

## Tolerability of Combined Treatment With Lithium and Paroxetine in Patients With Bipolar Disorder and Depression

ANDREA FAGIOLINI, MD\*, DANIEL J. BUYSSE, MD\*, ELLEN FRANK, PHD\*, PATRICIA R. HOUCK, MSH†, JAMES F. LUTHER, MA\*, AND DAVID J. KUPFER, MD\*

\*Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic; †University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

**Patients with bipolar disorder are often prescribed lithium in combination with a selective serotonin reuptake inhibitor. Doubts still remain, however, about the safety of the combination, particularly with regard to the risk of developing a serotonin syndrome. The authors retrospectively evaluated the safety of the combination of lithium and paroxetine when the two medications were sequentially prescribed in patients with bipolar disorder. The authors examined a sample of 17 patients with bipolar disorder who were treated with lithium during a depressive episode and who required paroxetine as an adjunctive antidepressant to ongoing lithium treatment. Averaging across all subjects, no statistically significant increase was found for any of the somatic symptoms that were assessed before and after paroxetine was added to ongoing lithium therapy. Examining the clinical records of each patient in detail; however, four patients who developed significant adverse events, possibly related to an emerging serotonin syndrome were identified. Clinicians should be aware of the possible development of a serotonin syndrome among patients in whom paroxetine is added to ongoing lithium treatment. (J Clin Psychopharmacol 2001;21:474-478)**

**L**ITHIUM IS CONSIDERED one of the treatments of choice for patients affected by bipolar disorder, both for prophylaxis and for treatment of manic and depressive episodes.<sup>1,2</sup> Patients with severe nonpsychotic bipolar disorder are often prescribed an antidepressant in combination with lithium, and selective serotonin reuptake inhibitors (SSRIs) are often chosen. However,

reports stating the development of a life-threatening serotonergic syndrome in patients treated with the combination of lithium and an SSRI or venlafaxine have raised concerns about the tolerability and safety of their concurrent use.

The most frequent clinical features of a serotonin syndrome include changes in mental status and behavior (agitation, excitement, hypomania, and obtundation), motor system function (myoclonus, hyperreflexia, tremor, restlessness, hemiballismus, motor weakness, dysarthria, and ataxia), and autonomic nervous system function (fever, shivering, nausea, vomit, diarrhea, dizziness, and sweating).<sup>3-4</sup> Sternbach<sup>3</sup> suggested criteria to diagnose serotonin syndrome in the following cases: (1) coincident to the addition of or increase in a known serotonergic agent to an established medication regimen, at least 3 of 10 features (mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever) are present; (2) other causes (e.g., infectious, metabolic, and substance abuse or withdrawal) have been ruled out; and (3) a neuroleptic had not been started or increased in dosage before the onset of the signs and symptoms listed above. Cases of serotonin syndrome have been reported after the combination of fluoxetine and lithium,<sup>5-10</sup> paroxetine and lithium,<sup>11</sup> paroxetine, dihydroergotamine and lithium,<sup>12</sup> fluvoxamine and lithium,<sup>13</sup> and venlafaxine and lithium.<sup>14</sup> To our knowledge, no systematic studies of the paroxetine/lithium combination have been published to date. This report deals with a sample of 17 patients with bipolar I disorder, enrolled in the Maintenance Therapies in Bipolar Disorder (MTBD) study (MH-29618, E. Frank, principal investigator) and treated with the combination of lithium and paroxetine. The aim of the study was to assess the safety of the combination of lithium and paroxetine and to evaluate the tendency to develop symptoms characteristic of the serotonin syndrome when the two medications are sequentially prescribed in patients with bipolar disorder.

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Address requests for reprints to: Andrea Fagiolini, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213. Address e-mail to: fagiolinia@msx.upmc.edu.

