BEST in Mental Health
BEST.awp.nhs.uk

Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults with bipolar disorder, how effective is lithium, compared to quetiapine, in managing symptoms of bipolar and improving patient outcomes?"

Clarification of question using PICO structure

Patients: Adults with bipolar disorder
Intervention: Lithium
Comparator: Quetiapine
Outcome: Managing symptoms of bipolar and improving patient outcomes.

Email: awp.BESTinMH@nhs.net Phone: 0117 378 4232/4233/4335 @BESTinMH

Clinical and research implications

Evidence from one systematic review and network meta-analysis and from one additional, large randomised controlled trial (RCT) indicates no significant difference in effectiveness of quetiapine compared to lithium, for the treatment of mania in people with bipolar disorder. Data from two large RCTs indicate that quetiapine may be more effective than lithium in managing depressive symptoms in people with bipolar disorder; this apparent differential treatment effect may warrant further investigation.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one systematic review,[1] and two additional randomised controlled trials (RCTs),[4,5] which reported data relevant to this evidence summary. The systematic review used a network meta-analysis to produce estimates of the comparative effectiveness of 14 antimanic drugs and placebo for the treatment of acute mania in adults with bipolar I disorder.[1] An additional RCT compared continuation of quetiapine to switching to lithium or placebo, in patients with bipolar I disorder who had been stabilised on quetiapine; outcome measures were time to recurrence of any mood episode, depressive mod episode, or manic mood episode.[4] The second RCT compared quetiapine, lithium and placebo for the treatment of depressive episodes in patients with bipolar I or II disorder.[5]

Main Findings

The systematic review included two studies which provided data for direct comparison of quetiapine vs. lithium. The summary estimate of change in Young Mania Rating Scale (YMRS), baseline to 3 weeks, derived from these two studies indicated no statistically significant difference between the two treatments.[1] The results of the network meta-analysis also indicated no statistically significant difference in change in YMRS score between quetiapine and lithium.[1] When all drugs were ranked in order of their overall probability of being the best treatment (in terms of both efficacy and drop out rate) quetiapine was ranked 4th (68%), after risperidone, olanzapine and haloperidol, and lithium was ranked 8th (43%).[1] Results of the discontinuation RCT indicated that continuation of quetiapine was associated with a significantly longer time to recurrence of any mood event than switching to lithium, HR 0.66 (95% CI: 0.49 to 0.88).[4] However, when data were stratified by type of mood event (depressive or manic), the effect was only significant for depressive events, HR 0.54 (95% CI: 0.35 to 0.84).[4] Similarly, when data were stratified by disease type (rapid cycling or non-rapid cycling), quetiapine was only associated with a significantly longer time to recurrence of any mood event than lithium in patients who were not rapid-cycling, HR 0.68 (95% CI: 0.50 to 0.94).[4] The second RCT found that quetiapine (600 mg/d) was associated with significantly greater improvements in depressive symptoms (baseline to 8 weeks) than lithium; the differences in Montgomery-Åsberg Depression Rating Scale (MADRS) score and Hamilton Depression Rating Scale (HDRS) score were -2.49 ($p = 0.013$) and -1.81 ($p = 0.026$), respectively.[5]

Authors Conclusions

A systematic review, which included network meta-analysis, concluded that overall, antipsychotic drugs were significantly more effective than mood stabilisers for the treatment of manic episodes in bipolar disorder, and that risperidone, olanzapine, and haloperidol should be considered as among

the best of the available treatment options. One additional RCT concluded that quetiapine was more effective than placebo for the treatment of episodes of acute depression in bipolar disorder, whilst lithium did not significantly differ from placebo on the main measures of efficacy. A further RCT concluded that, in patients stabilised with quetiapine treatment, continuation of quetiapine significantly increased time to recurrence of any mood, manic, or depressive event compared with switching to placebo; switching to lithium was also more effective than placebo for the prevention of manic and depressive events.

