

Letters to the Editor

Can Bilateral Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) Induce Mania? A Case Report

Sir: Bilateral repetitive transcranial magnetic stimulation (rTMS) using high-frequency (hf-rTMS) and low-frequency (lf-rTMS) stimulation over the left and right dorsolateral prefrontal cortex (DLPFC), respectively, was theorized to enhance antidepressant outcome.¹ Although efficacy is discussed controversially,^{2,3} this stimulation paradigm at least did not induce noxious cognitive impairments.^{2,4} Cases of affective side effects have been reported with use of hf-rTMS over the left DLPFC^{5,6} and with use of lf-rTMS over the right DLPFC.⁷ We report a 31-year-old woman experiencing a depressive episode in the course of DSM-IV bipolar I disorder who switched to mania on day 7 of a bilateral rTMS trial.

Case report. Ms. A's background included a family history positive for bipolar disorder. Her disease began in 1985 with a depressive episode followed by clear-cut manic episodes in 1987 and 1992 and a second depressive episode in 1998. While an inpatient, she was assigned to rTMS treatment in a randomized, double-blind, sham-controlled, 10-day rTMS add-on trial in June 2002.³ Each rTMS session included hf-rTMS (20 Hz, 100% motor threshold, 10 trains of 10 seconds) over the left DLPFC followed by a subsequent lf-rTMS (1 Hz, 120% motor threshold, 20 minutes) applied over the right DLPFC. On the first day of stimulation, the patient was administered 40 mg of citalopram and 10 mg of lorazepam. Prior to this trial, paroxetine had been tapered over 4 days.

At baseline, Ms. A had a score of 23 on the Hamilton Rating Scale for Depression,⁸ which declined to 4 at the end of treatment (day 7). This robust improvement of her depressive features reflects remission. On day 7, she developed manic symptoms, namely motor restlessness, hyper-talkativeness, grandiose ideas, and newly emerged racing thoughts. Both rTMS and antidepressant treatment were stopped immediately, and clozapine treatment (100 mg/day) was started. Within 5 days the patient's manic symptoms vanished, but she immediately cycled to another depressive episode. Citalopram treatment (40 mg/day) was restarted for a period of 4 weeks. Due to a lack of response, Ms. A was prescribed several antidepressant regimens over the next 3 months. Eventually, amitriptyline and carbamazepine showed antidepressant efficacy after 10 weeks, without signs of mania.

The question arises of whether the patient's switch to mania is to be attributed to an intrinsic effect of rTMS, citalopram,⁹ or both. If the switch is considered to be treatment-related, it seems reasonable to argue that the switch to mania is more closely associated with rTMS and/or add-on modalities than to citalopram alone, as the second course of citalopram treatment in our patient did not induce a manic episode. The switch might

also have been associated with discontinuation of the antidepressant paroxetine, despite adequate therapy with rTMS and citalopram.¹⁰ In addition, this brief manic episode might be seen as part of the natural course of the patient's disease. The ephemerality of the manic episode might be due to the introduction of clozapine or the withdrawal of rTMS and/or antidepressant. One might even argue that rTMS, at least in combination with citalopram, and despite lorazepam treatment, might modulate kindling and sensitization phenomena, which are hypothesized to enhance cycle acceleration.¹¹

Mood stabilizers are thought to protect from switches into mania,^{12,13} although this is not uncontested.¹⁰ Although tricyclic antidepressants are considered to induce switches substantially more often than are selective serotonin reuptake inhibitors,¹⁴ carbamazepine might have prevented a switch during the final amitriptyline/carbamazepine regimen, as well as in the sample of patients reported by Nahas et al.¹⁵ It might be that the described stimulation paradigm is not appropriate for bipolar patients with a specific risk for switch, such as a high genetic load for bipolar illness.¹⁶

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

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**A Case of Venous Thromboembolism
 Probably Associated With Hyperprolactinemia After
 the Addition of Olanzapine to Typical Antipsychotics**

Sir: Whereas there are numerous reports of venous thromboembolic complications in patients treated with typical antipsychotics, especially chlorpromazine, only a few cases of thromboembolisms associated with atypical antipsychotics such as olanzapine and quetiapine are documented.¹ We report a case in which augmentation with olanzapine to alleviate chronic psychotic symptoms accompanied by intermittent manic episodes led to pulmonary thromboembolism. Since analysis of the physical condition of the patient revealed no well-known risk factor for thromboembolism, we speculate that hyperprolactinemia induced by olanzapine augmentation may be, at least in part, involved in the pathogenesis of thromboembolism.

