

### Quetiapine Treatment for Mania Secondary to Brain Injury in 2 Patients

**Sir:** In the only 2 studies that estimate prevalence of mania secondary to traumatic brain injury (TBI), Jorge et al.<sup>1</sup> diagnosed mania in 9% of 66 consecutive brain-injured patients and Van Reekum et al.<sup>2</sup> found 22% of 18 TBI patients developed a bipolar spectrum disorder after mild or moderate TBI. Both of these estimates are higher than the known lifetime prevalence of bipolar I disorder, which is 0.4% to 1.6%.<sup>3</sup>

Several other differences suggest mania secondary to TBI is phenomenologically distinct from primary mania. First, 4% to 24% of first-degree relatives of those with bipolar I disorder also have bipolar I disorder,<sup>3</sup> but none of Jorge and colleagues' subjects had a first-degree relative with bipolar disorder.<sup>1</sup> Also, the average age at onset of mania is 20 years,<sup>3</sup> but mania secondary to TBI has been reported in subjects aged as young as 10 years<sup>4</sup> to as old as 70 years.<sup>5</sup> Finally, brain injury-related bipolar disorder may result in more rapid cycling<sup>6</sup> or prolonged manic states<sup>7</sup> compared to primary mania.

These phenomenological differences account for the controversy over considering these syndromes within the bipolar spectrum, as mood disorders secondary to general medical condition, versus neuropsychiatric sequelae of TBI. Regardless of how these disorders are characterized, medication management of psychiatric symptoms following TBI is commonplace.

The pharmacologic management of mania secondary to TBI is complicated by animal studies suggesting some antiepileptics and antipsychotics interfere with cognitive or motor recovery. Rats exposed to diazepam after experimental brain injury had persistent sensorimotor asymmetry.<sup>8</sup> Brain-injured rats treated with phenobarbital had significantly delayed recovery in somatosensory deficits.<sup>9</sup> Phenytoin increases the severity of cortical hemiplegia in rats.<sup>10</sup> Haloperidol impairs cognitive performance after traumatic brain injury in rats,<sup>11</sup> retards motor recovery,<sup>12</sup> and blocks the acceleration in motor recovery caused by amphetamine.<sup>13</sup>

No controlled trials of treating mania secondary to TBI have been published, but there are case reports of successfully using chlorpromazine and carbamazepine,<sup>14</sup> haloperidol alone,<sup>14</sup> haloperidol and chlorpromazine,<sup>15</sup> haloperidol and clonazepam,<sup>16</sup> clonidine,<sup>17</sup> lithium alone,<sup>4,18,19</sup> lithium and thioridazine,<sup>20</sup> valproate alone,<sup>21</sup> valproate and olanzapine,<sup>22</sup> carbamazepine and lithium,<sup>23</sup> and carbamazepine and chlorpromazine.<sup>24</sup> Others have reported failed treatment with electroconvulsive therapy, carbamazepine, verapamil, neuroleptics, lorazepam, trazodone, alprazolam, phenelzine, valproate, phenytoin and clozapine,<sup>7</sup> carbamazepine,<sup>17</sup> and lithium.<sup>25</sup>

In an open-label flexible-dose study, Kim and Bijlani<sup>26</sup> reported quetiapine was effective for treating irritability and aggression following TBI at doses from 25 to 300 mg/day. That study was only of the target symptoms of aggression and irritability, however, not the full syndrome of mania. We report the first 2 cases in the literature of mania secondary to TBI successfully treated with quetiapine.

**Case 1.** Mr. A, a 27 year-old man with DSM-IV alcohol dependence since adolescence but no family or personal history of mood disorders, was involved in a motor vehicle accident while intoxicated in 2007. At the scene, he was spontaneously moving all extremities, but was combative; initial Glasgow Coma Scale<sup>27</sup> score was 8 (intubated). A head computed tomography scan at the receiving hospital revealed extensive

subarachnoid hemorrhages in the interpeduncular, perimesencephalic, and suprasellar cisterns extending inferiorly, anterior to the brainstem, to the level of the cervical medullary junction, and small intraventricular hemorrhages in the lateral ventricles. He had multiple facial and upper extremity fractures.

