, or measures of mood depression, anxiety and anger), health-related quality of life and function. There was also no significant difference between the groups in self-reported use of psychoactive medication or psychotherapy. During the study, one woman in the treatment group and two in the control group initiated medications to treat their mood, but there was no change in the number of women receiving psychotherapy.</p> <p>Participants in the SWEEP group had a significantly greater rate of decline in depression than those in the control group (SE = 1.43, p<.01); at the end of the six month study period 35% of women in the SWEEP group remained depressed, cf. 80% of women in the control group (p < 0.001).</p> <p>Participants in the SWEEP group had significantly greater rates of decline in trait anxiety than the control group (SE = 1.46, p<.01), but there was no significant difference in the rate of decline of state anxiety.</p> <p>Participants in the SWEEP group had a significantly greater rate of decline in anger expression than those in the control group (SE = 0.22, p<.05), but there were no significant differences between the groups in state or trait anger.</p>	<p>lists were generated using a random seed number by the statistician; participants were matched on level of depression.</p> <p>Assignment to groups was made after baseline assessment.</p> <p>The participants, the data collector, and the intervention staff (nurse and psychologist) were not blinded to the</p>
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	<p>State-Trait Anger Expression Inventory was used. The Diagnostic Interview Schedule was also another primary outcome. Secondary outcomes included Glycemic Control and Health Related Quality of Life. Assessments were carried out at Baseline, 3 Months and 6 Months.</p>		<p>There were no significant differences in glycaemic control between the SWEEP and control groups.</p> <p>Women in the SWEEP group had significantly greater rates of improvement in overall quality of life and in psychological and spiritual satisfaction than those in the control group (SE = 0.47, $p < .05$ and SE = 0.33, $p < .01$, respectively); there was no significant difference between the groups in the health and functioning outcome.</p> <p>Functional status measures indicated that SWEEP was associated with a significantly greater increase in mental health function (SE = 1.54, $p < .05$), but not in physical health function, compared to the control condition.</p>	<p>group assignment. Results of ITT analyses were reported</p> <p>Results were reported for all specified outcome measures.</p>
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Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Baumeister 2012					

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Penckofer 2012						

 Low Risk

 High Risk

 Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
<i>SRs and Guidelines</i>			
NICE			
DARE	(diabetes adj2 mellitus) IN DARE 1116 Delete 2 ((typ* adj (2 OR II)) adj3 diabet*) IN DARE 642 Delete 3 ((keto?resist* OR non?keto*) adj6 diabet*) IN DARE 0 Delete 4 (((late Or adult* Or matur* Or slow OR stabl*) adj3 onset) AND diabet*) IN DARE 6 Delete 5 (MODY OR NIDDM OR T2DM) IN DARE 14 Delete 6 MeSH DESCRIPTOR Diabetes Insipidus EXPLODE ALL TREES 1 Delete 7 MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES 2024 Delete 8 MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES 1000 Delete 9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 2400 Delete 10 (depress*) IN DARE 1934 Delete 11 MeSH DESCRIPTOR Depression EXPLODE ALL TREES 487 Delete 12 MeSH DESCRIPTOR Depressive Disorder EXPLODE ALL TREES 875 Delete 13 MeSH DESCRIPTOR Depressive Disorder, Major EXPLODE ALL TREES 275 Delete 14 (anxi*) IN DARE 1153 Delete	19	

	15 MeSH DESCRIPTOR Anxiety EXPLODE ALL TREES 226 Delete 16 MeSH DESCRIPTOR Anxiety Disorders EXPLODE ALL TREES 407 Delete 17 #10 OR #11 OR #12 OR #13 2372 Delete 18 #14 OR #15 OR #16 1415 Delete 19 #17 AND #18 807 Delete 20 #9 AND #19		
CDSR			
Primary studies			
CENTRAL	1 "type 2 diabetes" 8341 #2 "Diabetes mellitus type 2" 8528 #3 "non insulin dependent diabetes" 2696 #4 "adult onset diabetes" 23 #5 NIDDM 1087 #6 #1 or #2 or #3 or #4 or #5 12340 #7 MeSH descriptor: [Depressive Disorder] explode all trees 7069 #8 depression 32154 #9 MeSH descriptor: [Anxiety Disorders] explode all trees 4591 #10 anxiety 20850 #11 #7 or #8 or #9 or #10 47169 #12 #6 and #11 403 #13 CBT 2323 #14 "Cognitive behavio* therapy" 3982 #15 MeSH descriptor: [Cognitive Therapy] explode all trees 4419 #16 mindfulness 626 #17 MeSH descriptor: [Mindfulness] explode all trees0 #18 "solution focused therapy" 44 #19 "solution focused brief therapy" 12 #20 SFTB 0	20	