Reliability of conclusions/Strength of evidence

One high quality Cochrane systematic review concluded that antipsychotic drugs were significantly more effective than mood stabilisers for the treatment of manic episodes in bipolar disorder.[1] However, with respect to the question posed by this evidence summary, results of both the network meta-analysis and a direct comparison random effects meta-analysis indicated no statistically significant difference in effect on mania symptoms (YMRS) between quetiapine and lithium.[1] One additional, large, high quality RCT reported that quetiapine was more effective than lithium for the treatment of depressive symptoms in people with bipolar disorder.[5] A second large discontinuation trial, which had some reporting issues and which excluded inadequately monitored lithium patients from its 'ITT analysis, found that continuation of quetiapine treatment was associated with significantly longer time to recurrence of a depressive episode (but not a manic episode) than switching to lithium.[4] These results are likely to be reliable.

What do guidelines say?

Drug treatment for acute mania for people not taking antimanic medication;

"If a patient develops acute mania when not taking antimanic medication, treatment options include starting an antipsychotic, valproate or lithium. When making the choice, prescribers should take into account preferences for future prophylactic use, the side-effect profile, and consider:

- prescribing an antipsychotic if there are severe manic symptoms or marked behavioural disturbance as part of the syndrome of mania
- prescribing valproate or lithium if symptoms have responded to these drugs before, and the person has shown good compliance
- avoiding valproate in women of child-bearing potential
- using lithium only if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate." (pp.22)

"If treating acute mania with antipsychotics, olanzapine, quetiapine or risperidone should normally be used, and the following should be taken into account:

- individual risk factors for side effects (such as the risk of diabetes)
- the need to initiate treatment at the lower end of the therapeutic dose range recommended in the summary of product characteristics and titrate according to response
- that if an antipsychotic proves ineffective, augmenting it with valproate or lithium should be considered
- that older people are at greater risk of sudden onset of depressive symptoms after recovery from a manic episode." (pp.22)

Drug treatment of acute mania for people taking antimanic medication;

"If a patient already taking an antipsychotic experiences a manic episode, the dose should be checked and increased if necessary. If there are no signs of improvement, the addition of lithium or

valproate should be considered."

"If a patient already taking valproate* experiences a manic episode, the dose should be increased until:

- symptoms start to improve, or
- side effects limit further dose increase.
- If there are no signs of improvement, the addition of olanzapine, quetiapine, or risperidone should be considered. Patients on doses higher than 45 mg per kilogram should be monitored carefully." (pp.23)

The evidence included in this summary is consistent with current guidance, with the additional note that quetiapine may be more effective than lithium for the management of depressive symptoms in people with bipolar disorder.

Date question received: 12/02/2014
Date searches conducted: 20/02/2014
Date answer completed: 03/03/2014

References

SRs

1. Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., Purgato, M., Spineli, L.M., Goodwin, G.M. and Geddes, J.R. (2011) Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet 378* pp.1306-15.

RCTs

2. Weisler, R.H., Nolen, W.A., Neijber, A., Hellqvist, A. and Paulsson, B. (2011) Continuation of Quetiapine Versus Switching to Placebo or Lithium for Maintenance Treatment of Bipolar I Disorder (Trial 144: A Randomized Controlled Study). *Journal of Clinical Psychiatry 72* (**11**) pp.1452-64.
3. Young, A.H., McElroy, S.L., Bauer, M., Philips, N., Chang, W., Olausson, B., Paulsson, B. and Brecher, M. (2010) A Double-Blind, Placebo-Controlled Study of Quetiapine and Lithium Monotherapy in Adults in the Acute Phase of Bipolar Depression (EMBOLDENI). *Journal of Clinical Psychiatry 71* (**2**) pp.150-162.

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.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Cipriani et al. (2011)		*Participants:* Adults with a primary diagnosis of bipolar I disorder (manic or mixed episode) (n=16,073) *Intervention:* An active antimanic drug at therapeutic dose range; aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate or ziprasidone. Combination and augmentation studies were also included. *Comparator:* Another active antimanic drug (from the list above), or oral placebo. *Outcomes:* Primary: Change on Young Mania Rating Scale (YMRS) and drop out rate (treatment period 3 weeks). Secondary: Proportion of patients who responded to treatment. *Study design:* Randomised, double-blind trials.	n= 68 (two studies provided direct comparison data for quetiapine vs. lithium)	This review aimed to use network meta-analysis methods to provide estimates of the comparative effectiveness of all antimanic dugs for the treatment of acute mania in people with bipolar disorder. Included studies provided data for 14 treatments: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, paliperidone, quetiapine, risperidone, topiramate, ziprasidone, and placebo. The mean duration of studies was 3·4 ± 1.1 weeks, and the mean sample size was 105·7 patients per group (range 7 to 458). Fifty two of the 68 included studies, with 13,436 (76%) of participants, were conducted in people with moderate to severe manic symptoms, and 66 of the 68 studies were conducted in in-patient settings. Two studies, with a total of 360 participants provided data for a direct comparison	The review reported a clearly stated research question and defines appropriate inclusion criteria. The search strategy included a number of bibliographic databases, as well as measures to identify un-published studies. There were no apparent language, or publication status restrictions. The article used data form a Cochrane review, which followed

