

## A Case of Sodium Oxybate Treatment of Tardive Dyskinesia and Bipolar Disorder

**Sir:** Sodium oxybate is increasingly being used off-label to treat the fibromyalgia syndrome defined by pain, fatigue, nonrefreshing sleep, and fluency loss.<sup>1</sup> This compound has a complicated mechanism of action with agonist binding on  $\gamma$ -aminobutyric acid (GABA)-B receptor, agonist binding on the  $\gamma$ -hydroxybutyrate (GHB) receptor, and possible stoichiometric signaling effects as an intermediary in GABA and glutamate metabolism. Its clinical effect is a profound increase in the duration of stage III and IV slow wave sleep. This case describes a profound effect of oxybate on bipolar disorder and tardive dyskinesia presenting jointly with fibromyalgia.

**Case report.** Ms. A, a 51-year-old woman, presented for treatment of bipolar disorder in 2003. Chart review described a continuously circular course with 4 manic episodes yearly. She was on social security disability. She had failed to improve on treatment with lithium, carbamazepine, oxcarbazepine, divalproex, and benzodiazepines due to lack of efficacy or problems with tolerability. Antidepressants uniformly gave agitation. Olanzapine exposure, 10 mg daily over an 8-month period, produced a slowly progressive tardive dyskinesia marked by subjective truncal dyskinesia, vocal tics, and dysphagia. Benzotropine 6 mg instituted as a possible treatment actually increased her choreiform movements. Neurologic examination 2 weeks after discontinuation of olanzapine revealed fairly striking, widespread, and both proximal and distal choreiform movements. Serial neurologic consultation over the subsequent year, in conjunction with brain magnetic resonance imaging and appropriate serology, resulted in the exclusionary diagnosis of tardive dyskinesia.

Four months after olanzapine discontinuation, given comorbid diagnosis of fibromyalgia secondary to ankylosing spondylitis, the patient was prescribed sodium oxybate, titrated to a total of 8 g daily. Response was dramatic. Dyskinesias ceased. She was able to bathe and keep her own house without an attendant. She stopped her long-term medications: opioids (hydrocodone 15 mg) and benzodiazepines (alprazolam 0.5 mg). Mood control improved to the degree that her therapist of many years recommended termination of therapy and reentrance into the workforce.

After 3 months, insurance authorization difficulties produced an interruption in supply. Insomnia and dyskinesia returned rapidly. When supply resumed a month later, function returned again, albeit with a consistent 2-week latency.

Three years later on maintenance dosing, she continues to be free of tardive dyskinesia and major mood disturbance. She has worked as a waitress briefly but has returned to disability due to fatigue.

Given clinical experience that sleep regularity has profound salutary effects on mood disorder, further exploration of this compound seems justified. Its advantages in terms of reducing unwanted side effects, such as weight gain, drug-induced dyskinesia, and daytime somnolence, relative to commonly used sedating antipsychotics, are noted. The minimal potential target population is relatively large given an estimated 10% comorbidity of bipolar disorder with fibromyalgia.<sup>2</sup>

An important research question relates to the causality of observed effect in this case. The current prominent hypothesis for oxybate clinical effect focuses on treatment of pathologic alpha intrusion by induction of slow-wave sleep most likely

mediated by GABA-B receptor activation in thalamic nuclei.<sup>1</sup> Oxybate clinical effects possibly could derive from other signaling mechanisms, directly by binding to GHB receptors in the dendrites of nerve cells<sup>3</sup> or indirectly by stoichiometric feedback in mitochondrial enzymatic pathways. Note that closely related GABA metabolic enzymes are uniquely upregulated in the brain relative to mitochondrial enzymes in other tissues.<sup>4</sup> Given low population prevalences of the isolated syndromes in this case (bipolar disorder, fibromyalgia, and tardive dyskinesia) and elevated prevalences of these syndromes in known mitochondrial disorders,<sup>5</sup> Bayesian reasoning would suggest further examination of the metabolic signaling hypothesis.