Initially, he was reported to have made rapid progress in acute rehabilitation, but was mildly agitated and restless, though without significant behavioral problems. Sixteen days after the injury, he was at level VI–VII on the Rancho Los Amigos Level of Cognitive Functioning Scale.<sup>28</sup> Twenty-three days following the injury, he reported increasing anxiety and depression. His Beck Depression Inventory<sup>29</sup> score was 15, indicating mild to moderate symptoms, and a course of supportive psychotherapy was initiated, but not antidepressant medications.

Six weeks following the injury, the patient was noted to have increasing mood lability, irritability, and verbal outbursts. On psychiatric examination, his mood was elevated and irritable; he had psychomotor agitation, decreased need for sleep, rapid speech, distractibility, and demanding behavior; and he was moderately disheveled. At the time of the first psychiatric evaluation, he had already been prescribed valproic acid 1000 mg daily (blood drug level = 51 µg/mL). His initial Young Mania Rating Scale (YMRS)<sup>30</sup> score was 26. Quetiapine was started and titrated to 350 mg daily, in divided doses, over 7 days.

After the first week of treatment with quetiapine, his YMRS score was 25 and quetiapine was increased to 600 mg daily in divided doses. During this time, the valproic acid dosage was also increased to 2000 mg daily, yielding a blood drug level of 76 µg/mL. After 2 weeks of treatment with quetiapine, his YMRS score dropped to 18 and one further increase in quetiapine was made, to a dose of 750 mg daily. One week later, his YMRS score was 13. His mood was euthymic, speech and thought process were normal, there was less disruptive and aggressive behavior, and grooming/self-care was improved. On the Functional Independence Measure,<sup>31</sup> he was rated as independent in activities of daily living, and he was deemed ready for discharge. He tolerated the quetiapine well and denied experiencing any side effects.

**Case 2.** Mr. B, a 21-year-old man with a childhood history of attention deficit/hyperactivity disorder but no family or personal history of mood disorders, was injured in an explosion in 2005 resulting in a right frontoparietal penetrating brain injury. He underwent a temporoparietal craniectomy, and his postoperative course was complicated by seizures treated first with valproate, then phenytoin, and finally carbamazepine 800 mg twice a day, yielding a blood drug level of 9.5 µg/mL. On admission to a rehabilitation hospital 10 weeks after the injury, he was at level IV on the Rancho Los Amigos Level of Cognitive Functioning Scale.

Twelve weeks following the injury, he began to have anxiety and nightmares, with psychomotor agitation, irritability, and impulsivity. He was started on a trial of citalopram 10 mg daily for anxiety and quetiapine 12.5 mg at bedtime for sleep. On treatment with these medications, he became increasingly agitated, aggressive, and irritable, with pressured speech, disorganized thought process, distractibility, and paranoid ideation. Citalopram was discontinued, and quetiapine was titrated to a dose of 650 mg daily in divided doses.

Over the following 2 weeks, his mood gradually stabilized and he experienced good control of irritability and agitation, but cognitive deficits persisted. At 6-month follow-up, his

mood remained stable and he was tolerating quetiapine well, but he had gained 41 pounds.

In both of the cases presented here, the patients were prescribed a mood-stabilizing antiepileptic prior to starting quetiapine, yet each developed manic symptoms 6 to 12 weeks after a traumatic brain injury. The less severely injured patient had a quicker and more complete response with quetiapine, and his case was not complicated by the possibility that manic symptoms were precipitated by an antidepressant.

Previous work by our group has found quetiapine is usually prescribed in low doses to treat organic brain syndromes, including nonspecific agitation ( $117.2 \pm 105.0$  mg), delirium ( $140 \pm 67.5$  mg), and dementia ( $48.8 \pm 33.6$  mg).<sup>32</sup> The 2 cases reported here indicate that the usual mood-stabilizing doses of quetiapine can be a useful adjuvant therapy for mania secondary to TBI when an antiepileptic alone does not stabilize mood.