## Methods

MTBD<sup>15</sup> is a randomized, controlled trial comparing Interpersonal and Social Rhythm Therapy<sup>16</sup> with an intensive clinical management approach in patients with bipolar I disorder. All patients enrolled in the study provided informed consent. Pharmacotherapy was provided according to a protocol that has the goal of stabilizing the maximum number of patients receiving lithium alone. Patients with major depression who do not stabilize with lithium alone receive either tranylcypromine or, if unwilling to take a monoamine oxidase inhibitor (MAOI), paroxetine or another antidepressant in addition to their lithium treatment. Patients who cannot tolerate lithium receive divalproex or carbamazepine. Patients are assessed at each visit by an independent evaluator using the Hamilton Rating Scale for Depression (HAM-D-25) (a 25-item version of the HAM-D,<sup>17</sup> which includes the original 17 items plus 8 additional items developed by our group to rate reverse neurovegetative symptoms<sup>18</sup>) and a 22-item Somatic Symptom Checklist (SSC). The SSC is administered by the treating psychiatrist at each visit to the clinic and rates the patient's perception of the severity of 22 somatic complaints (dizziness, clumsiness, blurred vision, headache, nervousness, nausea, sexual difficulties, diarrhea, constipation, dry mouth, increased thirst, decreased appetite, increased appetite, increased urination, difficulty urinating, palpitations, tiredness, skin rash, tremor, increased perspiration, weight gain, and weight loss) on a 3-point scale (0 = not present, 1 = present, but tolerable, 2 = present and causing significant distress or incapacity).

For the purposes of this report, we selected patients who were treated with lithium during a depressive episode and who required paroxetine as an adjunctive antidepressant to ongoing lithium treatment. Seventeen acutely depressed patients with bipolar I were chosen for this study. All the patients were white. Twelve patients (70.6%) were women and 5 (29.4%) were men. The mean age was 38.4 years (SD = 11.0). None of the patients had significant medical illnesses. To evaluate medication side effects, we considered clinical progress notes, SSC scores, and scores on seven specific items of the HAM-D-25 including the following: difficulty falling asleep, sleep continuity difficulties, agitation, psychological anxiety, somatic anxiety, loss of libido, and hypersomnia. The highest value for each item of the SSC and HAM-D-25 in the 3 weeks before beginning the paroxetine was compared with the score obtained in the first assessment that followed the beginning of paroxetine treatment. The second score was obtained, on average, 10.5 ± 7.8 days after the addition of paroxetine. Each symptom was considered moderate if it received a score of 1 on the SSC item or on a 3-point (0–2)

HAM-D scale item, and severe if it scored 2 on the same scales. For the items scored on a 5-point scale on the HAM-D-25 (Agitation, Psychological Anxiety, and Somatic Anxiety), scores of 1 or 2 were considered moderate and scores of 3 or 4 were considered severe. A comparison was also made between the highest item score in the 3 weeks before the beginning of paroxetine and the score for the same item in the first assessment that followed (8.9 ± 4.4 days) the maximum prescribed dose of paroxetine. This analysis reduced the possibility of attributing an increase in the score to a fluctuation of symptoms unrelated to paroxetine treatment.

### Data analysis

To evaluate tolerability of the paroxetine/lithium combination, contingency tables were constructed for each of the SSC items and items 4, 5, 6, 9, 10, 11, 14, and 18 of the HAM-D. The tables were tested for marginal homogeneity, a generalization of the McNemar test,<sup>19</sup> which determines whether or not the pretreatment response rate equals the posttreatment response rate. The *p* values of this test are exact and indicate the probability of obtaining a table as extreme as the one observed if the null hypothesis is true (i.e., if the pre- and post-treatment response rates are equal). Bonferroni correction was not used because no statistically significant increase was found for any of the somatic symptoms assessed in the scales. Data analyses were carried out using StatXact 4 for Windows software.<sup>20</sup>

## Results

### *Dosage of medications, duration of treatment, and response to treatment*

Plasma lithium concentrations were available the week before the beginning of paroxetine for 16 of the 17 patients. Mean lithium concentration was 0.86 mEq/L (SD = 0.16; range, 0.62–1.19). One subject did not have lithium blood concentration assessed the week before starting paroxetine. However, a concentration of 0.71 mEq/L had been obtained 4 weeks before paroxetine was started for this patient. All patients had received lithium carbonate for at least 3 weeks (mean, 17.1 weeks; SD = 13.1; range, 3.0–49.1) before supplementation with paroxetine. In 16 of the 17 patients, the mean lithium concentration in the week after paroxetine was started was 0.80 mEq/L (SD = 0.19; range, 0.43–1.13). The patient whose value of lithium concentration was missing had a lithium level of 0.88 mEq/L, 1 week before paroxetine was started and 0.78 mEq/L, 3 weeks after. In the whole sample, the mean value of lithium concentration during the third week after the addition of paroxetine was 0.80 mEq/L (SD = 0.21; range, 0.34–1.15). Paroxetine was started at a dose of 5 mg in one patient, at 10 mg in nine

patients, and 20 mg in seven patients. The maximum dose of paroxetine reached was 5 mg in one patient, 10 mg in one patient, 20 mg in three patients, 30 mg in four patients, 40 mg in six patients, and 50 mg in two patients. Paroxetine was discontinued after a mean of 11.3 (SD = 9.2) weeks. Paroxetine was discontinued because of remission of depressive symptoms as determined by clinical and psychometric assessments (reduction >50% in HAM-D and HAM-D-25, and total HAM-D <7) in four patients (23.5%); nonresponse or emerging clinical features that suggested the use of a different medication in seven patients (41.2%); the emergence of mania in two patients (11.8%); and adverse events in three patients (17.6%). In one patient paroxetine was not discontinued after remission of depressive symptoms.

