

## Letters to the Editor

### Combined Antidepressant Treatment: A Risk Factor for Switching in Bipolar Patients

**Sir:** We read with great interest the recent article by Henry et al.<sup>1</sup> identifying risk factors for antidepressant-induced hypomania/mania (switching) in bipolar patients. The authors reported a high rate of switching induced by antidepressant medications, i.e., 24%, and suggested that a hyperthymic temperament and lack of concurrent lithium treatment might be risk factors for mood switches.

We want to highlight another risk factor—the use of combined antidepressant treatment. We report a patient with bipolar depression who switched into hypomania 3 days after combined antidepressants were started.

**Case report.** Ms. A is a 55-year-old woman with a 25-year history of DSM-IV bipolar I disorder. For approximately 1 year, she was euthymic on treatment with bupropion, 300 mg/day, and carbamazepine, 600 mg/day, until she had a relapse of a major depressive episode, consisting of dysphoria, loss of interest, low energy, and decreased concentration. Results of a medical workup, including assessment of thyroid functions, were within normal range. Blood carbamazepine level was therapeutic. Bupropion was increased to 400 mg/day, with no improvement. Valproate or lithium was not an option due to Ms. A's severe side effects with these agents in the past. Paroxetine (20 mg/day) as an augmentor was added. Three days later, the patient developed hypomania. Initially, the treatment regimen was not changed, with anticipation that the patient's symptoms would resolve. However, 1 week later, the symptoms persisted. Paroxetine was then decreased to 10 mg/day, resulting in the resolution of her hypomania. Unfortunately, 1 week later, the patient became depressed again. Paroxetine was then increased to 20 mg/day, and at the same time, bupropion was slowly discontinued in hope of preventing another switch. Depression persisted, necessitating an increase in paroxetine dose to 40 mg/day. Ms. A had a good therapeutic response and remained stable over the next 6 months.

Treating bipolar depression is a complicated task due to the risk of switching induced by antidepressants, as highlighted by Henry et al.<sup>1</sup> All antidepressant treatments, both pharmacologic and nonpharmacologic (e.g., electroconvulsive therapy), have been implicated in the switching phenomena.<sup>1,2</sup> Overall, the current available data suggest that paroxetine and bupropion are the safest from the perspective of switching.<sup>2</sup> The potential risk conferred by combined antidepressant treatment, which is a recommended strategy for refractory bipolar depression,<sup>3</sup> has not been adequately studied. Although in their report Henry et al. categorized the risk posed by different antidepressants, they failed to address the role of combined antidepressants as a risk factor for switching. There is 1 case report<sup>4</sup> that documents a switch into mania in a bipolar patient occurring after 4 days of

bupropion treatment (200 mg/day), which was started 2 days after discontinuing a failed trial with fluoxetine (20 mg/day). The authors speculated that, due to the long half-life of fluoxetine, the manic episode might have been caused by the combination of bupropion and fluoxetine.<sup>4</sup>

Our case report suggests caution in the use of combined antidepressants in treatment of bipolar illness, even when using the safest antidepressants, such as bupropion with paroxetine, in the presence of a mood stabilizer. It is possible that a pharmacokinetic phenomenon exists between these 2 agents, as both are inhibitors of the cytochrome 2D6 enzyme system, resulting in a higher blood level of paroxetine, since paroxetine is metabolized by this enzyme.

We recommend that these agents be used cautiously when combined, with slow upward titration.

*The authors report no financial or other relationships related to the subject matter in this communication.*

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#### Dr. Henry Replies

**Sir:** Many factors may contribute to mood switches in bipolar patients, including pharmacologic manipulations such as those reported both in the article by my colleagues and me<sup>1</sup> and in the comment by Gabbay et al., which describe drug-related triggering of manic or hypomanic episodes. I agree with Dr. Gabbay and colleagues on the risk of mood switch induced by the use of combined antidepressant treatment in bipolar patients, and their case report highlights this risk, which, as they noted, was not assessed in our study. Their report raises the issue of the need to first try another type of antidepressant before prescribing a combination of antidepressants in bipolar patients during persisting depression. However, the second case report referred to

in the comment from Zubieta and Demitrack<sup>2</sup> seems to illustrate another effect of antidepressant treatment in triggering manic episodes, i.e., the induction of mania by abrupt withdrawal of selective serotonin reuptake inhibitors (SSRIs). Zubieta and Demitrack<sup>2</sup> reported a switch that occurred 4 days after the onset of bupropion treatment and 2 days after discontinuing fluoxetine. The authors speculated that, due to the length of the half-life of fluoxetine, the manic episode might have been caused by the combination of bupropion and fluoxetine. Four days from the beginning of bupropion treatment to the occurrence of the switch appears to be a very short time interval, as the onset of antidepressant activity and the switches induced by bupropion usually occur later.<sup>3</sup>

