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Induction of Mania With Serotonin Reuptake Inhibitors

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Serotonin reuptake inhibitors (SRIs) are now considered the first-line treatment for depression, but they have not been well studied in bipolar disorder. Recently, some authors have recommended that patients at risk for antidepressant-induced mania be treated with SRIs rather than tricyclic antidepressnats (TCAs). Clinical information about 11 patients who developed mania during treatment with SRIs is described. These patients were found to have personal or family histories of hypomania or mania, but these disorders were not usually recognized at the time of the patients' initial treatment for depression. The SRI-induced manic episodes were also quite severe, having psychotic features or requiring patients to be secluded for extreme agitation, but patients responded completely to antimanic treatment. The risk of treatment-emergent mania with SRIs is not trivial, especially among patients at risk for bipolar disorder. Additional research is needed to compare the actual rate of drug-induced mania with SRIs and TCAs in patients with different bipolar subtypes, while controlling for concurrent antimanic drug use. (J Clin Psychopharmacol 1996;16:425–427)

THE TREATMENT OF depression in patients with bipolar disorder has received surprisingly little research attention.[1] These patients are vulnerable to drug-induced mania or rapid cycling.[2] Whether particular antidepressants are more effective in bipolar depression[3] or are less prone to induce mania or rapid cycling[4] has not been established. The safety and tolerability of the serotonin reuptake inhibitors (SRIs) have made these drugs the standard first-line treatment for depression. Anecdotal reports have described drug-induced mania with the SRIs,[5] but they have not been well studied in bipolar depression. In this paper, I describe 11 patients who developed mania during treatment with SRIs.

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Methods

Eleven patients who were treated at the Western Psychiatric Institute and Clinic for a manic episode that was precipitated by an SRI are described. Eight patients had been treated elsewhere as outpatients and were identified by the author after they were hospitalized for severe drug-induced mania. Three were seen by the author during outpatient treatment. Patients' medical records were reviewed to obtain information about their previous clinical and treatment history, family psychiatric history, clinical condition at the time of presentation, approximate time from the start of their antidepressant to the development of mania, and treatment outcome from their manic episode.

Results

Characteristics of the patients are summarized in Table 1. The patients were mostly young (mean age 33 years) women. Most had previous episodes of depression; only two patients had definite prior manic episodes. In five patients, past periods of possible hypomanic symptoms were retrospectively recognized by the patients themselves or their families. Only two had ever received pharmacotherapy before. All had significant family histories of psychiatric illness. Eight patients became psychotic, and four were secluded for severe agitation.

Only one patient (No. 5) was taking a concurrent medication when the mania developed. She was receiving maintenance treatment with thiothixene, 4 mg/day, when she became depressed and was treated with fluoxetine. Severe mania developed within 2 weeks after she increased fluoxetine from 40 to 60 mg/day and simultaneously decreased thiothixene to 2 mg/day. Patient No. 1 first developed mania within 2 weeks after receiving fluoxetine. She responded well to lithium, but was not compliant. Seven months later she was rehospitalized for major depression, and she developed a second manic episode within 1 week of taking paroxetine. Patient No. 2 initially developed hy-

TABLE 1. Patient characteristics[a]

Patient No.	Age (yr)	Gender	SRI	No. of Weeks[b]	Previous History: Depression	Mania	Prior Treatment	Psychosis	Seclusion	Family History
1	41	F	Flu	2	Yes	?	Psychotherapy	Yes	No	Dep, Etoh
			Par	1						
2	43	F	Flu	2	?	?	None	Yes	Yes	BP
			Flu	2						
3	19	M	Flu	8	No	No	None	Yes	Yes	Dep, Etoh
			Flu	3						
4	46	F	Par	4	Yes	?	Psychotherapy	Yes	No	Dep, Schiz
5	42	F	Flu	2	Yes	Yes	Li, NLP	Yes	Yes	Dep
6	29	F	Flu	8	Yes	?	Psychotherapy	Yes	No	Dep, Etoh
7	23	F	Flu	6	Yes	Yes	Li, TCA, MAOI, NLP, AC	No	No	BP, Dep, Etoh
8	33	M	Ser	8	Yes	No	Psychotherapy	Yes	No	Dep
9	36	F	Ser	16	Yes	?	Psychotherapy	No	No	Dep, Schiz
10	19	F	Flu	4	No	No	Psychotherapy	Yes	Yes	BP
11	29	M	Flu	4	Yes	No	Psychotherapy	No	No	Dep, Etoh

[a]SRI, serotonin reuptake inhibitor; ?, possible; Dep, depression; BP, bipolar; Schiz, schizophrenia; Etoh, alcohol; Li, lithium; NLP, neuroleptic; AC, anticonvulsant; Flu, fluoxetine; Par, paroxetine; Ser, sertraline; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor.
[b]Approximate number of weeks to development of mania.