Case report. Ms. A, a 54-year-old Japanese woman with chronic schizoaffective disorder (DSM-IV), had had several previous admissions to mental institutions. Her major psychiatric symptoms included both treatment-resistant delusions and hallucinations and repeated occurrences of manic mood. Twenty-two years after illness onset, at the age of 41 years, she attempted suicide and was admitted to a mental hospital. Since then, she had been receiving inpatient treatment because of her chronic schizoaffective symptoms. She had been treated with haloperidol 12 mg/day, levomepromazine 125 mg/day, lithium carbonate 600 mg/day, clonazepam 2 mg/day, biperiden 6 mg/day, promethazine hydrochloride 75 mg/day, and magnesium oxide 1.5 g/day for more than 5 years without onset of thromboses.

Ten years after admission, due to the exacerbation of manic mood, olanzapine (initial dose = 10 mg/day, highest dose = 40 mg/day for 2 weeks) was additionally administered. In general, 20 mg/day of olanzapine was continuously prescribed as maintenance therapy. In October 2003, half a year after beginning this regimen, Ms. A exhibited acute dyspnea followed by respiratory dysfunction including cyanosis. At that time, she had no history of pulmonary thromboembolism and her physical activity had never been restricted. She was not obese (body mass index = 22) and had no medical history that would increase the risk of venous thromboembolism, such as trauma, recent surgery, or heart failure.

Since a precise examination was required, she was moved to the psychiatric unit of Hiroshima University Hospital (Hiroshima, Japan). Computed tomography scan revealed a pulmonary embolism in the patient's right lung and several deep venous thromboses throughout her right leg. Blood analysis showed elevated concentrations of C-reactive protein, fibrinogen, and D-dimer. Additionally, Ms. A's serum prolactin level was elevated to 863 mU/L (normal level, < 400 mU/L). Laboratory investigations ruled out deficiencies of antithrombin III and proteins C and S. No antiphospholipid antibodies (immunoglobulin lupus anticoagulants and anticardiolipin antibodies) were found.

Soon, standard anticoagulant treatment (warfarin) was started, and 16 days later, Ms. A's dyspnea was moderately improved. Computed tomography scan revealed the amelioration of venous thromboembolisms. Additionally, the patient's previously elevated levels of serum fibrinogen and D-dimer had normalized. Soon after the prescription of olanzapine was terminated, her manic symptoms reappeared. Because the patient's history indicated limited efficacy of mood stabilizers (such as valproate), sultopride was substituted in her regimen. To date, she has been in partial remission, and the thrombosis has not recurred for a year.

The incidence of venous thromboembolism is known to be very low among Asians.² In addition, neither the factor V Leiden mutation nor the prothrombin G20210A mutation has been detected in the Japanese population. For these reasons, we did not test for these mutations in this patient, as it is unlikely that they were involved in the pathogenesis of pulmonary thromboembolism in this case.

To our knowledge, there are only 2 European reports of pulmonary thromboembolism associated with olanzapine, and other well-known risk factors were present in those cases. Hägg et al.³ reported 3 elderly patients who developed pulmonary embolism after starting treatment with olanzapine, one of whom had a malignant tumor and was taking the estrogen receptor modulator tamoxifen. The other report, by Waage and Gedde-Dahl,⁴ described a young man who also developed pulmonary embolism associated with olanzapine, but the patient was overweight (body mass index = 28.5). The present case differed completely from the previous 2 reports because the patient had no well-known risk factors for thrombosis. It has been indicated that the various mediators, such as drug-induced sedation, obesity, and antiphospholipid antibodies, play a role in the pathogenesis of thromboembolism associated with antipsychotics. In this case, there was no well-known risk factor of pulmonary thromboembolism, although the patient did have hyperprolactinemia.

