BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"For adult patients with bipolar disorder using mood stabilisers, does treatment of low mood with SSRIs increase the risk of mania/hypomania, compared with treatment of mood stabilisers alone?"

Clarification of question using PICO structure

Patients:	Adult patients with bipolar disorder using mood stabilisers
Risk Factor:	Selective Serotonin Reuptake Inhibitors (SSRIs)
Outcome:	Mania/hypomania

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

Clinical and research implications

No definite clinical implications can be made from the available evidence; no randomised trials were identified that directly compared SSRIs with mood stabilisers alone. Two studies with very small sample sizes were included in this BEST summary, and while it appears that the SSRIs may be associated with low switch rates into mania/hypomania, the results are inconclusive. The authors of both studies suggested that more research is needed.

What does the evidence say?

Number of included studies/reviews (number of participants)
One randomised controlled trial (RCT) (Shelton and Stahl 2004) and one observational study (Fonesca et al. 2006) met the inclusion criteria for this BEST summary.

Main Findings
The trial by Shelton and Stahl (2004) evaluated the effectiveness of risperidone plus placebo, risperidone plus paroxetine, and paroxetine plus placebo, in 30 bipolar patients also treated with mood stabilisers. While the authors did not evaluate the SSRI respiridone vs. a mood stabiliser alone, some information can be gained by examining the comparison risperidone plus paroxetine vs. paroxetine plus placebo. After 12 weeks of treatment, the authors reported significant changes in depression ratings from baseline to endpoint, but there were no significant differences between the groups (assessments included MADRS, HAM-D, BDI, CGI, YMRS, SAS, BAS). There were no cases of mania in any group, although there was one case of mild hypomania in the paroxetine plus placebo group.

Fonesca et al. (2006) evaluated the efficacy and safety of escitalopram as an adjunctive therapy for bipolar depression types I and II - in 20 patients with poor response to ongoing treatment with mood stabilisers. After 12 weeks of treatment, they found significant improvements, including mean reductions from baseline in both the HAM-D total score and CGI-S ($p<0.001$ for both). Four dropouts occurred: one due to manic switch, two due to hypomanic symptoms, and 1 due to the emergence of suicidal ideation and psychosis.

Authors Conclusions
Shelton and Stahl (2004) concluded that risperidone, paroxetine, and a combination of the two are equally, but modestly effective when added to a mood stabiliser in bipolar depression.

Fonesca et al. (2006) concluded that the use of escitalopram as adjunctive therapy to mood stabilisers in patients with moderate-to-severe bipolar depression types I and II may be a useful strategy, and that more double-blind RCTs of escitalopram are warranted.

Reliability of conclusions/Strength of evidence
The trial by Shelton and Stahl (2004) had a small sample size and a high risk of bias. The authors appropriately noted, however, that their results should be considered preliminary and interpreted with caution. The reliability of the results of the Fonesca et al. (2006) study are unlikely to be reliable given the small sample size, and the uncontrolled and un-blinded study design.

What do guidelines say?

Scottish Intercollegiate Guidelines Network (SIGN) guidelines, *Bipolar Affective Disorder* (CG82), make the following recommendations regarding the use of starting antidepressants for treating depressive episodes for patients with bipolar disorder who are already being treated using mood stabilisers:

"Recommendations for the treatment of acute depression
An antidepressant in combination with an antimanic drug *(lithium, semisodium valproate or an antipsychotic drug)*, or lamotrigine is recommended for the treatment of acute bipolar depression in patients with a history of mania.
Patients maintained on mood stabilisers who suffer a depressive episode should be started on an antidepressant after optimising their mood stabiliser.
Interactions between serotonergic antidepressants, antipsychotic drugs and lithium and the risk of triggering mania or rapid cycling should be considered when selecting an antidepressant." (p.13)

National Institute of health and Care Excellence (NICE) guidelines, *Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care* (CG185), make the following recommendations:

"If a person develops mania or hypomania and is taking an antidepressant (as defined by the BNF) in combination with a mood stabiliser, consider stopping the antidepressant." (p.24)

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

References

RCTs:

Shelton, R. C., & Stahl, S. M. (2004). Risperidone and paroxetine given singly and in combination for bipolar depression. *Journal of Clinical Psychiatry*, *65*(12), 1715-1719.