*The authors report no financial affiliation or other relationship relevant to this letter.*

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#### Gender Imbalance in Clinical Trials in Schizophrenia

**Sir:** A recent study on the prevalence of schizophrenia in the general population using a structured clinical interview evidenced no sex difference in lifetime prevalence: 0.82% (95% CI = 0.56 to 1.19) for men and 0.91% (0.65 to 1.27) for women.<sup>1</sup> These figures are in agreement with a review of 1721 prevalence estimates of schizophrenia from 188 epidemiologically heterogeneous studies (published between 1965 and 2002) showing no significant differences between genders.<sup>2</sup> Our own records from Puente de Vallecas Health Center in Madrid, Spain, which is the referral mental health center for approximately 250,000 inhabitants, showed a male/female ratio of 1.33 among the 1104 patients who received a diagnosis of schizophrenia (based on ICD-9 criteria) between 1990 and 2005.

Despite such evidence, most large clinical trials in schizophrenia have used samples with imbalanced male/female ratios, e.g., 2.85 (N = 1460) in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.<sup>3</sup> This gender imbalance has not been related to any greater refusal to participate in clinical trials of women with mental illness than their male counterparts.<sup>4</sup> Furthermore, it has been pointed out that this imbalance could be partially attributed to more restrictive inclusion/exclusion criteria for women.<sup>4</sup> A recent review of sex selection bias in clinical trials in schizophrenia (published between 1993 and August 2005) showed that the median

percentage of women was 33.3%.<sup>5</sup> Younger patients, trials conducted in North America, and sampling from inpatient settings have been proposed as factors associated with the lower percentage of women in clinical trials in schizophrenia.<sup>5</sup> Indeed, it was pointed out that more recent studies had even lower proportions of women.<sup>5</sup>

The crucial fact is that, nowadays, women are underrepresented in clinical trials in schizophrenia. Hence, as response to antipsychotic treatment may be gender related,<sup>6</sup> it would be helpful for clinical trials in schizophrenia to provide their results by gender.

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### Urinary Retention Associated With Ziprasidone: A Case Report

**Sir:** While urinary hesitancy or retention is a well-known side effect of those first-generation antipsychotics that have significant anticholinergic properties, it is rare with second-generation antipsychotics. Occasional cases have been reported for risperidone,<sup>1</sup> quetiapine,<sup>2</sup> and, more recently, olanzapine<sup>3</sup> and ziprasidone.<sup>4,5</sup> Here we report another case of urinary retention associated with use of ziprasidone and briefly discuss this rare side effect.

**Case report.** Ms. A, a 46-year-old woman with a 13-year history of schizoaffective disorder, bipolar type (DSM-IV criteria), who had discontinued her psychiatric medications for 2 years, was hospitalized for an acute psychotic episode. She presented with marked delusions of persecution and suicidal ideation. For the first week, she was treated with risperidone (titrated to 4 mg/day) and clonazepam (4 mg/day), but her delusions persisted. Ziprasidone was then added and titrated to 200 mg/day. The patient soon improved and her care was transferred to the outpatient setting.

While being monitored as an outpatient, Ms. A mentioned some urinary hesitancy, but its potential relationship to ziprasidone

was not realized. She continued as an outpatient, but about 2 months after first starting ziprasidone, she worsened again and developed marked fearfulness and persecutory delusions. Ziprasidone was increased to 240 mg/day and clonazepam to 5 mg/day. Previous plans to taper risperidone were deferred, and escitalopram 10 mg/day was added to address the developing depressive symptoms.

Almost immediately after increasing the ziprasidone dosage to 240 mg/day, the urinary hesitancy worsened, and Ms. A had to make several trips to the bathroom before being able to void. In addition, her psychiatric status continued to worsen. She was readmitted to the mental health unit and within a day developed almost complete urinary retention. She required repeated urinary catheterization to relieve the urinary retention. Urology consultation was obtained, and all of Ms. A's psychotropic medications were withheld. A urinary tract infection was diagnosed and treated with ciprofloxacin. After structural defects were ruled out and normal voiding returned, Ms. A's psychotropic medications were cautiously resumed, one at a time. Escitalopram, the first to be restarted, was tolerated without any difficulty in voiding. Ziprasidone was begun next (80 mg on the first day, followed by 160 mg/day thereafter), but after just 2 doses of ziprasidone, Ms. A again developed marked urinary hesitancy.