	#21 #13 or #14 or #15 or #16 or #17 or #18 or #19 7265 #22 #12 and #21 55 Central only 20		
PsycINFO	<ol style="list-style-type: none"> 1. PsycINFO; "type 2 diabetes".ti,ab; 3322 results. 2. PsycINFO; "non insulin dependent diabetes".ti,ab; 163 results. 3. PsycINFO; NIDDM.ti,ab; 91 results. 4. PsycINFO; "adult onset diabetes".ti,ab; 22 results. 5. PsycINFO; "Diabetes mellitus type 2".ti,ab; 70 results. 6. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5; 3559 results. 7. PsycINFO; "DEPRESSION (EMOTION)"/ OR exp MAJOR DEPRESSION/; 110220 results. 8. PsycINFO; (depression OR "depressive disorder*").ti,ab; 170825 results. 9. PsycINFO; ANXIETY/ OR ANXIETY DISORDERS/; 54825 results. 10. PsycINFO; anxiety*.ti,ab; 129601 results. 11. PsycINFO; 7 OR 8 OR 9 OR 10; 274756 results. 12. PsycINFO; 6 AND 11; 507 results. 13. PsycINFO; CBT.ti,ab; 7246 results. 14. PsycINFO; "Cognitive behav*".ti,ab; 26796 results. 15. PsycINFO; COGNITIVE BEHAVIOR THERAPY/; 10651 results. 16. PsycINFO; Mindfulness.ti,ab; 4016 results. 17. PsycINFO; MINDFULNESS/; 2911 results. 18. PsycINFO; "solution focus* therapy".ti,ab; 378 results. 19. PsycINFO; "Solution focused brief therapy".ti,ab; 319 results. 20. PsycINFO; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19; 32673 results. 	15	

	21. PsycINFO; 12 AND 20; 15 results.		
Embase	<p>22. EMBASE; "type 2 diabetes".ti,ab; 92833 results.</p> <p>23. EMBASE; "non insulin dependent diabetes".ti,ab; 9730 results.</p> <p>24. EMBASE; NIDDM.ti,ab; 7916 results.</p> <p>25. EMBASE; "adult onset diabetes".ti,ab; 394 results.</p> <p>26. EMBASE; "Diabetes mellitus type 2".ti,ab; 2355 results.</p> <p>27. EMBASE; 22 OR 23 OR 24 OR 25 OR 26; 107153 results.</p> <p>28. EMBASE; "DEPRESSION (EMOTION)"/ OR exp MAJOR DEPRESSION/; 36050 results.</p> <p>29. EMBASE; (depression OR "depressive disorder*").ti,ab; 283378 results.</p> <p>30. EMBASE; ANXIETY/ OR ANXIETY DISORDERS/; 149951 results.</p> <p>31. EMBASE; anxiety*.ti,ab; 146545 results.</p> <p>32. EMBASE; 28 OR 29 OR 30 OR 31; 420431 results.</p> <p>33. EMBASE; 27 AND 32; 2181 results.</p> <p>34. EMBASE; CBT.ti,ab; 7288 results.</p> <p>35. EMBASE; "Cognitive behav*".ti,ab; 21380 results.</p> <p>36. EMBASE; COGNITIVE BEHAVIOR THERAPY/; 33228 results.</p> <p>37. EMBASE; Mindfulness.ti,ab; 2437 results.</p> <p>38. EMBASE; MINDFULNESS/; 185 results.</p> <p>39. EMBASE; "solution focus* therapy".ti,ab; 100 results.</p> <p>40. EMBASE; "Solution focused brief therapy".ti,ab; 57 results.</p> <p>41. EMBASE; 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40; 44149 results.</p> <p>42. EMBASE; 33 AND 41; 67 results.</p>	40	

