

[Antidepressant medicines in individuals with a depressive episode in bipolar disorder](#)**Q9: In individuals presenting with a depressive episode in bipolar disorder, are antidepressant medicines effective and safe?****Background**

Depressive episodes are common during the course of bipolar disorder and pose considerable management challenge. While treatment of a depressive episode by antidepressant medicines seems logical and is a widespread practice, there are unresolved questions on its effectiveness and safety, particularly on the likelihood of precipitating a manic episode.

Population/Intervention(s)/Comparator/Outcome(s) (PICO)

- Population: adults with bipolar depression
- Interventions: antidepressants or adjunctive antidepressants
- Comparisons: placebo, or mood stabilizer and placebo
- Outcomes: symptoms severity
disability and functioning
adverse effects of treatment
quality of life
mortality
treatment adherence
users' and families' satisfaction with care

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List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Gijsman HJ et al (2004). Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *American Journal of Psychiatry*,161:1537-47.

EXCLUDED FROM GRADE TABLES

National Institute for Health and Clinical Excellence (2006). Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. National Clinical Practice Guideline Number 38.

Yatham LN et al (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disorders*, 11:225-55.

Soares-Weiser K et al (2007). A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technology Assessment*, 11:iii-iv, ix-206.

PICO Table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Antidepressant / Placebo	Symptoms severity Disability and functioning Adverse effects of treatment Quality of life Mortality Treatment adherence	Gijsman et al, 2004 No evidence available Gijsman et al, 2004 No evidence available No evidence available No evidence available	

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		Users' and families' satisfaction with care	No evidence available	
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Narrative description of the studies that went into the analysis

Gijsman et al, 2004 included the following 5 controlled trials randomizing 287 patients to an antidepressant and 492 to placebo.

Study	N	Diagnostic	Outpatients %	Duration (weeks)	Antidepressant versus placebo	Concurrent medication
Tohen et al, 2003	456	DSM-IV bipolar I	87	8	Fluoxetine	100% olanzapine
Nemeroff et al, 2001	117	DSM-III bipolar I	100	10	Paroxetine	100% lithium
Cohn et al, 1989	89	DSM-III bipolar I	100	6	Fluoxetine	25% lithium
Himmelhoch et al, 1982	59	DSM-III bipolar I and II	100	6	Tranlycypromine	None
Mendlewicz & Youdim, 1980	58	Bipolar disorder with Feighner criteria	0	5	Deprenyl	None

GRADE Tables

Table 1

Author(s): Lorenzo Tarsitani

Date: 2009-08-25

Question: Should Antidepressants vs placebo be used for bipolar depression?

Settings: Largely Outpatient Service

Bibliography: Gijsman HJ et al (2004). Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *American Journal of Psychiatry*,161:1537-47.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Antidepressants	placebo	Relative	Absolute		

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studies						considerations			(95% CI)			
Symptoms severity - Clinical Response												
4	randomised trials	serious ¹	serious ²	no serious indirectness	no serious imprecision	none	123/213 (57.7%)	153/449 (34.1%)	RR 1.86 (1.49 to 2.30)	293 more per 1000 (from 167 more to 443 more)	⊕⊕○○ LOW	CRITICAL
Symptoms severity - Clinical Remission												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/160 (43.1%)	129/413 (31.2%)	RR 1.41 (1.11 to 1.80)	128 more per 1000 (from 34 more to 250 more)	⊕⊕⊕○ MODERATE	CRITICAL
Disability and functioning												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Adverse events - Switching to Mania												
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	11/287 (3.8%)	23/492 (4.7%)	RR 1.00 (0.47 to 2.13)	0 fewer per 1000 (from 25 fewer to 53 more)	⊕⊕○○ LOW	CRITICAL
Quality of life												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Treatment adherence												

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0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Users' and families' satisfaction with care												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

¹ The overall dropout rate was 32% in the antidepressant group, 49% in the placebo group, and 43% in total. Dropouts in each trial are not reported.

² Significance test for heterogeneity: I squared =71.4%

³ CI crosses 1, 0.5, and 2.0

Additional information that was not GRADEd

Gijsman et al, 2004: included also six trials comparing tricyclic antidepressants versus other antidepressants for the treatment of bipolar depression. This comparison includes 134 patients from the antidepressant arms of two trials in which two antidepressants were compared with placebo and 236 patients from four trials with two antidepressant arms and no placebo group. In total, 201 of the 370 patients (54%) distributed throughout all of these studies were receiving co-therapy with mood stabilizers. The authors conclude that tricyclic antidepressants may be less effective than other antidepressants, but this did not reach statistical significance (risk ratio=0.84, 95% CI=0.67 to 1.06). On average, tricyclic antidepressants caused more switching to mania than other antidepressants (risk ratio=2.92, 95% CI=1.28 to 6.71). The rate of switching for tricyclic antidepressants was 10%, and for other antidepressants combined, was 3.2%. This gives an absolute risk difference of 6.8% (95% CI=1.7% to 11.9%).

