

## Reasons for Inadequate Utilization of Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder

**Sir:** Cognitive-behavioral therapy (CBT) has repeatedly been found to be effective in the treatment of obsessive-compulsive disorder (OCD),<sup>1</sup> and the Expert Consensus Guidelines for the Treatment of OCD<sup>2</sup> recommend CBT as a first-line treatment of adult OCD along with serotonin reuptake-inhibiting drugs. However, many OCD sufferers never receive adequate CBT treatment; for example, Mancebo et al.<sup>3</sup> recently found that only 38% of OCD sufferers taking part in a longitudinal study of OCD at a major medical center had undergone an adequate trial of CBT in their lifetime. We undertook an Internet-based survey study to better understand this phenomenon in the larger OCD population.

**Method.** We prepared an Internet survey, hosted by the [www.surveymonkey.com](http://www.surveymonkey.com) Web site, consisting of questions for OCD sufferers 18 years or older, asking about demographics, OCD symptoms, and treatment history. This survey was advertised on the Web site of the Obsessive Compulsive Foundation ([www.ocfoundation.org](http://www.ocfoundation.org)), an international not-for-profit organization of OCD sufferers and their families with more than 10,000 members, and was available online between November 11 and December 1, 2006.

**Results.** Two hundred thirty individuals self-identified with OCD responded to the survey and completed at least some of the survey questions. The authors read each survey participant's description of his or her obsessions and/or compulsions to confirm that the survey participant had a likely diagnosis of OCD and eliminated 8 individuals from the sample who were clearly not suffering from OCD.

This left 222 respondents upon whom this report is based. While 84% reported having sought drug treatment for their OCD, only 53% reported having sought CBT treatment and only 31% reported having been treated by a specialist in CBT (and those treated by specialists in OCD, regardless of degree, were significantly more likely to report having responded to CBT by a score of 1 or 2 on the Clinical Global Impressions [CGI] scale<sup>4</sup>: OR = 6.9, 95% CI = 1.5 to 32.7). We found no significant differences in gender, ethnicity, family income, or type of medical insurance between OCD sufferers who had sought CBT treatment versus those who had not. However, those diagnosed with OCD by a mental health professional were significantly more likely to seek CBT treatment than those diagnosed by their primary care doctor or a nonprofessional (OR = 2.5, 95% CI = 1.3 to 5.0). In response to 4 possible reasons as to why they did not seek CBT treatment, subjects chose: "I didn't think it would help" (31%), "I wasn't aware of this treatment" (28%), "There was no specialist near my home" (25%), and "I couldn't afford it" (15%).

In summary, approximately one half of OCD sufferers visiting the Obsessive Compulsive Foundation Web site (which provides extensive information about CBT on its home page and throughout the Web site) had sought CBT, and fewer than one third had received this first-line treatment from an OCD specialist. Surprisingly, cost and unavailability of CBT experts were given less often as reasons than thinking the treatment would not help or being unaware of CBT.

Thus, besides the recognized public health challenges of making expert CBT more widely available and educating sufferers and non-mental health providers about CBT treatment for

OCD, we also need to modify the common attitude among sufferers that nondrug treatment is inferior to drug treatment (a difficult challenge, given American society's apparent preference for "magic bullet" drug treatments for health problems).

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

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## Late-Onset Hypersensitivity Reaction With Leukopenia and Thrombocytopenia Induced by Oxcarbazepine Treatment in a Patient With Schizoaffective Disorder

**Sir:** Oxcarbazepine is an anticonvulsant with similar chemical structure to carbamazepine.<sup>1</sup> Oxcarbazepine is not only effective in epileptic therapy, but also useful in the treatment of refractory bipolar and schizoaffective disorders.<sup>1-5</sup> Compared to carbamazepine, rare hematologic suppression side-effect had been reported with oxcarbazepine treatment.<sup>6-8</sup> Here, we present an adult female with schizoaffective disorder complicated with delayed onset of leukopenia and thrombocytopenia following oxcarbazepine treatment.