#### *Additional medications*

When paroxetine was added to lithium, four patients (23.5%) were receiving no medication other than lithium and paroxetine. Four patients (23.5%) were receiving one other drug, six (35.3%) were receiving two drugs, and three (17.6%) were receiving three or more drugs. Additional medications included lorazepam in three patients, benztropine in three patients, valproate in two patients, clonazepam in one patient, trifluoperazine in one patient, perphenazine in one patient, risperidone in one patient, olanzapine in one patient, levothyroxine in one patient, and gemfibrozil in one patient.

#### *Adverse events*

We compared the score for somatic symptoms, as assessed with SSC and HAM-D-25, for the 3 weeks before beginning the paroxetine (highest value entered), with that for the first assessment after beginning paroxetine treatment and with that for the first assessment after the maximum prescribed dose of paroxetine. The comparison of scores obtained from the SSC and the HAM-D showed no statistically significant increase for any of the somatic symptoms. We examined the clinical records of each patient in detail to identify symptoms of serotonin syndrome that may have been missed, by looking at symptoms averaged across all patients. This procedure identified four patients who developed significant adverse events after paroxetine was added to the ongoing lithium therapy. Three patients required the discontinuation of paroxetine and one required the discontinuation of lithium.

#### *Case histories*

The first patient was a 63-year-old white woman with a long-standing history of bipolar disorder and an episode of depression with psychotic features. After a period of 5 months in which she was treated with lithium, per-

phenazine, benztropine, and lorazepam, paroxetine 10 mg was added. In the subsequent days the patient experienced severe tremor, nervousness, psychic and somatic anxiety, difficulty falling asleep, hypersomnia, psychic retardation, nausea, dry mouth, increased thirst, and confusion. Some of the symptoms were present before paroxetine was started, but they greatly worsened when paroxetine was added to the ongoing treatment. Because of the adverse events mentioned above, paroxetine was discontinued after a total of 14 days, and the symptoms gradually disappeared or decreased in intensity.

The second patient was a 31-year-old white woman with bipolar disorder and generalized anxiety disorder who entered the MTBD study in an episode of depression, which had been immediately preceded by an episode of mania. Before paroxetine was added to lithium, this patient was unsuccessfully treated for a total of 6 months with lithium alone, lithium and bupropion, lithium and imipramine, and lithium and tranylcypromine. Paroxetine was added to lithium 14 days after the discontinuation of tranylcypromine, at 10 mg/day, and it was increased to 20 mg/day after 1 week and increased to 30 mg/day after 3 weeks. Five days after the dose of paroxetine was raised to 30 mg/day, the patient experienced nausea, vomiting, diarrhea, increased perspiration, oversleeping, and increased anxiety. Lithium levels were found to be within normal range. Paroxetine was discontinued and the symptoms gradually disappeared or decreased in intensity.

The third patient was a 36-year-old white woman with bipolar disorder and panic disorder who entered the MTBD study in an episode of depression. The patient was successfully treated with lithium and lorazepam (0.5 mg/day) for approximately 3 months when, because of an increase of symptoms of anxiety and the reappearance of mild symptoms of depression, 5 mg of paroxetine was added to her daily therapy. Immediately after the new medication was started, the patient developed diarrhea, irritability, increased anxiety, loss of appetite, tremor, and palpitations. The depressive symptoms greatly worsened and the patient presented low mood, guilt feelings, insomnia (early morning awakening), anergia, decreased libido, and psychic retardation. Paroxetine was discontinued, and the symptoms gradually disappeared or decreased in intensity.