Interestingly, Wallaschofski et al.⁵ recently reported that antipsychotic-induced hyperprolactinemia enhances platelet activation and subsequently increases the risk for venous thromboembolism. It is said that olanzapine elevates the serum prolactin level less often than other antipsychotic agents,^{6,7} but

in the report by Wallaschowski et al., 8 of 14 patients with anti-psychotic-induced hyperprolactinemia had been prescribed olanzapine. As in the present case, most of the patients had received 2 or 3 psychotropics other than olanzapine. Therefore, adverse interaction among several medications (including olanzapine) can lead to hyperprolactinemia followed by thrombosis.

Although further studies to examine the involvement of hyperprolactinemia in venous thromboembolism are required, psychiatrists should be aware of the possibility that hyperprolactinemia may increase the risk for venous thromboembolism in patients treated with antipsychotics.

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

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Prescribing Benzodiazepines for Patients With Substance Use Disorders

Sir: A review of physician prescribing practices for Medicaid beneficiaries in New Hampshire by Clark and colleagues¹ uncovered a disturbing trend showing that patients with co-occurring substance use disorders (SUDs) received larger doses of benzodiazepines and had higher rates of benzodiazepine use than those without SUDs. They noted that the American Psychiatric Association (APA) guidelines² recommend caution when prescribing benzodiazepines to persons with SUDs, and the authors rightly recommended that prescribing physicians reassess their use of these medications.

I am concerned, however, about the additional recommendation that physician prescribing practices of benzodiazepines should be a topic of investigation by policymakers. Regulations with the force of law tend to be blunt instruments when used to restrict the way physicians treat patients. They are generally appropriate in only the most clear-cut cases when the evidence unambiguously points to harm caused by a specific medical in-

tervention. Regulations of this nature are a substitute for, and place limitations on, the exercise of professional judgment.

Even apparently benign actions taken by regulatory agencies can come between a doctor and a patient and have far-reaching consequences. The recent recommendation by the U.S. Food and Drug Administration³ that patients starting treatment with an antidepressant should be closely monitored for worsening depression and the emergence of suicidality was accompanied by a clear statement that it is unknown if antidepressants contribute to these symptoms. Nonetheless, many psychiatrists found that their patients understood this health advisory to mean that antidepressants were highly dangerous compounds. To the degree that this fear leads depressed people to avoid effective treatment, it may have the unintended consequence of increasing the risk of suicide.

The risk of prescribing a benzodiazepine to a substance abuser must be evaluated on an individualized basis, which is why the APA guidelines recommend caution, not uniform avoidance. Additional data are needed before more specific recommendations can be made. For example, one review of the literature⁴ found little evidence to indicate that a history of substance abuse is a major risk factor for future benzodiazepine abuse or dependence, and that benzodiazepines do not appear to induce relapse of substance abuse in these patients.

Continuing to study this issue and seeking ways to help prescribing physicians become more aware of the APA guidelines will help to promote good clinical decision making. However, the use of public policy to address a medical issue should be used only as a last resort when it becomes necessary to place limitations on physicians' use of professional judgment.

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Dr. Clark and Colleagues Reply

Sir: We agree with Dr. Lieberman's concern that precipitate intervention by policymakers might restrict appropriate use of benzodiazepines. That concern is clearly identified in our conclusions, in which we state, "It would be a mistake to adopt overly restrictive prescription policies." The larger question is, what, if any, role should government play in addressing the apparent discrepancy between guidelines developed by physicians

and actual prescribing practice? Dr. Lieberman suggests that physicians can do better without policymakers' involvement.