**Case report.** Ms. A, a 58-year-old woman with a 10-year history of DSM-IV bipolar I disorder, had undergone treatment with valproic acid and with both conventional and atypical antipsychotics, including haloperidol and quetiapine, at a local psychiatric hospital. Owing to persistent manic agitation and treatment-refractory psychotic features for 3 months in the current episode, she was referred to our emergency department in 2007 and was admitted after receiving the diagnosis of schizoaffective disorder, bipolar type (DSM-IV criteria). Considering the clinical course as well as the patient's unstable mood and illogical delusions, we discontinued her medications and initiated treatment with olanzapine, titrating to 20 mg/day early in the hospitalization. Because disruptive behaviors and delusions were persistent, the oxcarbazepine was added as an adjuvant to control the psychotic disturbance and reduce the manic symptoms; the initial dosage was 300 mg/day, and the dosage was gradually titrated to 1200 mg/day within 9 days, at which time

Table 1. Complete Blood Cell Counts for a Patient Receiving Oxcarbazepine in the Treatment of Schizoaffective Disorder<sup>a</sup>

Oxcarbazepine Treatment	WBC	Differential Count, %					Hemoglobin	Platelet
	Count, $\times 10^3/\mu\text{L}$ (4.5–11.0 $\times 10^3/\mu\text{L}$ )	Neutrophil (40.0–74.0)	Lymphocyte (19.0–48.0)	Monocyte (3.4–9.0)	Eosinophil (0–7.0)	Basophil (0–1.5)	Count, g/dL (F: 12.0–16.0 g/dL)	Count, $\times 10^3/\mu\text{L}$ (150–400 $\times 10^3/\mu\text{L}$ )
At admission	6.90	...	...	...	...	...	11.1 <sup>b</sup>	207
After starting oxcarbazepine								
Day 14	3.50 <sup>b</sup>	64.6	20.5	10.8 <sup>c</sup>	3.8	0.3	10.9 <sup>b</sup>	162
Day 16	1.80 <sup>b</sup>	68.2	23.1	6.1	2.0	0.6	10.1 <sup>b</sup>	116 <sup>b</sup>
Day 17	1.86 <sup>b</sup>	73.0	20.0	4.0	3.0	0.0	10.8 <sup>b</sup>	105 <sup>b</sup>
After stopping oxcarbazepine								
Day 1	1.70 <sup>b</sup>	35.2 <sup>b</sup>	52.4 <sup>c</sup>	11.9 <sup>c</sup>	0.2	0.3	10.8 <sup>b</sup>	139 <sup>b</sup>
Day 5	6.50	52.6	39.4	7.2	0.3	0.5	10.9 <sup>b</sup>	265
Day 12	6.60	65.0	25.3	6.7	2.3	0.7	10.4 <sup>b</sup>	303

<sup>a</sup>Reference ranges shown in parentheses.

<sup>b</sup>Below the average.

<sup>c</sup>Above the average.

Abbreviations: F = reference range in female subjects, WBC = white blood cell.

Symbol: ... = value not ascertained at admission.

the psychotic features and manic symptoms were remarkably reduced. Her score on the Clinical Global Impressions-Severity of Illness scale (CGI-S)<sup>9</sup> was diminished from 7 (at admission) to 4, and her score on the CGI-Improvement scale (CGI-I)<sup>9</sup> was 2.

However, a spike of high fever (up to approximately 39°C to 40°C), sore throat, dry cough, chilliness, general malaise, lymphadenopathy, marked uvula edema, and pharyngitis developed 2 weeks after the start of oxcarbazepine treatment. The complete blood cell (CBC) count showed a lower white blood cell (WBC) count of 3500/ $\mu\text{L}$  (down from 6900/ $\mu\text{L}$  at admission) and platelet count of 162,000/ $\mu\text{L}$  (down from 207,000/ $\mu\text{L}$  at admission) (Table 1). On the 16th day of oxcarbazepine treatment, the patient presented with remarkable hematopoietic suppression, and her WBC count was down to 1800/ $\mu\text{L}$  and her platelet count down to 116,000/ $\mu\text{L}$ . At that time, findings of a series of metabolic panels were within normal limits, and no infiltration was noted per chest X-ray. Consultation with an internist and otolaryngology/head-and-neck surgeon to evaluate the problems of high fever, leukopenia, and thrombocytopenia revealed no evidence of the possibility of active infectious disease.