The urinary hesitancy again resolved on discontinuing ziprasidone, though escitalopram and clonazepam were continued. Aripiprazole was started as an alternative and successfully treated the psychosis without leading to any urinary symptoms. In outpatient follow-up, the patient continued to take the same medications for over a year with no recurrence of either psychosis or urinary hesitancy.

We use the criteria of Naranjo et al.<sup>6</sup> to assess the relationship of the urinary retention to ziprasidone. Of the 10 criteria, the following 6 supported the association of the urinary retention to ziprasidone in this case: the symptom occurred after starting ziprasidone, it abated after ziprasidone was stopped, it reappeared when ziprasidone was reintroduced, alternative causes for the symptom are not plausible, it became more severe when the dose of ziprasidone was increased, and it was confirmed by objective evidence (in that Ms. A required repeated catheterization to relieve the retention). Of the remaining 4 criteria, it is not clear if one of them applies and so here we consider it absent: there are previous reports of this symptom, but it is not clear whether they should be considered conclusive as required by the criteria. Another criterion that is absent is the patient's having had the symptom in previous exposure to the same or similar medication. The other 2 criteria were not applicable in this case: whether or not the symptom reappeared when a placebo was given, and whether or not the medication was detected in the blood or other fluids in concentrations known to be toxic. The total score is +9; using the authors' scoring system,<sup>6</sup> the urinary hesitancy/retention is considered a "definite" side effect of the ziprasidone.

Ms. A had no history of urinary retention or other urologic problems prior to taking ziprasidone. Regarding potential alternative causes, although she was taking other medications—escitalopram and clonazepam—during a period of rechallenge, neither of these medications caused a return of urinary hesitancy. Also, the urinary hesitancy had already started prior to her taking escitalopram. Similarly, although the urinary hesitancy initially started while the patient was on treatment with both risperidone and ziprasidone, it occurred only after ziprasidone was started, and it later recurred with the use of ziprasidone alone. Thus, only ziprasidone seemed to have a direct and almost immediate temporal correlation with the onset, worsening, resolution, and recurrence of urinary hesitancy.

Urinary hesitancy is recognized in the product information as a rare side effect of ziprasidone, although urinary retention is not specifically mentioned.<sup>7</sup> We followed the literature search strategy recommended for case reports of rare side effects of medications.<sup>8</sup> In PubMed, we used the textword *ziprasidone* along with the MeSH term *urinary retention* and with the textword *urinary* (on July 3, 2007). Only 2 reports of urinary retention associated with ziprasidone were found.<sup>4,5</sup> These 2 publications also did not cite any additional reports of ziprasidone-induced urinary retention. A search of EMBASE, SCOPUS, and the manufacturer's Web site done on July 3, 2007, also did not reveal any additional cases. A repeat search on February 4, 2008, showed an additional case report<sup>9</sup> that attributed the urinary retention to the combination of a selective serotonin reuptake inhibitor (SSRI) and ziprasidone. However, that patient had clear episodes of urinary retention prior to starting ziprasidone.

Of these 2 prior case reports of ziprasidone-associated urinary hesitancy and retention, the first was in a 20-year-old male patient without any history of urinary symptoms, occurred after 6 months of treatment with ziprasidone 160 mg/day, and resolved promptly with discontinuation of ziprasidone.<sup>4</sup> The second case occurred during an open-label clinical trial of intramuscular ziprasidone for agitation in elderly patients with schizophrenia. An elderly man with a prior diagnosis of benign prostatic hypertrophy developed acute urinary retention following a second injection of intramuscular ziprasidone (concomitant medications were not listed).<sup>5</sup>

Urinary hesitancy or retention with first-generation antipsychotics is most closely correlated with the degree of their anticholinergic effects. On the other hand, the mechanism by which ziprasidone, or other second-generation antipsychotics, occasionally cause urinary retention is not known. We can speculate on the potential role of ziprasidone's effects on noradrenergic, serotonergic, and dopaminergic systems in causing this side effect. Stimulation of  $\alpha_1$  receptors causes contraction of sphincter and relaxation of detrusor muscle thereby causing hesitancy and retention,<sup>10</sup> whereas  $\alpha_1$  antagonists are used in the treatment of urinary hesitancy. Ziprasidone has minimal  $\alpha_1$  blocking properties, but is a potent norepinephrine reuptake inhibitor and may lead overall to increased  $\alpha_1$  stimulation. Descending serotonin pathways from the raphe nucleus inhibit bladder contractions,<sup>11</sup> and SSRIs have been associated with urinary retention. Thus, ziprasidone's serotonin reuptake blocking property could also be involved in this side effect. Lastly, central acute dopamine-2 ( $D_2$ ) receptor stimulation seems to be associated with a reduction of bladder capacity and detrusor overactivity,<sup>12</sup> which suggests that acute  $D_2$  blockade by antipsychotics may be a factor in urinary hesitancy.