Harel & Levkovitz, 2008: According to this review, most of the standard randomized controlled trials report the efficacy of antidepressants in the acute phase of BPD, but the data also indicate higher switch rates to mania and acceleration of mood cycle with their use. Nevertheless, a recent large effectiveness study (Sachs et al, 2007) found no superiority or risk of adjunct antidepressants to a mood stabilizer in the treatment of BPD.

Licht et al, 2008: This critical review of the literature addresses whether switch of depression into hypomania or mania or cycle acceleration in patients with bipolar disorder is caused by antidepressants or whether this phenomenon is attributable to the natural history of bipolar disorder itself. There is a scarcity of randomized studies addressing the question, and the available studies all suffer from various forms of bias. However, there is some evidence suggesting that antidepressants given in addition to a mood stabilizer are not associated with an increased rate of switch when compared with the rate associated with the

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mood stabilizer alone. Whether antidepressants may accelerate episode frequency and/or may cause other forms of destabilization in patients with bipolar disorder remain to be properly studied.

NICE 2006:

Patients not taking antimanic medication

- A patient who is prescribed antidepressant medication should also be prescribed an antimanic drug. The choice of antimanic drug should be compatible with decisions about future prophylactic treatment, the likely side effects and whether the patient is a woman of child-bearing potential.
- When initiating antidepressant treatment for a patient who is not already taking antimanic medication, prescribers should explain the risks of switching to mania and the benefits of taking an adjunctive antimanic agent. People who are not willing to take antimanic medication, should be monitored carefully. Antidepressant treatment should begin at a low dose and be increased gradually if necessary.

Patients taking antimanic medication

- If a person has an acute depressive episode when taking antimanic medication, prescribers should first check they are taking the antimanic agent at the appropriate dose and adjust the dose if necessary.

Patients with mild depressive symptoms

- For patients with acute mild depressive symptoms, a further assessment should be arranged, normally within 2 weeks ('watchful waiting') if:
 - previous episodes of mild depression have not developed into chronic or more severe depression in this patient, or
 - the patient is judged not to be at significant risk of developing a more severe depression.

If the patient is judged to be at significant risk of worsening or on review continues to be unwell, they should be managed as for moderate/severe depression particularly if functional impairment is evident.

Patients with moderate or severe depressive symptoms

- For patients with moderate or severe depressive symptoms, prescribers should normally consider:

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- prescribing an SSRI antidepressant (but not paroxetine in pregnant women), because these are less likely than tricyclic antidepressants to be associated with switching, or

- adding quetiapine, if the patient is already taking antimanic medication that is not an antipsychotic

- If a trial of drug treatment at an adequate dose and with adequate compliance does not produce a significant improvement for moderate depressive symptoms, a structured psychological treatment should be considered. This should focus on depressive symptoms, problem solving, promoting social functioning, and education about medication.

Antidepressant treatment and risk monitoring

- Antidepressants should be avoided for patients with depressive symptoms who have:

- rapid-cycling bipolar disorder

- a recent hypomanic episode

- recent functionally impairing rapid mood fluctuations.

Instead, consider increasing the dose of the antimanic agent or the addition of a second antimanic agent (including lamotrigine*).

Stopping antidepressants after an acute depressive episode

- When a patient is in remission from depressive symptoms (or symptoms have been significantly less severe for 8 weeks), stopping the antidepressant medication should be considered, to minimise the risks of switching to mania and increased rapid cycling. The dose of antidepressant should be gradually reduced over several weeks, while maintaining the antimanic medication. Particular care is needed with paroxetine and venlafaxine because they are associated with a higher risk of discontinuation/withdrawal symptoms.

Reference List

Cohn JB et al (1989). A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. *International Clinical Psychopharmacology*, 4:313–22.

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Gijsman HJ et al (2004). Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *American Journal of Psychiatry*, 161:1537-47.

Harel EV, Levkovitz Y (2008). Effectiveness and safety of adjunctive antidepressants in the treatment of bipolar depression: a review. *Israel Journal of Psychiatry and Related Sciences*, 45:121-28.

Himmelhoch JM, Fuchs CZ, Symons BJ (1982). A double-blind study of tranylcypromine treatment of major anergic depression. *Journal of Nervous and Mental Disease*, 170:628-34.

Licht RW et al (2008). Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. *Acta Psychiatrica Scandinavica*, 118:337-46.