Owing to suspicion of drug-related effects, the oxcarbazepine was tapered within 2 days, and the patient started treatment with the oral corticosteroid betamethasone at 2 mg/day to diminish the inflammatory reactions. To avoid opportunistic and potential bacterial infections, prophylactic treatment with the antibiotics cefepime (2.0 g/day) and esepamicin (400 mg/day) was begun. On the 18th day (the first day of discontinuing oxcarbazepine), the fever subsided. By the fifth day after discontinuation of oxcarbazepine, the WBC (6500/ $\mu\text{L}$ ) and platelet counts (265,000/ $\mu\text{L}$ ) had returned to within their respective reference ranges (as shown in Table 1).

During the fever episode, a series of laboratory examinations, including liver function, renal function, CBC, blood culture, inflammatory sources and immunological markers, were performed. High levels of C-reactive protein (3.26 mg/dL; reference value < 0.5 mg/dL) and immunoglobulin E (IgE) (serum level up to 348.0 IU/mL; reference value < 165.0 IU/mL (IMMAGE IgE reagent, Beckman Coulter Inc., Galway, Ireland) were found. There was no significant elevation of blood IgM titers for anti-cytomegalovirus and anti-Epstein-Barr virus antibodies. The blood coagulation profiles, such as fibrinogen 483 mg/dL (200–400), fibrin degradation products (FDP) 10–40

$\mu\text{g/mL}$  (< 10), and D-dimer 992 ng/mL (< 500), prolongation of partial thromboplastin time (PTT) (33.4 seconds compared to 28.2 seconds in healthy individuals) also demonstrated the evidence of coagulopathy. The serum levels of complement proteins C3 and C4 and rheumatic factor were all within normal limits, so the exacerbation of existing immune disease could be ruled out. On the basis of chronological clinical course and the laboratory findings, the possibility of oxcarbazepine hypersensitivity syndrome as the cause of leukopenia, thrombocytopenia, and coagulopathy was first considered.

The patient's fever and drug-related hypersensitivity syndrome subsided after discontinuation of oxcarbazepine. However, the psychotic and manic symptoms relapsed again (CGI-S score = 6, CGI-I score = 5). Therefore, lithium 600 mg/day was prescribed and titrated to 900 mg/day within 3 days, and olanzapine was maintained at 20 mg/day. The manic and psychotic symptoms subsided gradually; she was discharged after her mental condition became stable (CGI-S = 4, CGI-I = 3).

The cause-and-effect relationship between the development of hematopoietic suppression and treatment with oxcarbazepine has been postulated in this schizoaffective patient because previously normal WBC and platelet counts were decreased following oxcarbazepine treatment and returned to their previous range when the agent was discontinued. Otherwise, neither evidence of acute infectious nor potential immunologic disease were found from the comprehensive laboratory results such as blood cultures, IgM titers, and levels of C3 and C4. It is worth noting that the spike of high fever, general malaise, lymphadenopathy, uvula edema, and pharyngitis, as well as leukopenia and thrombocytopenia, developed after 2-week oxcarbazepine treatment. On the basis of clinical course and laboratory profiles, oxcarbazepine-induced delayed-onset hypersensitivity reactions with fever and hematopoietic suppression were highly suspected.

Oxcarbazepine was created from carbamazepine through structural modifications at the keto-derivative chain. The structural variations and changes in drug metabolism could reduce and help patients avoid adverse effects, such as Stevens-Johnson syndrome, hypersensitivity syndrome, and hematologic suppression, caused by carbamazepine and its metabolites. Although oxcarbazepine-related headache, dizziness, and asymptomatic hyponatremia were demonstrated, there was also presence of the rarely reported adverse effect of blood dyscrasia.

sias. In the literature review, only 2 case reports evidenced oxcarbazepine-associated hematopoietic suppression effect.<sup>7,8</sup> One report indicated oxcarbazepine-induced thrombocytopenia in a 63-year-old woman with history of psychotic depression, and the other indicated complication with pancytopenia in a 40-year-old woman with bipolar disorder.