When prescribed any second-generation antipsychotic, patients with risk factors for developing urinary hesitancy, such as a previous history of urologic difficulties or prostatic abnormalities, should be cautioned that these medications may be associated with urinary hesitancy or retention in rare cases. Elderly patients in particular should probably be screened for such risk factors prior to being prescribed an antipsychotic. It is possible that concomitant use of an SSRI and ziprasidone (as in our patient) or other second-generation antipsychotics may increase the risk of urinary hesitancy due to an additive effect, given that SSRIs have also been associated with urinary hesitancy.<sup>13</sup> Although multiple case reports of urinary hesitancy or retention with a combination of an antidepressant and an antipsychotic have been published, it is not usually possible to determine whether the adverse effect was due to the combination rather than to the medication temporally related to its onset. If

urinary hesitancy or retention that is attributed to a second-generation antipsychotic occurs, dose reduction may be an option in some cases since this side effect seems to be dose related, as in our patient and others.<sup>3</sup> Alternatively, successful treatment with another second-generation antipsychotic has been possible, as in our case. Whether a particular second-generation antipsychotic would be a better choice in preventing urinary hesitancy in high risk patients, or as an alternative if this side effect occurs, is not clear.

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## Treating Schizophrenia With Comorbid Depressive or Demoralization Symptoms

**Sir:** Two of us (I.D.G., J.M.D.) recently had an article published in the *Journal*<sup>1</sup> which suggested that concomitant psychotropic medications (CPMs) may not improve outcome of antipsychotic monotherapy for stabilized patients with nonacute schizophrenia. In the article, we stated that “to our knowledge, there have been no published reports of prospective investigations of systematic discontinuation of concomitant medication in this patient population (i.e., nonacute, stabilized patients with schizophrenia).”<sup>1(p1262)</sup>

As it happens, one prospective, double-blind, randomized, controlled study of the discontinuation of adjunctive antidepressant medication, during maintenance-phase treatment had been conducted.<sup>2</sup> However, this study, which was done with stringent methodology in patients who had had syndromally defined postpsychotic depression responsive to the addition of imipramine to their stable fluphenazine decanoate/benzotripine medication regimens, yielded the powerful and clinically meaningful finding that patients were benefited not only by being less likely to fall back into a more depressed state if the adjunctive imipramine was continued ( $p < .001$ ), but also by being less likely to experience a worsening of psychotic symptomatology if the imipramine was maintained ( $p < .05$ ). This is an important study, as we all agree, indicating that there may be “some” (percentage unknown) patients with schizophrenia who may benefit from an antidepressant.

The key differences in the 2 studies were as follows:

- (1) The Glick et al. study was naturalistic, whereas the Siris et al. study was controlled.
- (2) The Glick et al. study may have used a more chronically ill sample, which had not recently had “postpsychotic depression,” although they did have residual negative symptoms and definitely had demoralization (in contrast to DSM-IV depressive symptoms).
- (3) The Siris et al. sample was composed of patients who all had initially appeared to benefit (i.e., had scores of either much improved or very much improved on the Clinical Global Impressions scale) after the addition of the antidepressant medication to their antipsychotic regimen, whereas the Glick et al. sample did not adhere to such a requirement for initial appearance of benefit.
- (4) The Glick et al. sample were receiving second-generation antipsychotics, whereas subjects in the Siris et al. study were receiving fluphenazine decanoate, a first-generation antipsychotic (and thus presumably had better compliance).
- (5) The Siris et al. study involved imipramine, a tricyclic antidepressant, whereas the Glick et al. study mostly involved patients treated with antidepressants other than tricyclic antidepressants.
- (6) Finally, the Siris et al. study made a concerted attempt to reduce the possibility of neuroleptic-induced akinesia, which can have a similar appearance to depression and/or negative symptoms, by co-administration of benzotripine (2 mg p.o. t.i.d.) before the adjunctive antidepressant was added to the antipsychotic agent. Additionally, this benzotripine dosage was continued in all patients in both treatment groups throughout the trial of antidepressant maintenance treatment versus antidepressant discontinuation.