A key factor in defining the need for policy intervention is whether potential harm outweighs potential benefits. This is where existing research fails us. There is certainly evidence that inappropriate benzodiazepine use can be harmful. Use in combination with opioids can be fatal. But to be useful for policy purposes, information must take into consideration the balance of risks and benefits based on *typical practices*. Relatively little published research on benzodiazepine use is conducted in "real world" settings, and study designs make it difficult to compare the potential benefits and drawbacks. In the absence of clear and compelling evidence, we have clinical wisdom expressed in the form of prescribing guidelines. However, when practice is clearly at variance with such guidelines, we must ask who is right, the practitioners or the guidelines? If it is the former, then guidelines should be changed; if it is the latter, and the potential harm is significant, some corrective action should ensue. Neither our study, nor others currently in the literature, provide a satisfactory answer to this question. Data presented in our article do suggest that current guidelines are largely being ignored, hence the need for change.

The role that policymakers can play here is not to make rules (at least not yet), but to encourage more rigorous research into the potential harm and benefits of benzodiazepine prescribing practices. A particular focus of this research should be persons with severe mental illness treated in outpatient settings, who have high rates of substance use disorders and are more likely than others to be prescribed benzodiazepines.

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Anger in Depressive Mixed States

Sir: Mammen et al.,¹ in an article on anger attacks in bipolar (I and II) depression, reported that anger attacks responded to citalopram and had no relationship to depressive symptoms or hypomanic symptoms within depressive episodes in a secondary analysis of data.

The small sample they used, which included only 15 bipolar II disorder patients, could lead to type II error. The mean score on the Young Mania Rating Scale (YMRS), used to assess hypomanic symptoms within depressive episodes, was only 3.3 (scale range, 0–60), meaning few symptoms were present and few of the patients' depressive episodes included hypomanic symptoms. However, the YMRS is for assessment of mania whereas the Hypomania Interview Guide² better assesses hypomania. Taking these aspects of the study into consideration, it is difficult to support the conclusion that there was no relationship between anger attacks and depressive mixed state (DMX; i.e., a major depressive episode [MDE] plus concurrent hypomanic symptoms^{3–7}).

Following the study methods reported previously, an analysis of the updated sample (N = 602) from DMX studies^{3–8} conducted

by my colleagues and me was performed. The sample consisted of consecutive patients with MDEs: 348 had bipolar II disorder, and 254 had major depressive disorder (MDD).

The bipolar II sample was 67.8% female and had a mean (SD) age of 41.5 (13.2) years. They had a mean of 3.0 (1.4) hypomanic symptoms, 59.7% met anger criteria (persistent anger plus anger outbursts, according to the DSM-IV definition of irritability-anger), and 62.3% met DMX3 criteria (i.e., MDE plus 3 or more hypomanic symptoms, according to Akiskal and Benazzi³). Of those who had MDEs with anger, 80.2% had DMX3. The bipolar II patients had a mean of 7.5 (1.7) depressive symptoms, 47.7% had a family history of bipolar (I and II) disorder, and their mean Global Assessment of Functioning (GAF)⁹ score was 50.3 (9.3).

The MDD sample was 61.4% female and had a mean (SD) age of 46.7 (14.7) years. They had a mean of 1.9 (1.3) hypomanic symptoms, 37.4% met anger criteria, and 33.4% met DMX3 criteria. Of those who had MDEs with anger, 66.3% had DMX3. The MDD patients had a mean of 7.3 (1.9) depressive symptoms, 16.4% had a family history of bipolar disorder, and their mean GAF score was 50.6 (9.6).

Univariate logistic regression revealed the following associations with MDEs with anger: DMX3, odds ratio (OR) = 9.9 (95% CI = 6.8 to 14.4, p = .000); number of hypomanic symptoms, OR = 2.7 (95% CI = 2.2 to 3.2, p = .000); number of depressive symptoms, OR = 1.1 (95% CI = 1.0 to 1.2, p = .015); bipolar II diagnosis, OR = 2.4 (95% CI = 1.7 to 3.4, p = .000); and family history of bipolar disorder, OR = 2.2 (95% CI = 1.5 to 3.4, p = .000). Findings support a close link between anger and hypomanic symptoms within MDEs and also support a link with bipolar family history. Multivariate logistic regression examining the association of MDEs with anger and number of hypomanic and depressive symptoms found that for hypomanic symptoms, OR = 2.8 (95% CI = 2.3 to 3.4, p = .000) and for depressive symptoms, OR = 0.8 (95% CI = 0.7 to 0.9, p = .040), further supporting the link between MDEs with anger and hypomanic symptoms within MDEs.