Aromatic anticonvulsants such as phenytoin and carbamazepine are occasionally associated with allergic hypersensitivity leading to fever and skin rash. The anticonvulsant hypersensitivity syndrome has an unpredictable clinical course, can necessitate discontinuing the medications, and has potential fatal medical consequences caused by multiple organ involvement.<sup>10,11</sup> The idiosyncratic reactions may be due to initiating an autoimmune-like attack through drug-modified protein or the drug's own metabolites. Compared to carbamazepine-induced hypersensitivity reaction, the adverse symptoms in the present case gradually progressed following repeated oxcarbazepine exposures and would subside after withdrawal of the agent. In this case, the hypersensitivity reaction was demonstrated following 2-week oxcarbazepine treatment and clinical symptoms subsided after discontinuing the drug. Furthermore, the patient had 2-fold elevation of serum IgE level, also indicating hypersensitivity reaction in this episode. The evidence suggests that oxcarbazepine can induce late-onset hypersensitivity syndrome with hematopoietic suppression, but the individual variation and susceptibility in the idiosyncratic reaction need further clarification.

Coincidentally, all individuals from previous reports, as well as the patient in our case, are female and had mood disorder complicated to different extents with leukopenia and thrombocytopenia. Otherwise, our patient's only history of allergy was to penicillin. It is intriguing that subjects who have drug allergy history may have increased vulnerability to hypersensitivity reaction to another drug such as oxcarbazepine. From the case report, it is worth noting the insidious development of the side effect of hematologic suppression, which is easy to neglect and potentially has serious clinical consequences in the treatment course with oxcarbazepine. Therefore, when screening blood profiles and monitoring allergic symptoms, physicians should be alert and aware if the patient has allergy diathesis during oxcarbazepine treatment. In addition, the combination of a corticosteroid and prophylactic antibiotics to alleviate inflammatory symptoms and avoid opportunistic infection could be considered.

*The authors report no financial or other relationship relevant to the subject of this letter.*

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#### Metabolic Syndrome in Patients With Bipolar Disorder

**Sir:** We previously reported a 30% prevalence of the metabolic syndrome in the first 171 participants in our Bipolar Disorder Center for Pennsylvanians study.<sup>1</sup> However, the American Heart Association and the National Heart, Lung, and Blood Institute have recently issued a scientific statement that has suggested a modification of the diagnostic criteria for the metabolic syndrome as follows: (1) the threshold for serum levels of impaired fasting glucose should be reduced from 110 to 100 mg/dL; (2) the low high-density lipoprotein (HDL) cholesterol criterion should be considered as endorsed also when HDL cholesterol is within normal limits if the patient is undergoing drug treatment for reduced HDL cholesterol; and (3) the hypertension criterion is endorsed also if only the systolic blood pressure or only the diastolic blood pressure is elevated ( $\geq 130$  and  $\geq 85$  mm Hg, respectively).<sup>2</sup> Therefore, we decided to reevaluate the prevalence of the metabolic syndrome using the new diagnostic criteria in a considerably expanded sample of 441 subjects (mean age = 44.4 years, SD = 15.3 years) with bipolar I disorder (N = 321), bipolar II disorder (N = 95), bipolar disorder not otherwise specified (N = 15), or schizoaffective disorder bipolar type (N = 10).

The percentage of patients meeting the diagnosis for metabolic syndrome and endorsing each of its diagnostic criteria changed as follows: metabolic syndrome, from 30% to 40%; abdominal obesity, from 49% to 51%; hypertension, from 39% to 55%; low HDL cholesterol, from 23% to 45%; hypertriglyceridemia, from 48% to 47%; and high fasting serum glucose, from 8% to 19%. Subjects with waist-defined obesity had significantly worse mean (SD) scores on the Clinical Global Impressions-Severity of Illness scale for bipolar disorder<sup>3</sup> (2.4 [1.2] vs. 2.6 [1.2];  $t = 2.01$ ,  $df = 422$ ,  $p = .045$ ) and Global Assessment of Functioning<sup>4</sup> (60.7 [11.4] vs. 58.2 [11.0];  $t = 2.08$ ,  $df = 367$ ,  $p = .038$ ) in the month prior to the assessment than subjects without waist-defined obesity. Also, subjects with the metabolic syndrome were significantly more likely than subjects without the metabolic syndrome to have a lifetime history of suicide attempts ( $\chi^2 = 5.39$ ,  $df = 1$ ,  $p = .020$ ), as were those with body mass index-defined obesity ( $\chi^2 = 7.98$ ,  $df = 1$ ,  $p = .005$ ) and those with waist-defined obesity ( $\chi^2 = 6.27$ ,  $df = 1$ ,  $p = .012$ ) compared with their non-obese counterparts.