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

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## Aripiprazole Joins the Family of Second-Generation Mood Stabilizers

**Sir:** In my recent letter to the *International Journal of Neuropsychopharmacology*,<sup>1</sup> I proposed a modified definition of the mood stabilizer as "a drug that if used as monotherapy (1) acts therapeutically in mania or/and in depression, (2) acts prophylactically against manic or/and depressive episodes as demonstrated in a trial of at least 1 year's duration, and (3) does not worsen any therapeutic or prophylactic aspect of the illness outlined above."<sup>(p709)</sup> On the basis of a recent trial by Keck et al.<sup>2</sup> published in this journal, it is evident that aripiprazole meets these criteria.

The introduction of individual mood stabilizers occurred more than 4 decades ago. A mood-stabilizing property was first suggested for lithium in the early 1960s,<sup>3,4</sup> for valproates at the turn of the 1960s/1970s,<sup>5,6</sup> and for carbamazepine in the early 1970s.<sup>7,8</sup> This may justify the naming of lithium, carbamazepine, and valproates as first-generation mood stabilizers. The common mechanism of first-generation mood stabilizers is connected with the phosphatidylinositol pathway,<sup>9</sup> and the main role of this pathway in bipolar disorder has recently been confirmed by molecular-genetic studies.<sup>10</sup>

The suggestion that the atypical antipsychotic drug clozapine had a mood-stabilizing action was first advanced in this journal in 1995,<sup>11</sup> and a similar claim was made for lamotrigine

in the early 2000s.<sup>12</sup> Therefore, atypical neuroleptics and lamotrigine can be considered second-generation mood stabilizers.

Among second-generation mood stabilizers, lamotrigine has already been given the name "mood stabilizer from below," since it has primarily antidepressant and depressive recurrence prevention properties.<sup>12</sup> In contrast, clozapine, which is highly effective in mania and in the prophylaxis of bipolar illness, including in refractory cases,<sup>13,14</sup> but is devoid of distinct antidepressant properties, can be named a "mood stabilizer from above."

The efficacy of both olanzapine and quetiapine in mania and in the long-term prevention of manic and depressive recurrences has been demonstrated in open and controlled trials.<sup>15,16</sup> In a study of bipolar depression in which olanzapine, olanzapine plus fluoxetine, and placebo were compared, it was found that although the combination had the best antidepressant efficacy, olanzapine alone exerted some antidepressant action.<sup>17</sup> Distinct antidepressant efficacy of quetiapine in bipolar depression has been shown.<sup>18</sup> On the basis of these results, both olanzapine and quetiapine may deserve to be named second-generation mood stabilizers in the first place, as well as atypical antipsychotic drugs.

For aripiprazole, therapeutic efficacy in mania<sup>15</sup> and in augmentation of antidepressants<sup>19</sup> has been reported. The results of the Keck et al.<sup>2</sup> study also point to long-term prophylactic action of aripiprazole monotherapy against manic recurrences. Such long-term trials are still needed for risperidone and ziprasidone, for which therapeutic efficacy in mania<sup>15</sup> and in augmentation of antidepressants<sup>20,21</sup> has been shown.

Another conspicuous result of Keck and colleagues' study was an enormous attrition rate of long-term aripiprazole monotherapy. Previously, we have demonstrated that "excellent lithium responders," i.e., patients with successful prophylaxis on lithium monotherapy for 10 years, comprise about 30% of bipolar patients.<sup>22</sup> The prophylactic monotherapy of any other mood stabilizer could not be better, as shown in a recent naturalistic study,<sup>23</sup> although the clinical features of responders to various mood stabilizers can be different.<sup>24</sup> Therefore, a prudent combination of mood stabilizers should be recommended in a majority of bipolar patients for obtaining optimal prophylactic results.

*Dr. Rybakowski has been a member of the speakers/advisory boards for Adamed, Bristol-Myers Squibb, Janssen, Glaxo, Lundbeck, Organon, Pfizer, and Servier, in Poland, and has been a member of the international speakers/advisory boards for Eli Lilly and sanofi-aventis.*

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### Intrinsic Activity of Aripiprazole Is Not 30% of Dopamine, But Only About 6% Under Ideal Antipsychotic Therapy