pomania within 2 weeks after fluoxetine was increased from 20 to 40 mg/day. The drug was stopped, but was restarted at 20 mg/day 1 month later when she developed severe depression. She increased the dosage to 40 mg/day and was then hospitalized within 2 weeks with severe mania. Patient No. 3 initially developed severe mania during his first exposure to fluoxetine. He was stable on lithium and perphenazine until approximately 1 year later, when he was taken off these medications. He was treated several months later with fluoxetine alone for major depression and rehospitalized within 3 weeks for severe mania. Patient No. 7 had been treated previously with imipramine and tranylcypromine for major depression, but she did not develop mania, possibly because she was also taking lithium. These patients responded completely when the SRIs were stopped and appropriate antimanic treatment started.

Discussion

These 11 cases of SRI-induced mania were identified from a population of approximately 184 patients who were treated with various antidepressants, yielding an estimated incidence of about 6%. This finding cannot resolve the issue of whether certain antidepressants are more or less likely to precipitate mania, but it suggests that the risk of SRI-induced mania is not trivial. Moreover, their episodes were generally quite severe. By contrast, a recent study found that treatment-emergent mania tended to be less severe than spontaneous mania.[6]

A recent study by Peet[7] examined pooled data from published and unpublished trials of various SRIs and tricyclic antidepressants (TCAs). Treatment-emergent mania was uncommon among unipolar depressives (less than 1%) and was substantially greater among bipolar depressives treated with TCAs (11.2%) compared with SRIs (3.7%) and to placebo (4.2%). The author concluded that patients at risk for antidepressant-induced mania should be treated with SRIs rather than TCAs, but this study deserves closer scrutiny.

First, the rate of mania among the unipolar depressives[7] tends to increase linearly from the placebo (0.21%) to the TCA (0.52%) and to the SRI (0.72%) groups. The rates are significantly greater for active drug compared with placebo, but the statistical significance of the difference between the TCA and SRI groups is not reported. Although the difference may not be clinically meaningful, this trend hints at a possible heightened sensitivity to SRI-induced mania, albeit less so in unipolar than in bipolar patients. Fluoxetine[8–10] and monoamine oxidase inhibitors[3,11] may be more effective than TCAs in bipolar depression. Also, fluvoxamine was somewhat more effective in bipolar than in unipolar depression,[12] and clomipramine had a slightly greater antidepressant effect than maprotiline in bipolar depression,[13] although both studies are limited by the small number of patients. The superior efficacy of these antidepressants in bipolar depression may be due

to their more potent serotonergic effects.[3, 12] Interestingly, serotonin precursors (i.e., tryptophan) may have a greater antidepressant effect in bipolar than in unipolar patients.[14–16] These findings suggest that bipolar patients are more sensitive to the effects of serotonergic drugs and are at greater risk for SRI-induced mania.

Second, Peet's study[7] does not include information about concurrent antimanic drug use. Compared with the SRIs, TCAs have been used clinically for a much longer time, and there has been increasing concern about the adverse effects of TCAs in bipolar patients.[2] Thus, bipolar patients treated with the recently available SRIs may be more likely to receive concurrent antimanic treatment because of the historical experience of TCA-induced mania or rapid cycling, which would bias the rate of treatment-emergent mania.

Finally, this study[7] does not distinguish between bipolar I and II subtypes.[17, 18] Depressed patients with bipolar II disorder may be less likely to develop antidepressant-induced mania than those with bipolar I disorder.[3, 10, 19] However, Simpson and DePaulo[10] found that 3 of 16 depressed bipolar II patients (19%) developed hypomania with fluoxetine, whereas none had previously developed hypomania with TCAs. Moreover, bipolar I patients may be more likely to receive concurrent antimanic treatment because of a greater concern about treatment-emergent mania, or they may be selectively excluded from antidepressant trials.[1] A different proportion of bipolar subtypes could therefore bias the rate of drug-induced mania.

The problems associated with TCAs have been recognized only gradually and only after many decades of clinical use.[2, 19] By contrast, the SRIs are believed to be "safer," but there has not been sufficient clinical experience to support this notion. Claims about the superior safety of the SRIs, therefore, must be critically evaluated. Hypomania is notoriously underrecognized, but may presage more severe manias.[20] Because patients are more likely to seek treatment when they are depressed rather than hypomanic, a careful assessment of previous mood symptoms and family history is imperative before starting an antidepressant. The SRIs now enjoy widespread use, especially by nonpsychiatric physicians, and many depressed patients seek treatment in nonpsychiatric settings.[21] Hence, many depressed patients may not be adequately evaluated and may be at risk for SRI-induced mania. Additional research is needed comparing the relative risk of treatment-emergent mania among different antidepressants and also in different bipolar subtypes, while controlling for concurrent antimanic drug use.

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