The prevalence of the metabolic syndrome in patients with bipolar disorder is alarmingly high, and the use of the new diagnostic criteria identified a picture that is even more worrisome than we previously reported. In addition to being correlated to a severe cardiovascular and metabolic risk, the metabolic syndrome in general, and obesity in particular, are also correlated with a worse psychiatric outcome. The development and testing of specific interventions to prevent and treat the metabolic syndrome and obesity in patients with bipolar disorder are urgently needed.

*Trial Registration: clinicaltrials.gov Identifier: NCT00211263*

*Dr. Fagiolini is on the speaker bureau of Bristol-Myers Squibb and Pfizer and is a consultant for Bristol-Myers Squibb, Novartis, and Pfizer. Dr. Frank is a consultant for Pfizer Italia and Servier Amerique and has received grant/research support from Forest. Dr. Turkin is on the speaker bureau of GlaxoSmithKline and has received grant/research support from AstraZeneca, Bristol-Myers Squibb, and Novartis. Dr. Soreca is a consultant for Novartis. Dr. Kupfer has been a consultant for Servier Amerique. Ms. Houck has no personal affiliations or financial relationships with any commercial interests to disclose relative to this letter.*

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### Effect of Ribavirin, in Combination With Interferon in Patients With Hepatitis C, on the Bleeding Risk Associated With Selective Serotonin Reuptake Inhibitors

**Sir:** We read with great interest the recent article by Martin et al.<sup>1</sup> reporting that the bleeding risk associated with use of selective serotonin reuptake inhibitors (SSRIs) during antiviral therapy for chronic hepatitis C (CHC) is lower than that previously reported.<sup>2</sup> Several reports had revealed the increasing risk of bleeding, including retinal hemorrhages or gastrointestinal

bleeding, by administering SSRIs to patients receiving interferon- $\alpha$  therapy.<sup>3-6</sup>

Ribavirin was used in combination with interferon in the treatment of patients with CHC in the study by Martin et al.<sup>1</sup> We have reported that ribavirin in combination with interferon, and possibly alone, may reduce the need for clotting factors in hemophilic patients with CHC.<sup>7</sup> In our hospital, we observed a marked reduction in the use of clotting factors in 5 of the 8 hemophilic patients who were being treated for CHC with ribavirin plus interferon. In contrast, no reduction in the use of clotting factors was observed in 47 hemophilic patients previously treated for CHC with interferon alone in our hospital. These findings strongly suggested that the reduced use of clotting factors resulted from the addition of ribavirin.

In the same group of patients, we found that the procoagulant activity of factor VII was elevated in all patients after receiving ribavirin in comparison with activity of factor VII before ribavirin administration.<sup>8</sup> In patients with CHC, the international normalized ratio (INR; prothrombin time) decreased continuously during therapy with peginterferon plus ribavirin in patients both with and without coagulation disorder; INR increased to the pretreatment value after therapy (data not shown). It is possible that ribavirin enhanced coagulation factor activity in both types of patients, reducing the risk of bleeding during therapy. These findings suggest that addition of ribavirin to interferon may be the reason why the risk of bleeding was lower than during antiviral therapy for patients with CHC in the report by Martin and colleagues.<sup>1</sup>

Weinrieb et al.<sup>2</sup> reported that critical upper gastrointestinal bleeding occurred in a patient with CHC being treated with interferon plus ribavirin and an SSRI. However, this patient was suffering end-stage liver disease and was also being given aspirin. We believe that this patient was at risk for bleeding even without an SSRI administration.