Cohort Studies:

Fonseca, M., Soares, J. C., Hatch, J. P., Santin, A. P., & Kapczinski, F. (2006). An open trial of adjunctive escitalopram in bipolar depression. *Journal of Clinical Psychiatry*, *67*(1), 81-86.

Guidelines:

National Institute for Health and Care Excellence. (2014). *Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care, CG185*. London: National Institute for Health and Care Excellence. http://www.nice.org.uk/guidance/cg185/resources/guidance-bipolar-disorder-the-assessment-and-management-of-bipolar-disorder-in-adults-children-and-young-people-in-primary-and-secondary-care-pdf

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

Results

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Shelton and Stahl (2004)	*Participants*: Inclusion criteria: Meeting criteria for DSM-IV bipolar disorder I or II, currently in a depressed phase; receiving a clinically acceptable level of mood stabiliser; score of 18 or above on the Hamilton rating Scale for Depression (HRSD); score of 8 or below on the Young Mania Rating Scale (YMRS). Exclusion criteria: meeting DSM-IV criteria for current/past psychosis; meeting DSM-IV criteria for substance abuse in the past 6 months or substance dependence in the past 12 months; receiving any other psychotropic medication. *Intervention*: Paroxetine, alongside their current mood stabiliser. *Comparator*: (1) Risperidone, alongside their current mood stabiliser; (2) Risperidone plus paroxetine, alongside their current mood stabiliser. *Outcome*: Switch to mania was assessed using the YMRS.	*n* = 30	After 12 weeks of treatment, there was no significant difference between any of the groups for any of the assessments (including MADRS, HAM-D, BDI, CGI, YMRS, SAS, BAS). There were no cases of mania in any group, although there was one case of mild hypomania in the paroxetine plus placebo group. Remission (HAM-D score =<7 at endpoint) was achieved in 3 patients in the RIS + PAR group, 2 in the PAR + placebo group and one in the RIS + placebo group. Response (=>50% improvement in the HAM-D score at endpoint) occurred in 3 patients in the RIS + PAR group, 2 in the PAR + placebo group, and 3 in the RIS + placebo group. 5 patients dropped out of the RIS + placebo group, 4 dropped out of the RIS + PAR group and 2 dropped out of the PAR + placebo group (no significant difference between groups).	High (due to small sample size)

Cohort Studies

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Fonesca et al. (2006)	*Participants*: Inclusion criteria: at least 18 years old; meeting DSM-IV criteria for bipolar I or II, current major depressive episode; score a minimum of 16 on the 17-item Hamilton Rating Scale for Depression (HRSD); being treated on a mood stabiliser that had been at a stable dose for 4 weeks prior to study entry; baseline score of 12 or less on the Young Mania Rating Scale (YMRS). Exclusion criteria included: mixed or manic episode, psychotic features, acute suicidal ideation, and other Axis 1 disorder other than bipolar disorder, substance abuse/dependence within the last 6 months. *Intervention*: Escitalopram (10 mg per day), as adjunctive therapy to participants' ongoing treatment with mood stabilisers. *Risk Factor:* Switch from depression to mania, following escitalopram introduction. *Outcome*: Switch to mania was defined by a YMRS total score > 12 and DSM-IV criteria for a manic episode. Switch to a hypomanic episode was defined by DSM-	*n* = 20 (16 patients completed the study)	After 12 weeks of treatment, the mean reduction in the HAM-D total score from baseline was 12 points (20.9 [SD 4.2] at baseline compared with 8.9 [SD 4.2] at endpoint, p<0.001). The CGI-S mean reduction was 3.3 points (4.8 [SD 0.7] at baseline compared with 1.5 [SD 0.6] at endpoint, p<0.001). The authors stated that 12 (60%) patients met criteria for a positive treatment response at week 12; four patients (20%) showed a poor response (a reduction less than 50% from the baseline HAM-D total score). Four patients were taken off the protocol prior to the study endpoint: 1 patient switched to a manic episode and was dropped from the study at week 4; 1 patient was dropped at week 6 because of the emergence of psychotic symptoms and suicidal ideation; 2 patients developed mild hypomanic symptoms. 15 (75%) patients experiences at least one adverse event; the most common AE was headache (30%), 25% described mild somnolence; 10% insomnia; 5% cloudy vision; 5% dizziness; 5% anxiety; 25% nausea; 15% dry mouth; 5% iron taste; 5% vomiting; 10% sexual dysfunction; 5% joint pain; 5% dry eyes; 5% tachycardia.	High