The fourth patient was a 40-year-old white man with bipolar disorder who was in an episode of major depression. This followed a period of 6 months in which the patient was unsuccessfully treated with lithium, lithium and lorazepam, lithium and valproate, and lithium and olanzapine. Olanzapine was started 6 weeks before beginning paroxetine. Paroxetine was started at 10 mg/day and increased to 20 mg/day after 2 days. After the addition of

paroxetine, the patient began to experience anxiety, nausea, and worsening of his difficulty falling asleep. Those symptoms were still present when, after approximately 10 days from the beginning of paroxetine treatment, the patient experienced severe diarrhea. Lithium had to be discontinued for 2 days until it was possible to check the patient's blood levels, which were within normal limits. Paroxetine was not discontinued. After lithium discontinuation, the symptoms gradually improved. However, lithium was gradually restarted, reaching the previous dose in 5 days, without the symptoms appearing again.

### Discussion

Serotonin syndrome is a condition caused by central and peripheral serotonergic hyperstimulation<sup>21</sup> that can develop when drugs with different serotonin agonist effects are combined (e.g., SSRI and monoaminoxidase inhibitors) or, more rarely, under monotherapy with a serotonin agonist.<sup>22-24</sup> Two case reports in the literature have described the development of a serotonin syndrome in patients treated with lithium and paroxetine.<sup>11-12</sup> To our knowledge, however, no prospective or retrospective study has ever focused specifically on the incidence of the serotonin syndrome in groups of patients treated with paroxetine and lithium. Although it is clear that the difference between the serotonin syndrome and the occurrence of some of the common adverse effects caused by SSRIs alone consists of the clustering, severity, and duration of the symptoms, stringent criteria to clearly distinguish the two conditions have not yet been defined.<sup>25</sup>

The retrospective design of our study does not permit us to assess the presence of the full range of characteristic signs and symptoms of the serotonin syndrome in the four patients who developed adverse events after the combination of paroxetine with ongoing lithium therapy. It would have been interesting, for instance, to have more detailed data on the time course of the syndrome, neuromuscular abnormalities, autonomic nervous system dysfunction, and the blood concentration of paroxetine. Although Sternbach's<sup>3</sup> criteria for serotonin syndrome were met in all four cases, in the absence of information for the symptoms above, a diagnosis of full-blown serotonin syndrome for all four patients is questionable.

In the first patient, some of the symptoms that developed after the addition of paroxetine to lithium could be related to an increase of perphenazine blood concentration because of the inhibitory effect of paroxetine on cytochrome P450-2D6.<sup>26</sup> In the second patient, although the patient received the suggested 2-week washout of the MAOI, some of the symptoms could be related to residual effects of tranylcypromine interacting with

paroxetine. In the third patient, some of the symptoms could be explained by a worsening of the symptomatology of panic disorder, possibly induced by the new medication. Moreover, in the absence of a control group treated with paroxetine alone it is possible that symptoms could be ascribed to paroxetine alone, rather than to the combination of lithium and paroxetine. The fact that in one of the patients the symptoms remitted when lithium was discontinued, suggests the probable contribution of lithium. In that case, the symptoms improved when lithium was discontinued but did not reappear when lithium was started again after a few days; this is possibly because of the development of an adaptation to some of the somatic symptoms.

Lane and Baldwin<sup>25</sup> have recently suggested making the criteria for the serotonin syndrome more stringent, for instance, supplementing the criteria with a requirement for the triad of pyrexia, neuromuscular symptoms (of rigidity and hyperreflexia), and mental state changes (of confusion or hypomania). Our results clearly confirm such necessity and, at the same time, suggest caution regarding the potential for a serotonin syndrome. In fact, four patients in our sample experienced many of the characteristic symptoms of the syndrome, and those symptoms started or worsened soon after the combination of paroxetine with lithium and then remitted or improved when paroxetine or lithium were discontinued.

Our study is restricted to patients affected by bipolar I disorder in whom paroxetine was added to an ongoing lithium treatment. Therefore, our results may not necessarily apply to patients with different illnesses or to patients in whom lithium and paroxetine were combined in a different sequence. The relatively small percentage of the patients in our sample improved clinically after paroxetine was added to their lithium therapy reflects the severity and the difficulty of treating depression in bipolar patients<sup>15</sup> and is influenced by the particular features of the MTBD protocol. The patients who were treated with lithium and paroxetine, in fact, were patients who did not respond to lithium alone nor to the combination of lithium and tranylcypromine or were patients for whom this last combination was not appropriate. Two (12%) of the 17 patients included in this study developed manic features while receiving lithium and paroxetine, once again confirming that the ongoing use of a mood stabilizer is not always "protective" when an antidepressant is used in bipolar I patients. In summary, paroxetine remains a valid option for treating bipolar depression as long as clinicians are aware of the possibility of the development of a serotonin syndrome, a potentially serious condition that must be promptly recognized and followed by immediate discontinuation of the responsible agents.

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