**Sir:** We read with great interest the recent review by Weiden et al.<sup>1</sup> The authors state that the intrinsic activity of aripiprazole is 30% of dopamine in their review. This idea may be originally from the review by Grunder et al.<sup>2</sup> On the basis of positron emission tomography (PET) studies, it is widely accepted that D<sub>2</sub> receptor occupancy by D<sub>2</sub> antagonists is 60% to 80% (mean = 70%) when they produce an antipsychotic effect without extrapyramidal side effects (i.e., ideal antipsychotic therapy). Aripiprazole produced an antipsychotic effect without extrapyramidal symptoms at a therapeutic dose when about

90% of D<sub>2</sub> receptors were occupied.<sup>3</sup> Moreover, at doses above 30 mg/day, D<sub>2</sub> receptor occupancy reached 95%, but even at this dose, aripiprazole did not produce any extrapyramidal symptoms.<sup>4</sup> Therefore, on the basis of the above evidence, the intrinsic activity of aripiprazole is estimated to be approximately 30%. Occupancy of 70% of the D<sub>2</sub> receptors by antipsychotics means only that 30% of the D<sub>2</sub> receptors are available for dopamine binding, not that 30% of the D<sub>2</sub> receptors are occupied by intrinsic dopamine. If 100% of D<sub>2</sub> receptors were occupied by dopamine before treatment, the intrinsic activity of aripiprazole might be 30%, but this is not the case. Abi-Dargham et al.<sup>5</sup> estimated that 20% of the striatal D<sub>2</sub> receptors are occupied by dopamine in schizophrenic patients. Given this estimate, D<sub>2</sub> receptor occupation by intrinsic dopamine during ideal antipsychotic therapy is calculated by the following formula:  $0.3 \times 0.2 = 0.06$ , that is, 30% (available D<sub>2</sub> receptors) multiplied by 20% (proportion of D<sub>2</sub> receptors occupied by dopamine) equals 6%.

Frankle et al.<sup>6</sup> also estimated the occupancy based on their own theory and suggested that 8.9% of D<sub>2</sub> receptors are occupied by intrinsic dopamine during ideal antipsychotic therapy. Thus, D<sub>2</sub> receptor occupancy by intrinsic dopamine during ideal antipsychotic therapy may be between 6% and 8.9%. If this dopaminergic transmission equals aripiprazole with 90% D<sub>2</sub> receptor occupancy, the remaining 10% of D<sub>2</sub> receptors are available for endogenous dopamine binding. Therefore,  $0.1 \times 0.2 = 0.02$ , or 2% of D<sub>2</sub> receptors are occupied by dopamine during aripiprazole treatment. Aripiprazole with 90% occupation by itself exerts the same effect for (6 – 2)% to (8.9 – 2)% occupation by dopamine. Taken together, the intrinsic activity of aripiprazole is (4%/0.9) to (6.9%/0.9) = 4.4% to 7.7% of dopamine as a partial agonist in the human striatum.

In vitro experiments also demonstrated low intrinsic activity that supports our speculation. Burris et al.<sup>7</sup> examined the efficacy of stimulation of D<sub>2</sub> receptors by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) accumulation using human D<sub>2</sub> long (hD<sub>2</sub>L) expressed cells. They reported that 50% inhibition was achieved with occupancy by dopamine of 2%; in contrast, aripiprazole occupied 23% of D<sub>2</sub> receptors. Thus, aripiprazole's relative efficacy is  $2/23 = 8.7\%$ . Tadori et al.<sup>8</sup> also reported that forskolin-stimulated cAMP accumulation was inhibited by 50% with receptor occupancy of 1.56% by dopamine and 58.8% by aripiprazole using human D<sub>2</sub> short (hD<sub>2</sub>S) expressed cells. Thus, aripiprazole's relative efficacy is  $1.56/58.8 = 2.7\%$ . We propose that the intrinsic activity (= relative efficacy) of aripiprazole is only about 6% (4.4% to 7.7%) of dopamine under ideal antipsychotic therapy in schizophrenic patients.

*Drs. Hamamura, Kodama, and Harada report no financial affiliations or other relationships relevant to the subject of this letter.*

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#### Dr. Preskorn Replies

**Sir:** I appreciate the letter from Drs. Hamamura, Kodama, and Harada but must respectfully disagree with their argument as follows:

Dr. Hamamura and colleagues suggest that the intrinsic activity of a partial receptor agonist is derived mathematically from the percentage of the target receptor occupied by different doses of the partial agonist versus the percentage of that receptor occupied by its endogenous agonist under normal physiologic conditions. Instead, the intrinsic activity of a partial agonist is determined by measuring its maximal functional effect on its target receptor versus the maximal functional effect of the endogenous agonist of the same receptor. Admittedly, there should be some agreement between these 2 different concepts since the latter is a major determinant of the former.

