Review: antidepressants increase clinical response and remission in bipolar depression without increasing induction of mania

Gijsman HJ, Geddes JR, Rendell JM, *et al*. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004;**161**:1537–47.

Clinical impact ratings Psychiatry ★★★★★★☆ GP/FP/Mental health ★★★★★★★

Q What is the efficacy and safety of antidepressants for short term treatment of bipolar depression?

METHODS

Data sources: Cochrane Collaboration Depression, Anxiety, and Neurosis Controlled Trials register (December 2002), *Cochrane Library*, reference lists of identified studies, other relevant papers, and major textbooks.

Study selection and assessment: randomised, controlled, double blind trials published in any language that compared antidepressants with placebo or alternative drugs (ie, mood stabilisers, anticonvulsants, or other antidepressants) in patients with a current depressive or mixed depressive/manic episode with or without psychotic symptoms who had had ⩾1 previous episode of mania or hypomania. Quality of studies was assessed.

Outcomes: clinical response and remission rates (observer rated symptom reductions), induction of mania or hypomania, and overall dropout rate.

MAIN RESULTS

12 trials (n = 1088) met the selection criteria. Most participants were adults (⩽70 y) and women. Patients treated with antidepressants had higher clinical response and remission rates than those who received placebo (table). No difference was found between antidepressants and placebo for induction of mania (although there was limited power to detect a difference) (table). Fewer patients on antidepressants than placebo withdrew from studies (table). TCAs did not differ from other antidepressants (ie, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs), reversible MAO–AIs, or bupropion) for clinical response or study withdrawal (table) but were associated with increased induction of mania (table).

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CONCLUSIONS

In patients with bipolar depression, antidepressants increase clinical response and remission in the short term, with no evidence of increased induction of mania. Tricyclic antidepressants do not differ from other antidepressants for clinical response but do increase induction of mania.

Commentary

Management of depression is certainly the greatest challenge in the long term treatment of patients with bipolar disorder, accounting for the majority of long term morbidity and disability. In general, mood stabilising drugs appear to be more effective for long term prevention of manic episodes than for long term prevention of depression. Balancing the benefits (improved control of depression) and potential risks (precipitation of mania) of antidepressant treatment is a common dilemma for practising clinicians. The systematic review by Gijsman *et al* will reassure clinicians about the short term use of antidepressants in bipolar disorder. Over a treatment period of 4–10 weeks, antidepressants were superior to placebo as measured by either remission or clinical response. The overall rate of "switching" to mania during short term treatment was approximately 4% and did not significantly differ from placebo. Newer antidepressants appeared marginally superior to tricyclic drugs in efficacy and clearly superior with regard to risk of precipitating mania.

We are left with several additional questions about the role of antidepressants in the treatment of bipolar depression. Firstly, how long should an apparently effective antidepressant be continued, especially in patients with a history of chronic or recurrent depression? Secondly, are some patients more prone to emergence of mania during antidepressant treatment, and are there current or historical characteristics that argue against use of antidepressants? Thirdly, what is the role of subthreshold mood symptoms, both in identifying candidates for antidepressant treatment and assessing potential adverse outcomes? Depressive episodes in bipolar disorder often include some level of subthreshold manic symptoms. In addition to considering the precipitation of frank mania, clinicians must consider how antidepressant treatment could affect this subthreshold mixed symptom pattern.

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Short term antidepressant treatment for bipolar depression*

Comparison	Number of trials (n)	Outcomes at 4–10 wks	Event rates	RBI (95% CI)	NNT (CI)
Antidepressants *v* placebo	4 (662)	Clinical response	58% *v* 34%	86% (49 to 130)	5 (4 to 7)
	2 (573)	Clinical remission	43% *v* 31%	41% (11 to 80)	9 (5 to 33)
				RRR (CI)	
	5 (779)	Induction of mania	3.8% *v* 4.7%	0 (−113 to 53)	NS
	{5 (779)}†	Study withdrawal	32% *v* 49%	29% (12 to 42)	{6 (4 to 10)}†
				RBR (CI)	
Tricyclics *v* other antidepressants	5 (296)	Clinical response	47% *v* 56%	16% (−6 to 33)	NS
				RRI (CI)	**NNH (CI)**
	6 (370)	Induction of mania	10% *v* 3.2%	192% (28 to 571)	15 (9 to 59)
	{6 (370)}†	Study withdrawal	37% *v* 30%	23% (−8 to 64)	NS†

*NS = not significant. RBR = relative benefit reduction. Other abbreviations defined in glossary. All statistics based on a fixed effects model. RBI, RRR, RBR, and RRI calculated from data in article. †Data provided by author.