In turn, we could hypothesize that it is not the combination of the antidepressants, but rather the fluoxetine discontinuation that is responsible for the mood change. This effect has been described by Goldstein et al.,<sup>4</sup> who reported 6 cases of antidepressant discontinuation-related mania in bipolar patients, in spite of adequate concomitant mood-stabilizing treatment. I have observed effects of abrupt withdrawal of SSRIs: discontinuation of SSRIs in patients who initially presented with hypomanic symptoms has sometimes resulted in a real manic episode a few days after abrupt withdrawal. This phenomenon could be linked to the discontinuation syndrome and perhaps more specifically to the severe insomnia observed during withdrawal of some antidepressants. I now remove SSRIs more progressively, even after the beginning of hypomanic symptoms, and this helps to avoid the worsening of hypomania. In spite of a poor understanding of their neuropharmacologic substrate, collecting and discussing all of these observations of drug-induced manic and hypomanic episodes is very useful, because guidelines for antidepressant treatment in bipolar depression remain imperfect.

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**Palinopsia and Paroxetine Withdrawal**

**Sir:** I read with interest the letter by Drs. Ihde-Scholl and Jefferson,<sup>1</sup> which showed a case of palinopsia associated with mirtazapine and suggested that palinopsia is associated with 5-HT<sub>2</sub> antagonism or reduced 5-HT<sub>2</sub> receptor stimulation.

My colleagues and I<sup>2</sup> reported a case of a 56-year-old man suffering from palinopsia during maprotiline and levomepromazine treatment. Since both drugs have 5-HT<sub>2</sub> antagonistic effects,<sup>3,4</sup> 5-HT<sub>2</sub> antagonism may have played an important role in our patient's palinopsia.

Nonetheless, in the patient of Ihde-Scholl and Jefferson,<sup>1</sup> paroxetine was withdrawn just before mirtazapine administration. Paroxetine withdrawal is likely to induce discontinuation symptoms including visual symptoms.<sup>5</sup> Therefore, there is a possibility that paroxetine withdrawal by itself might have induced palinopsia in their patient. At least, the authors should have noted another possibility, that is, that serotonin decrement in synaptic cleft after paroxetine withdrawal could have augmented 5-HT<sub>2</sub> antagonistic effects of mirtazapine in their patient.

*Drs. Ihde-Scholl and Jefferson were shown this letter and declined to comment.*

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**Smoking in Bipolar and Schizophrenic Patients**

**Sir:** Itkin et al.<sup>1</sup> need to be congratulated for publishing the first study comparing smoking in bipolar and schizophrenic patients. However, the title was unfortunate; *habit* is not a good word to describe a frequently lethal addiction.

Nine of 10 worldwide studies suggested current smoking is significantly more prevalent in schizophrenia than in other psychiatric illnesses.<sup>2</sup> Two of them compared schizophrenia and mood disorders (depressive and bipolar disorders). Diwan et al.<sup>3</sup> reported significantly higher prevalences of ever and current smoking in 63 schizophrenic men compared with 20 men with mood disorders after correcting for potential confounding factors. There were no differences between smokers in the 2 groups in scores on the Fagerstrom Test for Nicotine Dependence (FTND). Similarly, after correcting for gender and other factors, we found significantly higher prevalences of ever and current smoking in 66 schizophrenic patients compared with 51 patients with mood disorders and no differences in FTND scores between smokers in the 2 patient groups.<sup>4</sup>

These 2 studies suggest consistently that when compared with mood disorders, schizophrenia is associated with higher rates of ever and current smoking, but has similar FTND scores in smokers. However, Itkin et al.<sup>1</sup> described a lack of significant differences in ever and current smoking as well as FTND scores between schizophrenic and bipolar patients. Surprisingly, Itkin et al. overlooked the fact that their own data provide significant evidence that prevalence of current smoking in male schizophrenic patients is higher than in male bipolar patients. Using

Figure 1 from their article, it can be calculated that 71% of male schizophrenic patients (22/31) and 34% of male bipolar patients (11/32) were current smokers. The significant odds ratio was 4.7 (95% confidence interval = 1.6 to 13.5). Thus, although not mentioned by Itkin et al., their data still suggest a significant difference between male schizophrenic and male bipolar patients in current smoking.

The lack of differences in current smoking between the schizophrenic and bipolar women in the study by Itkin et al. could be explained by the recruitment of a relatively small sample of atypical schizophrenic women. In fact, the prevalence of current smoking in the schizophrenic women was lower than the prevalence from the general population, which seems to be unusual.

In summary, studies all over the world suggest that schizophrenic patients, after correcting for gender effects, consistently have higher rates of current smoking than other severely mentally ill patients.<sup>2</sup> Certainly new and larger studies comparing schizophrenic and bipolar patients are needed.

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#### Dr. Einat Replies

**Sir:** The results of our study suggest that smoking prevalence may not be different between bipolar and schizophrenic outpatients in southern Israel.<sup>1</sup> In their letter, de Leon and Diaz raise 2 main concerns regarding these results, the first relating to other studies indicating higher smoking frequency in schizophrenic compared with mood disorders patients and the second relating to the large gender effect in our schizophrenic patients.