Mendlewicz J, Youdim MB (1980). Antidepressant potentiation of 5-hydroxytryptophan by L-deprenyl in affective illness. *Journal of Affective Disorders*, 2:137-46.

Nemeroff CB et al (2001). Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *American Journal of Psychiatry*, 158:906-12.

NICE (2006). Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. National Clinical Practice Guideline Number 38.

Sachs GS et al (2007). Effectiveness of adjunctive antidepressant treatment for bipolar depression. *New England Journal of Medicine*, 356:1711-22.

Soares-Weiser K et al (2007). A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technology Assessment*, 11:iii-iv, ix-206.

Tohen M et al (2003). Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of General Psychiatry*, 60:1079-88.

Yatham LN et al (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disorders*, 11:225-55.

From evidence to recommendations

Factor	Explanation
<p>Narrative summary of the evidence base</p>	<p>In terms of proportion of patients showing a clinical response (RR 1.86, 1.49 to 2.30) and remission (RR 1.41, 1.11 to 1.80), there is evidence that antidepressants were significantly more effective than placebo in the treatment of bipolar depression.</p> <p>In terms of proportion of patients showing a switching to mania, there is no evidence that antidepressants significantly increased the risk of switching to a manic episode compared to placebo (RR 1.00, 0.47 to 2.13). In three out of five trials patients were treated with a concurrent mood stabilizer.</p> <p>In terms of disability and functioning, quality of life, mortality, treatment adherence, and users' and families' satisfaction with care, there is no evidence available.</p>
<p>Summary of the quality of evidence</p>	<p>The quality of evidence was LOW for clinical response, MODERATE for clinical remission, and LOW for switching to mania.</p>
<p>Balance of benefits versus harms</p>	<p>In randomized controlled trials carried out in patients with bipolar depression, antidepressant medicines are associated with a beneficial effect.</p> <p>In terms of tolerability and safety, trials do not indicate higher switch rates to mania and acceleration of mood cycle with the use of SSRI.</p> <p>Tricyclic antidepressants are less effective than other antidepressants. On average, tricyclic antidepressants caused more switching to mania than other antidepressants (RR 2.92, 1.28 to 6.71). The rate of switching for tricyclic antidepressants was 10%, and for other antidepressants combined, was 3.2%. This gives an absolute risk difference of 6.8%, 1.7% to 11.9%.</p> <p>Anti-depressant treatment should begin at a low dose and be increased gradually if necessary. When a patient is in remission from depressive symptoms, stopping the antidepressant medication should be considered, to minimise the risks of switching to mania and increased rapid</p>

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	<p>cycling (NICE 2006).</p> <p>In many patients with bipolar disorder, major depressive episodes represent the most debilitating and difficult-to-treat phase. Patients spend significantly more time depressed than manic or hypomanic, and attempt suicide more frequently during this illness phase. The treatment of bipolar depression may prevent suffering to patients and their families and the economic burden of direct and indirect costs.</p>
<p>Values and preferences including any variability and human rights issues</p>	<p>Important issues are the short and long term consequences of disability, lack of functioning, and discrimination associated with major depressive episodes of bipolar disorder. In addition, depressive episodes can be life threatening conditions. However, even among mental health specialists there are significant concerns about the risk of switching to dangerous manic episodes associated with antidepressant treatment among bipolar patients.</p>
<p>Costs and resource use and any other relevant feasibility issues</p>	<p>Lithium and valproate are associated with low acquisition costs.</p> <p>Lithium and valproate requires regular blood monitoring.</p> <p>Lithium, valproate and fluoxetine are available in WHO Essential Medicine List as medicines used in mood disorders.</p>
<p>Recommendation(s)</p> <p>Antidepressant medicines, always in combination with a mood stabilizer (lithium or valproate), may be considered in the treatment of moderate or severe depressive episodes of bipolar disorder. Selective serotonin reuptake inhibitors (SSRI; fluoxetine) should be preferred to tricyclic antidepressants (TCA).</p> <p>Strength of recommendation: STANDARD</p> <p>Antidepressant treatment should begin at a low dose and be increased gradually if necessary. Individuals should be monitored carefully for early symptoms or signs of manic symptoms. Antidepressant medication should be stopped soon after remission of depressive symptoms, while mood stabilizer should be continued.</p> <p>Strength of recommendation: STRONG</p>	

Any additional remarks

Research evidence needs to be developed for those critical and important outcomes for which no evidence is available now.

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WLLC. Haloperidol versus chlorpromazine for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004278. DOI: 10.1002/14651858.CD004278.pub2.

Lobos AC, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD006633. DOI: 10.1002/14651858.CD006633.pub2.