Interferon plus ribavirin is now standard therapy for patients with CHC because the efficacy of this combination is higher than that of interferon monotherapy.<sup>9</sup> Morasco et al.<sup>10</sup> reported that use of prophylactic SSRIs to prevent interferon- $\alpha$ -induced depression in patients with CHC was not beneficial. Once a patient develops depressive symptoms, however, SSRIs can be successfully used to treat depression in patients with CHC who are receiving interferon- $\alpha$  therapy and ribavirin treatment. From Martin and colleagues' results<sup>1</sup> and ours, the risk of bleeding due to SSRIs looks likely to be relatively low when ribavirin is administered in addition to interferon for patients with CHC. When treating patients with CHC, physicians have to carefully observe whether bleeding episodes will increase after the reduction or stop of ribavirin due to ribavirin-induced anemia. In addition, when we treat other diseases, including chronic hepatitis B, leukemia, and renal cell carcinoma, with interferon alone, we may have to watch for bleeding during SSRI administration. Further randomized controlled studies of bleeding risk in patients given or not given SSRIs during therapy with interferon plus ribavirin are warranted.

*Dr. Martin was shown this letter and declined to comment.*

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

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### Comments on a Randomized, Double-Blind Comparison of Sertraline and Placebo for Posttraumatic Stress Disorder in a Department of Veterans Affairs Setting

**Sir:** Selective serotonin reuptake inhibitor antidepressants are first-line pharmacologic treatments of posttraumatic stress disorder (PTSD).<sup>1,2</sup> Robust effects have been seen in previous large studies of sertraline in civilian populations.<sup>3,4</sup> The recent (May 2007) study by Friedman and colleagues<sup>5</sup> failed to find evidence of efficacy of sertraline in a veteran population, despite a comprehensive analysis of potential moderator variables.

There was some evidence, however, of efficacy of sertraline in subjects with non-combat-related traumas, prompting the possibility that sertraline is only effective in persons with civilian trauma. While the authors make a decent case for why this is not true (including an argument for the treatment refractoriness of Vietnam veterans with PTSD), we are not entirely convinced and would like to see ongoing research to address this issue.

Such research into predictors of treatment efficacy in patients with PTSD could complement findings such as those from Davidson and colleagues,<sup>6</sup> which indicate that a marked improvement in anger/irritability after 1 week on sertraline treatment may be a useful prognosticator of eventual response.

In the current academic climate, we are pleased to see a large “negative” study such as this published in a major psychiatric journal, albeit in a delayed manner. Although such negative studies may be challenging to interpret and can raise more questions than they answer, they do add a much needed balanced perspective.

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

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### Dr. Friedman and Colleagues Reply

**Sir:** We certainly agree with Dr. Hussain that more research is needed regarding responsiveness of patients with combat-related (compared to non-combat-related) posttraumatic stress disorder (PTSD) to selective serotonin reuptake inhibitors (SSRIs), other medications, and psychotherapy. We also agree that further research on predictors of response would be very useful.

We recognize that negative results among chronic Vietnam veterans in Department of Veterans Affairs (VA) settings have prompted speculation that combat-related PTSD is somehow different and less treatment responsive than non-combat-related PTSD. As reviewed in our article,<sup>1</sup> the preponderance of the evidence suggests to us that it is the chronicity of illness in these VA cohorts rather than something unique about combat trauma that accounts for such negative findings. To this end, we cited some recent studies in which better outcomes to SSRI treatment were observed among (non-VA) participants with combat trauma.<sup>2,3</sup>

Given the fact that a number of medication (and psychotherapy) trials are currently underway with troops and veterans who developed PTSD as a result of combat in Afghanistan and/or Iraq, we will all have much more information on this important question before much longer.

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*Statements of the authors do not reflect official policy or opinions of the U.S. Department of Veterans Affairs.*

*Dr. Marmar has been a consultant to Sanofi Aventis and Acterion Clinical Research and has served on the advisory board for Pfizer. Dr. Sikes is an employee of and a stock shareholder in Pfizer. Dr. Farfel is an employee of Novartis and a stock shareholder in Pfizer. Drs. Friedman and Baker report no financial affiliation or other relationship relevant to the subject of this letter.*

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### Increasing Rates of Placebo Response Over Time in Mania Studies

**Sir:** There is indeed increasing concern about the high rates of placebo response in randomized controlled trials in psychiatry, and particularly in the field of mood disorders, as shown in the recent systematic review by Sysko and Walsh.<sup>1</sup> But there is an alternative conclusion to the one that these authors provide in their extensive review of placebo-controlled trials in mania, in which they state that factors related to study design account for high rates of placebo response: in our opinion, placebo response seems to increase over time because of publication bias.