In their letter, Drs. Hamamura, Kodama, and Harada speculate that the 30% figure cited in our review article<sup>1</sup> in the *Journal* supplement might have come from the review by Grunder et al.<sup>2</sup> That is incorrect. Our figure comes from the studies of Burris et al.<sup>3</sup> and Lawler et al.<sup>4</sup> who determined the intrinsic activity of aripiprazole using the approach I have just outlined.

Lawler et al.<sup>4</sup> examined the ability of aripiprazole to inhibit isoproterenol-stimulated cyclic AMP accumulation and reported that it was approximately 30% that of dopamine (D). In a complementary study, Burris et al.<sup>3</sup> examined the ability of aripiprazole to activate D<sub>2</sub> receptor-mediated inhibition of cyclic AMP using Chinese hamster ovarian cells expressing human recombinant D<sub>2</sub>L receptors in relation to dopamine. They found that the intrinsic activity of aripiprazole ranged from 25% of the full effect of dopamine in cells that lacked spare receptors for dopamine to 90% in cells with receptor reserve. The former are more comparable to postsynaptic D<sub>2</sub> receptors while the latter are more comparable to presynaptic autoreceptors. Thus, both studies in a complementary manner support the figure cited in the supplement.

In the interest of brevity, I will not discuss further the phenomena of spare receptors, receptor reserves, or the fact that G-protein coupled receptors such as the D<sub>2</sub> receptor exist in high- and low-affinity states and that agonists as a general rule recognize these different states, whereas antagonists do not. Readers interested in further exploring these topics are referred to the original articles by Burris et al.<sup>3</sup> and Lawler et al.,<sup>4</sup> as well as to more recent literature on these topics that can be located through PubMed.

In summary, the intrinsic activity of aripiprazole serves as a basis for understanding why aripiprazole can achieve a considerably higher degree of D<sub>2</sub> receptor occupancy without causing the extrapyramidal side effects commonly seen with D<sub>2</sub> receptor full antagonists such as haloperidol. Moreover, the fact that the dose of aripiprazole can be increased to occupy more receptors and thus produce more agonism of D<sub>2</sub> receptors than typically occurs with dopamine alone, as pointed out by Hamamura and colleagues, provides a basis for understanding why clinicians may sometimes see activation when switching a patient from chronic high doses of D<sub>2</sub> full antagonists to aripiprazole and why in such instances they may find it better to do a more gradual cross-taper.

I again thank Drs. Hamamura, Kodama, and Harada for their letter, which allowed me on behalf of my co-authors to discuss this topic further while fully admitting that it would take much more space than is possible here to fully address this subject.

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### Does Venlafaxine Maintenance Therapy Prevent Depression Recurrences or Drug Discontinuation Reactions?

**Sir:** We write in response to articles published in the July and August 2007 issues of the *Journal* describing the maintenance phases of the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study.<sup>1,2</sup> In this double-blind study, at the end of 8 months of venlafaxine treatment at a median daily dose of 225 mg, 258 subjects were

randomly assigned to continue venlafaxine or be tapered over 4 weeks to placebo. The primary outcome for the maintenance phase was recurrence of depression, defined in terms of increased score on the Hamilton Rating Scale for Depression (HAM-D). Venlafaxine subjects did significantly better on this outcome than those randomly assigned to placebo.

Our concern relates to the contribution of withdrawal of venlafaxine to these results. First, there is no reason to expect any skewing in the temporal distribution of recurrence of depression; on the other hand, discontinuation syndromes would be expected to cluster around the period immediately after treatment with active medication is reduced or stopped. The taper protocol is not reported in either article, but Dr. Kocsis has informed us that at 225 mg, the taper was 2 weeks at 150 mg/day, then 75 mg/day for the third week and 37.5 mg for the final week (electronic communication, October 2007). There is little science to tapering, but this approach is more abrupt than was recommended in a recent review.<sup>3</sup> Since data tables are not available in the PREVENT articles, readers must rely on figures, which show that the time of greatest risk for "recurrence" for the placebo group was at the end of the taper (see Figures 1 and 2 of Kocsis et al.<sup>1</sup> and Figures 2-5 of Keller et al.<sup>2</sup>). For example, over half of the final 19% difference in recurrence rates between venlafaxine and placebo at 12 months appeared abruptly at around 30 to 40 days.