As suggested by de Leon and Diaz, the results of other studies comparing smoking in schizophrenic and affective disorders patients show higher prevalence in schizophrenics (e.g., reference 2). However, these studies pooled major depressive disorder and bipolar patients into 1 group, whereas we examined only bipolar patients, a group that may be unique in the context of substance abuse and therefore also in regard to smoking. It is well documented that the frequency of substance abuse is high in manic patients<sup>3</sup> and that high frequency may be related to a variety of factors, including a generalized increase in hedonic and risk-taking behaviors that are fundamental components of the disorder. It is therefore possible that the lower frequency of smoking in affective disorders compared with schizophrenia reported in a number of studies is the consequence of pooling together 2 very different groups of patients (those with major depressive disorder and bipolar illness).

We did report a large gender effect in the schizophrenic group, with ever-smoking rates of 39% in women and 71% in men, and de Leon and Diaz are correct in indicating that the analysis of men only will result in higher smoking rates in schizophrenic than in bipolar patients. However, one may want to have a rationale to omit the female participants from the analysis; in contrast to such omission, I suggest that the gender differences may forward our understanding of smoking in schizophrenics. In our initial analysis, we did not include an ethnic background factor. Nevertheless, further analysis of the data shows that the relatively low rate of smoking in schizophrenic women is remarkably apparent in women of eastern European origin or heritage, of whom only 2 of 15 female schizophrenics reported current or ever smoking. This is interesting because previous studies examining smoking in the general population reported very large differences between men and women in the former Soviet Union,<sup>4</sup> differences that are very much larger than in the United States.<sup>5</sup> It is therefore feasible that a cultural effect is carried over from the general population to patients, but if this is the case and cultural background has such a strong effect, then environmental factors may play a much more significant role in schizophrenia-related smoking than any biological factors innate to the disease.

As suggested by de Leon and Diaz, larger studies are much needed to explore these possibilities.

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#### Sleep Apnea Associated With Antipsychotic-Induced Obesity

**Sir:** Weight gain and the development of obesity are known side effects of the novel antipsychotic drugs. We report 2 cases of obstructive sleep apnea that developed in the context of weight gain secondary to treatment with novel antipsychotic drugs.

**Case 1.** Ms. A is a 45-year-old African American woman with treatment-refractory DSM-IV schizophrenia who was treated with clozapine, 300 mg/day. During 16 months of clozapine therapy, she developed a voracious appetite and gained 40 pounds (18 kg), with an increase in body mass index (BMI) from 31 kg/m<sup>2</sup> to 37 kg/m<sup>2</sup>. This 19% increase in BMI was accompanied by the development of hypertriglyceridemia and glucose intolerance. She also experienced daytime sedation, difficulty

sleeping at night, loud snoring, and periods of apnea during sleep. Polysomnography revealed an overall apnea/hypopnea index value of 36 events/h, 80 events/h while supine, 9 events/h while lying on her side, and oxygen desaturation to 87%. These apnea/hypopnea index values reflect moderate sleep apnea in our laboratory. She was diagnosed with obstructive sleep apnea (OSA) and prescribed nasal continuous positive airway pressure (CPAP) with improvements in sleep difficulty, daytime somnolence, and sleep apnea.

**Case 2.** Mr. B is a 50-year-old Latino man with schizophrenia who was treated with risperidone. During treatment with risperidone, 6 mg/day, over a period of 31 months, he gained 65 pounds (29 kg), with a 41% increase in BMI (from 27 kg/m<sup>2</sup> to 38 kg/m<sup>2</sup>) and development of diabetes. In the setting of this weight gain, Mr. B reported difficulty sleeping, frequent daytime napping that left him unrested, and prominent snoring and apnea at night, according to his wife. Obstructive sleep apnea was diagnosed with oxygen desaturation to 71%. He was prescribed CPAP, resulting in overall improvement in sleep apnea symptoms.

A variety of sleep disturbances (decreased total sleep time, increased sleep latency, reduced rapid eye movement [REM] latency) have been found in association with schizophrenia.<sup>1-3</sup> Sleep apnea has also been reported in some patients with schizophrenia, with conflicting data on whether the prevalence of sleep-related respiratory dysfunction exceeds that of controls and an unresolved relationship to obesity and antipsychotic treatment.<sup>4-7</sup> Our patients developed OSA in the context of significant weight gain temporally related to novel antipsychotic therapy and other obesity-related health problems. These cases add to the growing literature on morbidity associated with novel antipsychotic-induced obesity and suggest that clinicians should consider the possibility of OSA when obese patients with schizophrenia present with symptoms of insomnia and excessive daytime sedation. OSA is a serious medical condition that can also lead to mood and cognitive disturbances, hypertension, cardiac failure, and sudden death.<sup>5,8</sup>

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