				between quetiapine and lithium. Summary estimates indicated no statistically significant differences between the two treatments, on any outcome measure: Change in YMRS, SMD –0·11 (95% CI: –0·43 to 0·20); response to treatment, OR 1·47 (95% CI: 0·67 to 3·23), and drop outs OR 0·45 (95% CI: 0·21 to 0·95). The network meta-analysis produced similar effectiveness results for the comparison lithium vs. quetiapine; change in YMRS, SMD –0·01 (95% CI: –0·18 to 0·17). However, this analysis indicated and small difference in drop out rates, favouring quetiapine OR 1·63 (95% CI: 1·06 to 2·54). When drugs were ranked in order of their overall probability of being the best treatment (in terms of both efficacy and drop out rate) quetiapine was ranked 4th (68%), after risperidone, olanzapine and haloperidol, and lithium was ranked 8th (43%). 15, 673 participants (63 studies) contributed to the efficacy analysis and 15,626 participants (65 studies) contributed to the acceptability analysis.	standard methods to minimise error and/or bias in the review process and included assessment of the methodological quality of studies. Robust meta-analytic methods were used.

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Weisler et al. (2011)	*Participants:* Pre-randomisation phase: Participants aged ≥18 years with DSM-IV-diagnosed bipolar I disorder and a current or recent manic, depressive, or mixed episode. Participants were recruited to the pre-randomisation phase from psychiatry units, community practices, and institutional review board–approved advertisements but were investigated only as outpatients during the study. During the pre-randomisation phase, participants were prescribed quetiapine (300–800 mg/d) for 4–24 weeks 100 mg on day 1, rising in 100-mg increments to 400 mg on day 4 and 600 mg on day 5. From day 6, the quetiapine dose was titrated by investigators between 300 and 800 mg/d, depending on efficacy and tolerance. Quetiapine was administered twice daily in divided doses. Exclusion criteria: DSM-IV diagnosis of anxiety disorder, treated with medication in the preceding year; known intillerance or lack of response to quetiapine or lithium; substance or alcohol dependence; Use of cytochrome P450 3A4	n=2438 enrolled in the pre-randomisation quetiapine phase, n=1226 randomised, n=1172 completed the full study.	This trial aimed to investigate the efficacy and safety of quetiapine monotherapy as maintenance treatment in bipolar I disorder, in comparison with switching to placebo, in patients who had stabilised from an acute episode during open-label quetiapine treatment. Switching to lithium monotherapy was included as a reference intervention, and comparisons of the efficacy of quetiapine versus lithium were included as supportive analyses. Baseline demographic and disease characteristics did not differ between patients in the quetiapine, lithium, and placebo groups in the ITT population. During the randomised phase, the mean dose in the quetiapine group (n = 404) was 546 ± 173 mg, with a median treatment duration of 158 days. For the lithium group (n = 364), the mean serum concentration was 0.63 ± 0.45 mEq/L, with a median treatment duration of 83 days. Continuation of quetiapine was associated with a significantly longer time to recurrence of any mood event than switching to lithium, HR 0.66 (95% CI: 0.49 to 0.88), p = 0.005. Continuation of quetiapine was also associated with a significantly longer time to recurrence of any depressive event, HR 0.54 (95% CI: 0.35 to 0.84), p = 0.006, but there was no significant difference in the time to recurrence of any manic event.	No details of randomisation procedure or allocation concealment were reported. The study was described as 'double-blind', but no details on blinding of outcome assessment were reported. Results were reported for all specified outcome measures. Analyses were described as