Hence, because these authors used publication date for their analysis of the sequence of placebo response across mania trials, and not the actual date of study completion, the fact that negative studies have not been published or have been significantly delayed in their publication has an obvious impact on their findings. For instance, trials with high rates of placebo response, such as one comparing lamotrigine, lithium, and placebo,<sup>2</sup> were conducted in the 1990s but were never published.

There are several further examples. Sometimes, the trial yielded positive results for the experimental compound, but the publication of a twin, more positive trial was given higher priority: this was the case for a study by Khanna et al.,<sup>3</sup> which yielded a placebo response rate of 35% and was published later despite having actually finished earlier than a study by

Hirschfeld et al.,<sup>4</sup> which had a placebo response rate of 23%. Trial publication delays and failures are related to several factors, the most important generally being the lack of interest of the patent owner to make public a negative outcome, but also the poor commitment of some investigators and ethics boards to ensure that trial results are published regardless of their outcome and, last but not least, the limited willingness of journal editors to publish negative studies.<sup>5</sup>

A further issue in the report by Sysko and Walsh,<sup>1</sup> as acknowledged at the end of their article, is that the apparent relationship between placebo response and year of publication was heavily influenced by 2 outliers. Hence, the trial by Pope et al.<sup>6</sup> yielded an unusually low placebo response rate, whereas the trial by Zhang et al.<sup>7</sup> showed the highest one (59%). These 2 trials were also unusual in issues related to blinding and treatment response rate (as high as 93%<sup>7</sup>!), which might explain their unexpectedly low and high placebo response rates, respectively. If either of these 2 trials was excluded from the analysis, the apparent relationship between publication date and placebo response rate would fade away.

We can only agree with the statement that placebo is still needed for truly qualified evidence on efficacy for new compounds and indications. Although placebo-controlled trials have very limited external validity, they remain the gold standard to establish efficacy in bipolar disorder<sup>8</sup>; ideally, though, trials aimed at registration of a given compound should have 3 arms—experimental, placebo, and active control—allowing for a fair assessment of assay sensitivity.

From the analysis by Sysko and Walsh,<sup>1</sup> one cannot possibly conclude that placebo response is increasing over time in mania trials, but it looks like publication bias and other related issues may indeed carry the risk of causing the most thoughtful systematic reviews and meta-analyses to be misleading. An effort is urgently needed from pharmaceutical companies, investigators, ethics and research boards, and journals to make sure that trials are not merely posted on a Web site, but published in a timely manner in a peer-reviewed journal irrespective of their outcome.

*Dr Vieta has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Novartis, Organon, Otsuka, Pfizer, Sanofi, and Servier; has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Novartis, Otsuka, Pfizer, Sanofi, Servier, and the Spanish Ministry of Science and Education; and has been on the speakers or advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Novartis, Organon, Otsuka, Pfizer, Sanofi, and Servier. Dr. Cruz reports no conflicts of interest relative to the subject of this letter.*

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### Drs. Sysko and Walsh Reply

**Sir:** We appreciate the points made by Drs. Vieta and Cruz in their comment on our recent review of controlled trials of bipolar mania.<sup>1</sup> Our review noted a relative paucity of data available for analysis and important differences across study designs in the trials included in the analysis, limiting our confidence in the indications that placebo response rates had changed over time.<sup>1</sup> We therefore restricted our discussion of factors that might have contributed to an increase in response rates, as it was not clear whether such changes had, in fact, occurred.

However, we agree with Drs. Vieta and Cruz that the role of publication bias is an important issue in interpreting the effect of time on published reports of treatment response. Unpublished studies and unknown but variable delays in the publica-

tion of controlled trials, because of factors like those mentioned by Drs. Vieta and Cruz, are reasons for continuing uncertainty about changes in the response to placebo and to medication over time. Evidence of increasing placebo response rates was much more compelling in our previous report of published studies of major depression,<sup>2</sup> and, in that report, we noted that publication bias was an important factor that might have influenced our findings. Similarly, we concur with Drs. Vieta and Cruz that, if placebo response rates in published studies of bipolar mania are increasing, publication bias may be a contributing factor.

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