In any case, we believe that the implication for the clinician is that for patients with chronic schizophrenia and moderate-to-severe depressive symptoms (and/or demoralization), there may be “some” who might benefit from an antidepressant. Patients who appear to have benefited from the addition of an antidepressant initially might well be candidates for long-term maintenance treatment with the antidepressant and, at the very least, should be very carefully observed during and following the discontinuation of an adjunctive antidepressant medication. For patients who initially did not seem to benefit from the addition of an antidepressant to their antipsychotic regimen, however, careful discontinuation of the antidepressant might well be advisable. Controlled studies are called for in the future to tease out important indicators of outcome in these various situations. For those already on treatment with an antidepressant combined with an antipsychotic, rechallenge during 3 to 4 months may determine if the antidepressant adds anything to outcome. If not, individual or family therapy may be useful for demoralization as well as other symptoms/problems. Individual, group, or family therapy and/or rehabilitation interventions may, of course, also be useful for demoralization or other symptoms in the depressive spectrum for schizophrenic patients.

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## Misdiagnosis of Bipolar II Disorder as Major Depressive Disorder

**Sir:** Table 2 of the recent ACADEMIC HIGHLIGHTS on preventing recurrent depression in patients with major depressive disorder (MDD)<sup>1</sup> reports that, despite maintenance treatment with antidepressants, recurrences may occur in 6% to 66% of patients with MDD (vs. 23% to 100% of patients with MDD who received placebo). This apparent high risk of recurrence in MDD has been attributed to placebo response, nonadherence,

and tachyphylaxis (explained as an emotional blunting due to selective serotonin reuptake inhibitors, not as a true recurrence).<sup>1</sup> Along with a possible loss of effect of antidepressants in the long run,<sup>2</sup> the problem of the high proportion of bipolar depression, especially the depression of bipolar II disorder, misdiagnosed as MDD<sup>3-5</sup> is not reported as a possible cause of recurrences.

The misdiagnosis of bipolar II disorder as MDD has several causes.<sup>2,3,6,7</sup> Apart from the probing skills and methods for assessing history of hypomania,<sup>2,3,7</sup> there is a subtype of bipolar II that can be diagnosed even if hypomania has a short duration (i.e., 1 to 3 days, or at least 2 days, which are below the DSM-IV-TR minimum duration of 4 days), because this bipolar II group is similar, on bipolar validators, to DSM-IV-TR bipolar II disorder.<sup>3,6-9</sup> At least 30% of patients with bipolar II disorder can have only short hypomanic episodes.<sup>3,8</sup> Short-duration hypomania can easily be missed if probing for history of hypomania is not careful and skilled, leading to misclassification of this bipolar II subtype as MDD.<sup>3,6-9</sup> If the interviewer were to strictly follow DSM-IV-TR criteria (a likely event), further misclassification would occur. Bipolar II disorder is associated with more recurrences of depression than is than MDD (reviewed by Benazzi<sup>8</sup>).

Furthermore, a not-uncommon MDD subtype is highly recurrent (defined by > 3 or > 4 episodes).<sup>2,8</sup> Recurrent episodes are a key feature of Kraepelin's unitary "manic-depressive insanity," which also includes recurrent melancholia (i.e., MDD).<sup>2</sup> A recurrent course may be more important than polarity (i.e., alternating manic/hypomanic and depressive episodes) for subgrouping mood disorders.<sup>2</sup> Therefore, highly recurrent MDD could be part of the bipolar spectrum,<sup>3,7,8</sup> which also includes mood disorders without mania/hypomania but with classic features of bipolar disorders (such as family history of bipolar disorder, early onset, and many recurrences).<sup>3,7,8</sup> Highly recurrent MDD could require long-term mood-stabilizing agents as used in bipolar disorders<sup>2,10</sup> instead of antidepressants.