	inducers in 14 days prior to enrolment; unstable medical illness; elevated TSH; diabetes mellitus; female of child baring age, not using reliable contraception or pregnant. Randomised phase: Participants who achieved stabilisation by at least week 20 and who maintained stability for at least 4 subsequent weeks defined by a YMRS total score ≤12 and a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≤12) were randomised to continue quetiapine, switch to lithium, or switch to placebo. Exclusion criteria: hospitalisation for mood episode or suicide or homicide attempt during pre-randomisation phase; electroconvulsive therapy during pre-randomisation phase; suicide or homicide attempt during pre-randomisation phase. *Intervention*: Continued quetiapine; dose was adjusted within the range of 300 to 800 mg/d, depending on efficacy and tolerance for 104 weeks. *Comparator:* Switch to placebo or lithium. Lithium dose was started at 600 mg/d and increased to		When data were stratified by rapid-cycling status, the time to recurrence of any mood event remained significantly longer in the quetiapine group compared to the lithium group, for patients who were not rapid-cycling, HR 0.68 (95% CI: 0.50 to 0.94), however, there was no significant difference between the groups in rapid-cycling patients. Time to all-cause discontinuation was significantly longer in the quetiapine than in the lithium group (P < .0001).	ITT, but fifty-four patients were excluded from the ITT population because of inadequate serum lithium concentration monitoring.

	900 mg/d at day 4. After 2 weeks and subsequently at every visit, blood samples were taken for determination of trough serum lithium concentrations, and lithium doses were adjusted to obtain concentrations between 0.6 mEq/L and 1.2 mEq/L. Both taken for 104 weeks. *Outcomes:* Time to recurrence of any mood event (manic, depressed or mixed). Recurrence was defined as at least 1 of the following: initiation of an antipsychotic, antidepressant, anxiolytic (other than lorazepam), or other medication to treat a mood event; hospitalization for a mood event; YMRS score " ≥20 or MADRS score " ≥20 at 2 consecutive assessments or final assessment if the patient discontinued; or discontinuation from the study if, according to the investigator, discontinuation was due to a mood event.			
Young et al. (201)	*Paricipants:* Adult outpatients aged 18-65 years with a diagnosis of bipolar I or II according to DSM-IV who were experiencing a recent major depressive episode, HDRS score ≥20 and HDRS item 1 (depressed mood) score ≥2. Exclusion criteria: active axis I disorders, requiring treatment, within 6	n=802 (n=265 quetiapine 300mg/d, n=268 quietpine 600 mg/d, n=136 lithium, n=133 placebo).	This trial aimed to compare the efficacy and tolerability of quetiapine and lithium monotherapy to placebo, for the treatment of major depressive episodes in bipolar disorder. Baseline demographic and disease characteristics did not differ significantly between the three groups. The mean age of study participants was 42.2 years and 59.3% were women.	Randomisation was stratified by bipolar diagnosis (I or II). Randomisation was centralised,

	months of study entry; total YMRS score >12; history of non-response to treatment with ≥2 classes of anti-depressant during the current episode; known non-response to quetiapine or lithium; substance dependence or abuse; current serious suicidal or homicidal risk; clinically relevant medical illness. *Intervention:* Quetiapine, initiated at a dose of 50 mg/d and increased to a target dose of 300 mg/d by day 4 or 600 mg/d by day 8. *Comparator:* Lithium 600-1800 mg/d or placebo. *Outcomes:* Primary: Change in depression (MADRS total score) from baseline to 8 weeks. Secondary: response (≥50% reduction in MADRS total score); remission (MADRS total score ≤12); Clincal Global Impressions-Bipolar Change (CGI-BP) resoponse at 8 weeks.	n = 783 included in the ITT analysis	Quetiapine 600 mg/d (but not 300 mg/d) was associated with significantly greater improvements in MADRS total score (baseline to week 8) than lithium; difference of -2.49 points at week 8, p = 0.013. At the end of week 8, 68.6% of patients treated with quetiapine 300 mg/d, 69.6% of patients treated with quetiapine 600 mg/d, and 62.5% of patients treated with lithium met the criteria for response; no comparative statistics for quetiapine vs. lithium were reported. At the end of week 8, 69.8% of patients treated with quetiapine 300 mg/d, 70.3% of patients treated with quetiapine 600 mg/d, and 62.5% of patients treated with lithium met the criteria for response; no comparative statistics for quetiapine vs. lithium were reported. At week 8, both doses of quetiapine were significantly better than lithium at improving HDRS total score; difference -1.62, p = 0.047 for 300 mg/d quetiapine and -1.81, p = 0.026 for 600 mg/d quetiapine. No comparative data for quetiapine vs. lithium were reported for HARS, CGI-BP, or measures of function (SDS and MOS Cog). However, for all these measures, only quetiapine treatment was associated with a statistically significant improvement compared to placebo.	numbers were not sequential within sites, and no member of the investigation team had access to the randomisation scheme during the study. Study participants and investigators were blind to treatment allocation; all medication and packaging was identical. Analyses were described as ITT (defined as patients who received at least one dose