Second, in the second year of the study, there were 2 placebo groups. One group (N = 48) had been receiving placebo throughout the maintenance phase and was therefore not subject to discontinuation effects in the second year; the second (N = 40) was tapered off venlafaxine treatment after 1 year.<sup>2</sup> The former group did as well (least squares mean [SE] HAM-D score = 5.2 [0.8]) as the group (N = 43) maintained on venlafaxine (least squares mean [SE] HAM-D score = 4.4 [1.0]). In contrast, for those withdrawn from venlafaxine at 12 months, the least squares mean (SE) HAM-D score was 8.8 (1.0).<sup>2</sup>

We can find no plausible reason other than discontinuation effects to explain why recurrence clusters around the taper, or why the group new to placebo in the second year should do worse than those who have already been treated with placebo for a year. The authors are clearly aware of the possibility of significant withdrawal effects in the studies; Kocsis et al. point out that the higher level of "discontinuation due to adverse events" in the placebo group might "reflect adverse events associated with discontinuation of venlafaxine."<sup>(p1020)</sup> Patients receiving placebo experienced significantly higher rates of dizziness and paresthesia, 2 symptoms that have been associated with discontinuation.<sup>1</sup>

It is by now routine to warn patients that it is sometimes difficult to differentiate between withdrawal symptoms and re-emergence of depression after they stop taking an antidepressant.<sup>4</sup> Why then does neither article consider the possibility that ongoing venlafaxine use prevents discontinuation syndrome rather than recurrence of depression?

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

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### Drs. Keller and Kocsis Reply

**Sir:** We appreciate the comments of Drs. Jureidini and Mintzes on the PREVENT study.<sup>1,2</sup> The first point they made was that “there is no reason to expect any skewing in the temporal distribution of recurrence of depression.” We do not agree. All patients in the PREVENT study had experienced at least 3 or more episodes of depression, a history that is consistently associated with a highly significantly shorter time to relapse and recurrence.<sup>3</sup> Furthermore, the temporal distribution of recurrence of depression seen in our study was quite similar to results in other published relapse- and recurrence-prevention studies of various antidepressants.<sup>4–7</sup>

The authors also suggested that the taper protocol used in the PREVENT study was more abrupt than recommended. In the review they cited by Warner and colleagues,<sup>8</sup> it was recommended that the dose of venlafaxine extended release (ER) be reduced by 37.5 to 75 mg/day every week with a final dose of 37.5 mg/day for 1 week before discontinuation. In the PREVENT study, the taper from the maximum dose allowed in the study, 300 mg/day, was 75 mg/day the first week (i.e., dose = 225 mg/day), 75 mg/day the second week (i.e., dose = 150 mg/day), 75 mg/day the third week (i.e., dose = 75 mg/day), and 37.5 mg/day the fourth week (i.e., dose = 37.5 mg/day). Therefore, the taper schedule in both maintenance phases was consistent with Warner and colleagues’ recommendations.

The authors question why the group new to placebo in the second year (i.e., placebo B) should have higher scores on the 17-item Hamilton Rating Scale for Depression (HAM-D<sub>17</sub>) at the end of the second year compared with the group that had already been receiving placebo for a year (i.e., placebo A). The final mean HAM-D<sub>17</sub> score for placebo B patients at the end of maintenance phase B (8.8 [SE = 1.0])<sup>1</sup> was similar to that observed for placebo A patients at the end of maintenance phase A (i.e., 9.1 [SE = 0.7]).<sup>2</sup> This indicates that patients in both placebo groups were behaving similarly after 1 year of placebo administration. By the second year in the placebo A arm, many of the patients with high scores would have dropped out, and only those who are doing comparatively well would have remained; therefore, the finding of somewhat better HAM-D scores in placebo A patients (on average) is not surprising. Furthermore, it has been demonstrated that a longer duration of recovery is associated with lower risk of recurrence.<sup>9</sup> Therefore, the lower scores could be a function of the long period of recovery in placebo A patients (i.e., 12 months) while receiving placebo; this differs from placebo B patients (who also were in recovery for 12 months) because the placebo A treatment condition did not change from year 1 to year 2.