	IV criteria for a hypomanic episode. *Study Type*: Prospective cohort study, assessed at baseline and 12 weeks.			

Risk of Bias:

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Shelton et al. (2004)	?	?	☺	?	☺	?

Cohort Studies

Study	RISK OF BIAS (ASSESSED USING SIGN GUIDANCE FOR COHORT STUDIES)					
	Question (clearly focussed)	Subject selection (comparable groups, loss to follow-up)	Outcome assessment (clearly defined, reliable and blinded to exposure)	Confounding (accounted for in design and analysis)	Statistical analysis (reporting of confidence intervals)	Overall assessment
Fonesca et al. (2006)	☺	?	☹	?	☺	☹

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	bipolar antidepressant mood stabiliser	5	2
DARE	(alaproclat* OR cericlamin* OR citalopram OR dapoxetin* OR escitalopram OR femoxetin* OR fluoxetin* OR fluvoxamin* OR paroxetin* OR sertralin* OR trazodone OR vilazodone OR zimelidine OR Celexa OR Cipramil OR Cipram OR Recital OR Emocal OR Dalsan OR Sepram OR Seropram OR Citox OR Priligy OR Lexapro OR Cipralex OR Seroplex OR Esertia OR Prozac OR Fontex OR Seromex OR Seronil OR Sarafem OR Ladose OR Motivest OR Fluctin OR fluox OR Lovan OR Luvox OR Fevarin OR Faverin OR Favoxil OR Movox OR Paxil OR Seroxat OR Sereupin OR Aropax OR Deroxat OR Divarius OR Rexetin OR Xetanor OR Paroxat OR Loxamine OR Zoloft OR Lustral OR Serlain OR Asentra) IN DARE 336 Delete 2 ((SSRI) OR (selective adj2 serotonin)) IN DARE 239 Delete 3 MeSH DESCRIPTOR Serotonin Uptake Inhibitors EXPLODE ALL TREES 273 Delete 4 #1 OR #2 OR #3 585 Delete 5 (bipolar OR manic OR mania) IN DARE 266 Delete 6 MeSH DESCRIPTOR Bipolar Disorder EXPLODE ALL TREES 166 Delete 7 #5 OR #6 323 Delete 8 #4 AND #7	40	1
Primary studies			
CENTRAL	#1 MeSH descriptor: [Bipolar Disorder] explode all trees 1581 #2 MeSH descriptor: [Tranquilizing Agents] explode all trees 6544 #3 lithium or lamotrigine or "valproic acid" or carbamazepine or oxcarbazepine 4744	17	2