	<p>43. EMBASE; random*.ti,ab; 881251 results.</p> <p>44. EMBASE; factorial*.ti,ab; 22898 results.</p> <p>45. EMBASE; (crossover* OR cross-over*).ti,ab; 69781 results.</p> <p>46. EMBASE; placebo*.ti,ab; 201296 results.</p> <p>47. EMBASE; (doubl* ADJ blind*).ti,ab; 144080 results.</p> <p>48. EMBASE; (singl* ADJ blind*).ti,ab; 14405 results.</p> <p>49. EMBASE; assign*.ti,ab; 239587 results.</p> <p>50. EMBASE; allocat*.ti,ab; 82914 results.</p> <p>51. EMBASE; volunteer*.ti,ab; 177839 results.</p> <p>52. EMBASE; CROSSOVER PROCEDURE/; 39783 results.</p> <p>53. EMBASE; DOUBLE BLIND PROCEDURE/; 120281 results.</p> <p>54. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 366508 results.</p> <p>55. EMBASE; SINGLE BLIND PROCEDURE/; 18961 results.</p> <p>56. EMBASE; 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55; 1419080 results.</p> <p>57. EMBASE; 42 AND 56; 40 results.</p>		
Medline	<p>22. MEDLINE; "type 2 diabetes".ti,ab; 61033 results.</p> <p>23. MEDLINE; "non insulin dependent diabetes".ti,ab; 8380 results.</p> <p>24. MEDLINE; NIDDM.ti,ab; 6779 results.</p> <p>25. MEDLINE; "adult onset diabetes".ti,ab; 369 results.</p> <p>26. MEDLINE; "Diabetes mellitus type 2".ti,ab; 1240 results.</p> <p>27. MEDLINE; 22 OR 23 OR 24 OR 25 OR 26; 72628 results.</p> <p>28. MEDLINE; "DEPRESSION (EMOTION)"/ OR exp MAJOR DEPRESSION/; 72369 results.</p> <p>29. MEDLINE; (depression OR "depressive disorder").ti,ab; 215616 results.</p> <p>30. MEDLINE; ANXIETY/ OR ANXIETY DISORDERS/; 71641</p>	25	

	<p>results.</p> <p>31. MEDLINE; anxiety*.ti,ab; 106121 results.</p> <p>32. MEDLINE; 28 OR 29 OR 30 OR 31; 322792 results.</p> <p>33. MEDLINE; 27 AND 32; 1338 results.</p> <p>34. MEDLINE; CBT.ti,ab; 4734 results.</p> <p>35. MEDLINE; "Cognitive behav*".ti,ab; 14417 results.</p> <p>36. MEDLINE; COGNITIVE BEHAVIOR THERAPY/; 14734 results.</p> <p>37. MEDLINE; Mindfulness.ti,ab; 1584 results.</p> <p>38. MEDLINE; MINDFULNESS/; 25 results.</p> <p>39. MEDLINE; "solution focus* therapy".ti,ab; 50 results.</p> <p>40. MEDLINE; "Solution focused brief therapy".ti,ab; 28 results.</p> <p>41. MEDLINE; 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40; 24178 results.</p> <p>42. MEDLINE; 33 AND 41; 35 results.</p> <p>43. MEDLINE; "randomized controlled trial".pt; 360179 results.</p> <p>44. MEDLINE; "controlled clinical trial".pt; 86981 results.</p> <p>45. MEDLINE; randomized.ab; 281196 results.</p> <p>46. MEDLINE; placebo.ab; 148873 results.</p> <p>47. MEDLINE; "drug therapy".fs; 1651543 results.</p> <p>48. MEDLINE; randomly.ab; 204629 results.</p> <p>49. MEDLINE; trial.ab; 289779 results.</p> <p>50. MEDLINE; groups.ab; 1309429 results.</p> <p>51. MEDLINE; 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50; 3233063 results.</p> <p>52. MEDLINE; 42 AND 51; 25 results.</p>		
Summary	NA	NA	

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