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Induction of Mania with Selective Serotonin Re-uptake Inhibitors and Tricyclic Antidepressants

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The rate of treatment-emergent switch into mania has been calculated from all available clinical trial data on the selective serotonin re-uptake inhibitors (SSRIs) fluoxetine, fluvoxamine, paroxetine, and sertraline, relative to comparative groups treated with tricyclic antidepressants (TCAs) or placebo. In predominantly unipolar depressives, the rate of manic switch is less than 1% and differences between drugs and placebo are statistically but not clinically significant. In bipolar depressives, manic switch occurs substantially more often with TCAs (11.2%) than with SSRIs (3.7%) or placebo (4.2%).
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Most psychiatrists are of the opinion that antidepressant drugs can precipitate hypomania or mania. However, this clinical impression has not always been supported when switches into mania during antidepressant treatment have been evaluated systematically. The area therefore remains somewhat controversial.

There were early reports suggesting that tricyclic antidepressants (TCAs) can induce mania, not only in bipolar patients but also in those with an apparently unipolar presentation (Ball & Kiloh, 1959). Case reports of manic reactions have continued to appear in the literature, not only with TCAs but also with the new drugs, such as selective serotonin re-uptake inhibitors (SSRIs) (Settle & Settle, 1984; Lebuegue, 1987; Hon & Preskorn, 1989; Nakra *et al*, 1989). Bunney (1978) reviewed 80 publications, including 3922 patients given TCAs or monoamine oxidase inhibitors, and reported a rate of 9.5% switch into mania or hypomania.

It is well recognised that switch into mania is not uncommon in the natural history of affective disorder. Before antidepressants can be implicated in the switch process, it is necessary to include a control group to take into account the rate of spontaneous switching in untreated patients. Lewis & Winokur (1982) looked at a retrospective casenote survey and found that switch into mania occurred during 23% of admissions when TCAs were used and in 34% of admissions when no treatment was given. They concluded that TCAs do not increase the risk of a switch into mania. However, treatment allocation was not random but was by the physician's choice, with the consequent risk of selection bias. Wehr & Goodwin (1987) collated data from 12 double-blind placebo-controlled trials of treatment with TCAs and monoamine oxidase inhibitors. They found a switch rate of 6–7% for hypomania and 1–2% for mania, the overall switch rate being significantly greater than the placebo control groups. However, although efforts were made to include predominantly unipolar depressives, most of the studies were conducted at a time when this distinction was not generally made for clinical trial purposes, so it is likely that a small proportion of these trial patients were in fact bipolar. A high switch rate has been reported for bipolar patients treated with TCAs (Wehr & Goodwin, 1979).

The development of SSRIs has provided a substantial new data base on the rate of swing into mania during antidepressant treatment.

Table 1
Mania during treatment with SSRIs or TCAs

	Rate (%) of manic switch		
	SSRI	TCA	Placebo
Unipolar	74/10 246** (0.72)	14/2716* (0.52)	8/3788 (0.21)
Bipolar	9/242† (3.7)	14/125 (11.2)	2/48 (4.2)

*$P<0.05$ v. placebo.
**$P<0.001$ v. placebo.
†$P<0.01$ v. TCA; no significant difference v. placebo.

Method

All available clinical trial data for the SSRIs paroxetine, sertraline, fluvoxamine and fluoxetine were obtained from the respective pharmaceutical companies and from published material (Henry *et al*, 1992). Data from all four SSRIs, and from comparative groups treated with TCAs or placebo, were pooled. Whenever possible, unipolar and bipolar patients were separated. The rate of manic switch was compared between the treatment groups using χ^2 statistics.

Results

The pooled data are shown in Table 1. Figures for unipolar patients include those treated with all four SSRIs. However, this may not be an entirely pure unipolar group. Patients with a history of bipolar disorder were usually, but not always, excluded from trial protocols. Known bipolar patients are not included in the data on paroxetine and sertraline, but a few may be included in the data on fluoxetine and fluvoxamine. It is not known how many patients were suffering from their first depressive episode and therefore they could not be classified properly as unipolar. Rates of switch into mania in this unipolar group are very low, less than 1%. The rate for both SSRIs and TCAs is significantly higher than that for placebo because of the very large patient numbers involved, but the differences are not clinically meaningful.

The data on bipolar depressives relates to clinical trials of sertraline and paroxetine. The separation of bipolar depressives was not available for the other two SSRIs but it is likely that very few patients were involved because of exclusion criteria in the trial protocols. The rate of manic switch in bipolar patients treated with SSRIs is no greater than that in the placebo-treated patients but is substantially and significantly lower than the 11.2% rate of manic switch in patients treated with TCAs.

Discussion

The use of pooled data has its limitations. Not all studies were conducted to the same protocol, and criteria for reporting drug-induced mania may have varied. Nevertheless, this is the best body of data available on the relative propensity of TCAs and SSRIs to provoke mania. In unipolar patients, differences between the two classes of antidepressant and placebo are not large enough to have any effect upon clinical practice. In bipolar depressives, it appears that antidepressant drugs of the SSRI group are less prone to provoke mania in bipolar depressives. This supports the notion that catecholamine rather than serotonin mechanisms are implicated in manic switching (Bunney, 1978). The difference is substantial enough to affect clinical practice. It is concluded, on the basis of currently available although imperfect evidence, that patients who are perceived as being at risk for antidepressant-induced mania should be treated with SSRIs rather than TCAs.

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