				of study medication and had at least one post-baseline assessment). Results were reported for all specified outcomes.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Cipriani et al. (2011)	☺	☺	☺	☺	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Weisler et al. (2011)	?	?	☺	?	☹	☺
Young et al. (2010)	☺	☺	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Quetiapine and bipolar	23	
DARE	(lithium OR camcolit OR carbolith OR liskonum OR litarex OR lithane OR lithocarb OR lithizine OR lithonate OR lithotabs OR manialith OR phasal OR priadel OR quilonorm OR quilonum OR li-liquid) IN DARE 113 Delete 2 (bipolar* OR bi-polar* OR manic* OR mania*) IN DARE 260 Delete 3 ((mood Or affective) adj2 disorder*) IN DARE 205 Delete 4 MeSH DESCRIPTOR Lithium EXPLODE ALL TREES 28 Delete 5 MeSH DESCRIPTOR Lithium Carbonate EXPLODE ALL TREES 11 Delete 6 MeSH DESCRIPTOR Bipolar Disorder EXPLODE ALL TREES 156 Delete 7 MeSH DESCRIPTOR Mood Disorders EXPLODE ALL TREES 1041 Delete 8 MeSH DESCRIPTOR Affective Disorders, Psychotic EXPLODE ALL TREES 159 Delete 9 #1 OR #4 OR #5 120 Delete 10 #2 OR #3 OR #6 OR #7 OR #8 1222 Delete 11 #9 AND #10	93	
Primary studies			
CENTRAL	#1 bipolar:ti,ab,kw (Word variations have been searched) 3601 #2 MeSH descriptor: [Bipolar Disorder] explode all trees 1501 #3 Enter terms for search manic or maniamanic or mania 1739 #4 Enter terms for search #1 or #2 or #3#1 or #2 or #3 4286 #5 Enter terms for search lithiumlithium 2060	47	

	#6 MeSH descriptor: [Lithium] explode all trees 643 #7Enter terms for searc#5 or #62060 #8Enter terms for searcquetiapine975 #9Enter terms for searc#4 and #7 and #8 92		
PsycINFO	1. PsycINFO; BIPOLAR DISORDER/; 18869 results. 2. PsycINFO; bipolar.ti,ab; 26597 results. 3. PsycINFO; mania.ti,ab; 8042 results. 4. PsycINFO; manic.ti,ab; 10616 results. 5. PsycINFO; hypomani*.ti,ab; 2563 results. 6. PsycINFO; "rapid cycling".ti,ab; 843 results. 7. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5 OR 6; 36997 results. 8. PsycINFO; LITHIUM/; 4853 results. 9. PsycINFO; lithium.ti,ab; 8790 results. 10. PsycINFO; 8 OR 9; 9114 results. 11. PsycINFO; quetiapine.ti,ab; 2565 results. 12. PsycINFO; QUETIAPINE/; 1421 results. 13. PsycINFO; 11 OR 12; 2610 results. 14. PsycINFO; 7 AND 10 AND 13; 194 results. 15. PsycINFO; CLINICAL TRIALS/; 7320 results. 16. PsycINFO; random*.ti,ab; 126518 results. 17. PsycINFO; groups*.ti,ab; 360184 results. 18. PsycINFO; (doubl* adj3 blind*).ti,ab; 18033 results. 19. PsycINFO; (singl* adj3 blind*).ti,ab; 1593 results. 20. PsycINFO; EXPERIMENTAL DESIGN/; 8944 results. 21. PsycINFO; controlled.ti,ab; 78803 results. 22. PsycINFO; (clinical adj3 study).ti,ab; 7741 results. 23. PsycINFO; trial.ti,ab; 66664 results. 24. PsycINFO; "treatment outcome clinical trial".md; 26059 results. 25. PsycINFO; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24;	100	