Misdiagnosing bipolar II disorder as MDD has important impacts on long-term treatment. Apart from lithium,<sup>10</sup> and lamotrigine in rapid-cycling bipolar II disorder,<sup>11</sup> no large, controlled studies on the maintenance treatment of bipolar II disorder have been conducted, although long-term use of mood stabilizing agents is suggested.<sup>2,10</sup> Better known is what should not be done in the maintenance treatment of bipolar II disorder. The current evidence suggests (but does not prove) that long-term treatment with antidepressants in bipolar disorders may increase cycling (as reviewed by Goodwin and Jamison<sup>2</sup>).

Furthermore, MDD may eventually shift to bipolar disorder in 40% to 50% of individuals with the more severe MDD subtype.<sup>12,13</sup> Although Coryell et al.<sup>14</sup> reported a high diagnostic stability of MDD, their findings probably related to individuals with a less severe MDD subtype. MDD seems a heterogeneous lumping of several subtypes.<sup>2</sup> As bipolar II disorder is often misdiagnosed as MDD,<sup>3</sup> and 1 in 2 depressive episodes among outpatients may be bipolar II disorder,<sup>3,8</sup> it is likely that many patients with bipolar II disorder misdiagnosed as MDD are treated with long-term antidepressants instead of mood-stabilizing agents.

Therefore, improving clinicians' skills in diagnosing bipolar II disorder should be a priority in the management of depression.<sup>3-7</sup> Bipolar II disorder is more severe than MDD, as recurrences, mixed depressive episodes, suicidality, Axis I and Axis II comorbidity, substance abuse, and complex pharmacologic treatments are more likely in patients with bipolar II disorder versus MDD.<sup>2,8,15,16</sup> Mood-stabilizing agents, and not antidepressants, are suggested for its long-term treatment.<sup>2,8,10</sup> Controlled, head-to-head pharmacologic studies are highly needed.

To date, quetiapine has been shown effective for acute bipolar II depression in only 1 large, controlled trial.<sup>17</sup>

*Dr. Benazzi reports no financial affiliation or other relationship relevant to the subject of this letter.*

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#### Drs. Dunner and Thase Reply

**Sir:** Dr. Benazzi is quite correct that individuals with bipolar disorder (and especially bipolar II disorder) are more likely to have recurrence of depressive episodes than patients with major depression. He is also correct that subjects were entered into the PREVENT study<sup>1</sup> on the basis of having depression meeting

DSM-IV-TR criteria, and we agree that structured interviews used to assess whether a patient has bipolar or recurrent major depression can miss subtle forms of hypomania and wrongly classify patients as unipolar when they are truly bipolar.

However, the acute treatment phase of the PREVENT study treated subjects with either venlafaxine (75–300 mg) or fluoxetine (20–60 mg). Treatment of subjects with bipolar II or bipolar spectrum disorders with relatively high doses of antidepressants to the point of response/remission would also entail some, if not most, of these subjects becoming hypomanic. Treatment-emergent hypomania was not observed in the acute phase of the PREVENT study.

Furthermore, responders and remitters to the acute phase were continued on their medication treatment for a 6-month continuation phase therapy study prior to randomization into the two 1-year maintenance phases. Treatment-emergent hypomania did not occur during the continuation phase or the maintenance phases. Thus, we are reasonably confident that the patients with recurrent major depressive disorder in the PREVENT study did not suffer from unrecognized bipolar II disorder.

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*Squibb, Forest, Roche Diagnostics, Cypress, Corcept, Janssen, Novartis, Shire, Somerset, Otsuka, and Healthcare Technology Systems; and has been a member of the speakers bureau for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Organon, and Forest. Dr. Thase has been a consultant and/or on the advisory boards for AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Sepracor, Shire, Supernus, and Wyeth; has received grant/research support from Eli Lilly and Sepracor; has been on the speakers bureau for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, Sanofi Aventis, and Wyeth; has given expert testimony in litigation involving Wyeth and GlaxoSmithKline; has equity holdings in MedAvante; and has received royalty/patent or other income from American Psychiatric Publishing, Inc., Guilford Publications, and Herald House. His spouse is the Senior Medical Director of Advogent (formerly Cardinal Health).*

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