Symptoms characteristic of abrupt venlafaxine discontinuation were reported in low proportions of the placebo patients in the 2 maintenance phases, and these symptoms do not typically overlap with symptoms of major depression. The PREVENT study results provided strong evidence that venlafaxine ER

maintenance was highly effective in preventing recurrence following recovery for patients with recurrent major depression. We do not believe that there is any evidence from this study to support discontinuation syndrome as an explanation for the results.

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### Increased Rate of Non-Right-Handedness in Patients With Bipolar Disorder

**Sir:** Non-right-handedness is more prevalent in subjects with mental disorders (up to 28%)<sup>1,2</sup> compared to the general population (8%–10%).<sup>3–6</sup> Data on the association of non-right-handedness to bipolar disorder specifically are ambiguous, with data suggesting increased, similar, and decreased rates of non-right-handedness in those with bipolar disorder compared to the general population.<sup>7–13</sup> Putative differences in handedness could yield insights into lateralized cerebral organization or dysfunction as a contributor to pathology in bipolar disorders. We assessed the rate and clinical correlates of non-right-handedness in a large cohort of patients with bipolar disorder

enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorders (STEP-BD).

**Method.** Detailed methods and procedures for this large national study are described elsewhere.<sup>14</sup> At entry into STEP-BD, subjects completed the 10-item Edinburgh Handedness Inventory (Oldfield scale),<sup>15</sup> which rates hand preference for 10 tasks, yielding a Laterality Quotient, with zero or negative scores indicating non-right-handedness, and positive scores indicating right-handedness. Mood state and medication status at the time of handedness evaluation were not standardized.

From the first 1000 patients enrolled, 796 were diagnosed with bipolar disorder type I or II and had complete handedness data. We determined non-right-handedness rate and relationships to demographic and clinical variables as described below.

**Results.** The mean  $\pm$  SD age of patients at the time of the evaluation and STEP-BD enrollment was  $41.18 \pm 12.64$  years. The majority of patients were female (59.6%), white (92.8%), and not married (62.5%) and had bipolar disorder type I (74.4%). Fifteen percent of bipolar patients were non-right-handed. No significant relationships were found between handedness and any of the assessed demographic (gender, race) or clinical (subtype of bipolar disorder, age at onset and family history of bipolar disorder, history of psychosis, suicide attempt, alcohol and substance abuse, attention-deficit/hyperactivity disorder, and generalized anxiety disorder) parameters. For example, the rates of non-right-handedness were only nonsignificantly higher in bipolar I disorder patients (15.4%) compared to bipolar II disorder patients (13.7%), in male (16.2%) compared to female (14.2%) patients, and in patients with (17.8%) compared to without (13.9%) a first-degree family history of bipolar disorder. In addition, the age at onset of mood elevation in non-right-handed compared to right-handed bipolar patients was only nonsignificantly lower (20.7 vs. 22.2 years), and age at onset of depression was only nonsignificantly higher in non-right-handed compared to right-handed (19.2 vs. 18.5 years) patients.

In the largest study to date assessing relationships between non-right-handedness and bipolar disorder, we found a 15% rate of non-right-handedness in bipolar disorder, which is about 50% greater than that commonly seen in the general population.<sup>3-6</sup> However, this increased rate of non-right-handedness in bipolar disorder had no significant correlations with demographic or clinical parameters. Admittedly, some assessments of relationships to clinical parameters of interest (e.g., current mood state, medication status, cognitive performance) were not performed. Nevertheless, interest in the role of lateralization in the neuropathology of bipolar disorder continues to be fueled and supported by reports indicating that asymmetry abnormalities in perception, cerebral distribution of monoamines, and cerebral activation are mood state dependent and are modulated by treatment. Further investigations are needed to assess whether non-right-handedness correlates with biological or functional hemispheric asymmetry parameters in patients with bipolar disorder.

*Trial registration: clinicaltrials.gov Identifier: NCT00012558*

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