	556904 results. 26. PsycINFO; 14 AND 25; 100 results.		
Embase	27. EMBASE; exp BIPOLAR DISORDER/; 39834 results. 28. EMBASE; bipolar.ti,ab; 56154 results. 29. EMBASE; mania.ti,ab; 10210 results. 30. EMBASE; manic.ti,ab; 10704 results. 31. EMBASE; hypomani*.ti,ab; 2878 results. 32. EMBASE; "rapid cycling".ti,ab; 1374 results. 33. EMBASE; 27 OR 28 OR 29 OR 30 OR 31 OR 32; 78746 results. 34. EMBASE; LITHIUM/; 40559 results. 35. EMBASE; lithium.ti,ab; 34039 results. 36. EMBASE; 34 OR 35; 55642 results. 37. EMBASE; quetiapine.ti,ab; 5165 results. 38. EMBASE; QUETIAPINE/; 15761 results. 39. EMBASE; 37 OR 38; 16036 results. 40. EMBASE; 33 AND 36 AND 39; 1783 results. 41. EMBASE; random*.tw; 887552 results. 42. EMBASE; factorial*.tw; 23037 results. 43. EMBASE; placebo*.tw; 202397 results. 44. EMBASE; (crossover* OR cross-over*).tw; 70115 results. 45. EMBASE; (doubl* adj3 blind*).tw; 144971 results. 46. EMBASE; (singl* adj3 blind*).tw; 16817 results. 47. EMBASE; assign*.tw; 241000 results. 48. EMBASE; allocat*.tw; 83495 results. 49. EMBASE; volunteer*.tw; 178672 results. 50. EMBASE; CROSSOVER PROCEDURE/; 40030 results. 51. EMBASE; DOUBLE-BLIND PROCEDURE/; 120717 results. 52. EMBASE; SINGLE-BLIND PROCEDURE/; 19074 results. 53. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 368196 results.	447	

	54. EMBASE; 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53; 1428235 results. 55. EMBASE; 40 AND 54; 447 results.		
Medline	56. MEDLINE; exp BIPOLAR DISORDER/; 30609 results. 57. MEDLINE; bipolar.ti,ab; 41359 results. 58. MEDLINE; mania.ti,ab; 7396 results. 59. MEDLINE; manic.ti,ab; 8371 results. 60. MEDLINE; hypomani*.ti,ab; 2009 results. 61. MEDLINE; "rapid cycling".ti,ab; 1015 results. 62. MEDLINE; 56 OR 57 OR 58 OR 59 OR 60 OR 61; 59264 results. 63. MEDLINE; LITHIUM/; 19776 results. 64. MEDLINE; lithium.ti,ab; 29179 results. 65. MEDLINE; 63 OR 64; 36135 results. 66. MEDLINE; quetiapine.ti,ab; 2968 results. 67. MEDLINE; 62 AND 65 AND 66; 182 results. 68. MEDLINE; "randomized controlled trial".pt; 363149 results. 69. MEDLINE; "controlled clinical trial".pt; 87554 results. 70. MEDLINE; randomi?ed.ab; 338394 results. 71. MEDLINE; placebo.ab; 149940 results. 72. MEDLINE; "drug therapy".fs; 1663524 results. 73. MEDLINE; randomly.ab; 206120 results. 74. MEDLINE; trial.ab; 292327 results. 75. MEDLINE; groups.ab; 1317964 results. 76. MEDLINE; 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75; 3263433 results. 77. MEDLINE; 67 AND 76; 156 results.	156	
Summary	**NA**	**NA**	

Disclaimer

BEST in MH answers to clinical questions are for information purposes only. BEST in MH does not make recommendations. Individual health care providers are responsible for assessing the applicability of BEST in MH answers to their clinical practice. BEST in MH is not responsible or liable for, directly or indirectly, any form of damage resulting from the use/misuse of information contained in or implied by these documents. Links to other sites are provided for information purposes only. BEST in MH cannot accept responsibility for the content of linked sites.