	#4 #2 or #3 10749 #5 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees 2381 #6 #1 and #4 and #5 17		
PsycINFO	1. PsycINFO; exp BIPOLAR DISORDER/; 19786 results. 2. PsycINFO; bipolar.ti,ab; 27872 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; MOOD STABILIZERS/ OR MOOD STABILIZING DRUGS/; 536 results. 27. PsycINFO; LITHIUM/; 4919 results. 29. PsycINFO; "valproic acid".ti,ab; 1084 results. 30. PsycINFO; lamotrigine.ti,ab; 1540 results. 31. PsycINFO; carbamazepine.ti,ab; 2958 results. 32. PsycINFO; oxcarbazepine.ti,ab; 461 results. 33. PsycINFO; 26 OR 27 OR 29 OR 30 OR 31 OR 32; 9777 results. 34. PsycINFO; exp SEROTONIN REUPTAKE INHIBITORS/; 10592 results. 36. PsycINFO; SSRis.ti,ab; 3430 results. 37. PsycINFO; exp ANTIDEPRESSANT DRUGS/; 32200 results. 38. PsycINFO; exp SEROTONIN ANTAGONISTS/; 4242 results. 39. PsycINFO; 34 OR 36 OR 37 OR 38; 38028 results. 40. PsycINFO; 25 AND 33 AND 39; 451 results. 41. PsycINFO; CLINICAL TRIALS/; 7925 results. 42. PsycINFO; random*.ti,ab; 133602 results. 43. PsycINFO; groups.ti,ab; 374352 results. 44. PsycINFO; (double adj3 blind).ti,ab; 18131 results. 45. PsycINFO; (single adj3 blind).ti,ab; 1441 results. 46. PsycINFO; EXPERIMENTAL DESIGN/; 9281 results. 47. PsycINFO; controlled.ti,ab; 82874 results. 48. PsycINFO; (clinical adj3 study).ti,ab; 8115 results.	161 RCTs 4 Cohort and Observational studies	1

	49. PsycINFO; trial.ti,ab; 70303 results. 50. PsycINFO; "treatment outcome clinical trial".md; 27839 results. 51. PsycINFO; 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50; 580366 results. 52. PsycINFO; 40 AND 51; 161 results. + 4 Obsverational and cohort studies		
Embase	59. EMBASE; MOOD STABILIZERS/ OR MOOD STABILIZING DRUGS/; 0 results. 60. EMBASE; LITHIUM/; 40304 results. 61. EMBASE; "valproic acid".ti,ab; 8408 results. 62. EMBASE; lamotrigine.ti,ab; 5960 results. 63. EMBASE; carbamazepine.ti,ab; 15284 results. 64. EMBASE; oxcarbazepine.ti,ab; 2144 results. 65. EMBASE; 59 OR 60 OR 61 OR 62 OR 63 OR 64; 64945 results. 66. EMBASE; exp SEROTONIN REUPTAKE INHIBITORS/; 0 results. 67. EMBASE; SSRis.ti,ab; 7536 results. 68. EMBASE; exp ANTIDEPRESSANT DRUGS/; 0 results. 69. EMBASE; exp SEROTONIN ANTAGONISTS/; 105319 results. 70. EMBASE; 66 OR 67 OR 68 OR 69; 111212 results. 71. EMBASE; 58 AND 65 AND 70; 2747 results. 81. EMBASE; 71 AND 80; 775 results. 82. EMBASE; 81 not 47; 0 results. 83. EMBASE; (cohort OR observational).ti,ab; 474996 results. 84. EMBASE; MOOD STABILIZER/ OR MOOD STABILIZING DRUG/; 5471 results. 85. EMBASE; exp ANTIDEPRESSANT AGENT/; 304102 results. 86. EMBASE; 65 OR 84; 68147 results. 87. EMBASE; 67 OR 85; 304491 results. 88. EMBASE; 58 AND 86 AND 87; 6193 results. 89. EMBASE; COHORT ANALYSIS/; 178129 results. 90. EMBASE; OBSERVATIONAL STUDY/; 60990 results.	90 RCTs 143 cohort and observational studies	0

	91. EMBASE; 89 OR 90; 232371 results. **92. EMBASE; 88 AND 91; 143 results.** 93. EMBASE; random*.ti,ab; 901764 results. 94. EMBASE; factorial*.ti,ab; 23344 results. 95. EMBASE; (crossover* OR cross-over*).ti,ab; 69903 results. 96. EMBASE; placebo*.ti,ab; 202258 results. 97. EMBASE; (doubl* ADJ blind*).ti,ab; 143607 results. 98. EMBASE; (singl* ADJ blind*).ti,ab; 14657 results. 99. EMBASE; assign*.ti,ab; 242394 results. 100. EMBASE; allocat*.ti,ab; 85358 results. 101. EMBASE; volunteer*.ti,ab; 177975 results. 102. EMBASE; CROSSOVER PROCEDURE/; 40265 results. 103. EMBASE; DOUBLE BLIND PROCEDURE/; 115501 results. 104. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 350374 results. 105. EMBASE; SINGLE BLIND PROCEDURE/; 18844 results. 106. EMBASE; 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105; 1434407 results. 107. EMBASE; 88 AND 106; 1024 results. **108. EMBASE; 107 [Limit to: Exclude MEDLINE Journals]; 90 results.**		
Medline	19. MEDLINE; exp BIPOLAR DISORDER/; 32228 results. 20. MEDLINE; bipolar.ti,ab; 44501 results. 21. MEDLINE; mania.ti,ab; 7847 results. 22. MEDLINE; "manic depress*".ti,ab; 3253 results. 23. MEDLINE; 19 OR 20 OR 21 OR 22; 61696 results. 24. MEDLINE; MOOD STABILIZERS/ OR MOOD STABILIZING DRUGS/; 0 results. 25. MEDLINE; LITHIUM/; 20254 results. 26. MEDLINE; "valproic acid".ti,ab; 6203 results. 27. MEDLINE; lamotrigine.ti,ab; 3907 results. 28. MEDLINE; carbamazepine.ti,ab; 11920 results. 29. MEDLINE; oxcarbazepine.ti,ab; 1403 results.	1383 RCTs 176 cohort and observational studies	0

	30. MEDLINE; 24 OR 25 OR 26 OR 27 OR 28 OR 29; 39772 results. 31. MEDLINE; exp SEROTONIN REUPTAKE INHIBITORS/; 31818 results. 32. MEDLINE; SSRis.ti,ab; 5003 results. 33. MEDLINE; exp ANTIDEPRESSANT DRUGS/; 123147 results. 34. MEDLINE; exp SEROTONIN ANTAGONISTS/; 46061 results. 35. MEDLINE; 31 OR 32 OR 33 OR 34; 168752 results. 36. MEDLINE; 23 AND 30 AND 35; 1652 results. 37. MEDLINE; "randomized controlled trial".pt; 389607 results. 38. MEDLINE; "controlled clinical trial".pt; 89898 results. 39. MEDLINE; randomized.ab; 309137 results. 40. MEDLINE; placebo.ab; 159829 results. 41. MEDLINE; "drug therapy".fs; 1748083 results. 42. MEDLINE; randomly.ab; 223158 results. 43. MEDLINE; trial.ab; 321888 results. 44. MEDLINE; groups.ab; 1407229 results. 45. MEDLINE; 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44; 3452231 results. 46. MEDLINE; 36 AND 45; 1442 results. 47. MEDLINE; (child* OR adolescent).ti,ab; 1078878 results. **48. MEDLINE; 46 not 47; 1383 results.** 49. MEDLINE; (cohort OR observational).ti,ab; 338112 results. 50. MEDLINE; exp COHORT STUDIES/; 1402497 results. 51. MEDLINE; OBSERVATIONAL STUDY/; 5131 results. 52. MEDLINE; 50 OR 51; 1404188 results. **53. MEDLINE; 36 AND 52; 176 results.**		
Summary	**NA**	**NA**	

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