In considering Mammen and colleagues'¹ finding that anger attacks responded to citalopram, it must be noted that mood-stabilizing agents were also used concurrently, which may have blocked any excitement induced by the antidepressant. A recent study¹⁰ found, in contrast, that in bipolar depression, patients with DMX were more likely to switch to hypomania compared with those without DMX when receiving antidepressants plus mood-stabilizing agents. Controlled studies are clearly required to test the impact of antidepressants on anger (and DMX) in bipolar depression. Clinical observations^{11–13} suggest that excitement should be controlled first by mood-stabilizing agents before starting treatment with antidepressants in DMX patients in order to prevent/reduce any worsening of hypomanic symptoms induced by antidepressants alone. This is even more important in bipolar II depression (often underdiagnosed), which may not have the background of mood-stabilizing agents of bipolar I (probably present in Mammen and colleagues' study).

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

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Dr. Mammen and Colleagues Reply

Sir: In his letter, Benazzi shares data from a large data set showing the predictive value of hypomanic symptoms for anger in major depressive episodes (MDEs). Here, we address 2 issues of research and clinical significance.

In Table 2 of our article,¹ we presented data on the prediction of anger attacks in bipolar depression when hypomanic symptoms, depressive symptoms, and trait anger were simultaneously entered as independent variables into the regression equation. These analyses showed that only trait anger was a predictor of anger attacks at baseline during treatment with mood stabilizers (time 1 [T1]) and after 8 weeks of open-label citalopram added to the mood stabilizers (time 2 [T2]). Current hypomanic symptoms were measured using the Young Mania Rating Scale (YMRS), and current depressive symptoms were measured using the Hamilton Rating Scale for Depression (HAM-D). For this letter, we reanalyzed our data to examine the bivariate relationship between hypomanic and depressive symptoms and anger attacks and the relationship between hypomanic symptoms and anger attacks after controlling for depressive symptoms.

At T1, we found the following bivariate relationships: the odds ratio (95% CI) for YMRS score was significant at 2.1 (1.1 to 4.1) and not significant for HAM-D score (2.6 [0.91 to 7.3]). YMRS score contributed to anger attacks after HAM-D score

was controlled for: odds ratio = 2.1 (95% CI = 1.02 to 4.11). At T2, YMRS and HAM-D scores did not contribute to anger attacks in any of the analyses.

In summary, similar to the findings by Benazzi, our data showed that hypomanic symptoms were a better predictor of anger attacks than depressive symptoms. However, our data also showed that the predictive value of hypomanic symptoms became nonsignificant after controlling for trait anger. While our data set is admittedly small, these findings suggest that it would be useful to examine the role of trait anger in future studies of anger and anger attacks in mood disorders. As noted in our article, it would be useful to know whether trait anger in mood disorders is an enduring personality trait independent of the mood disorder, a subthreshold bipolar symptom preceding the onset of major mood episodes, or a residual symptom persisting between acute episodes. Data sets such as those of Benazzi would be ideal for examining such questions.

Benazzi is right in pointing out that the presence of mood stabilizers probably reduced the risk for activation when the bipolar depressive patients in our sample were treated with citalopram. Given the interpersonal problems associated with anger attacks,² information on the management of this symptom is potentially important. Our data suggest that in bipolar depression, adding citalopram to mood stabilizers in bipolar depression is likely to treat anger attacks. In future research, it would be important to examine treatment response to different classes of agents (e.g., mood stabilizers, atypical antipsychotics, and antidepressants) in different phases of bipolar illness. It would be useful to know what number of threshold hypomanic symptoms in bipolar depression is an indicator of risk for poor treatment outcome for anger attacks. Unfortunately, our sample size was too small to examine this particular question. Such questions could potentially be answered if anger attacks were included as an outcome variable in treatment studies of bipolar disorder.

Dr. Chengappa has been a consultant to and received honoraria from AstraZeneca, Eli Lilly, and Ortho-McNeil; has received grant/research support from Janssen and Ortho-McNeil; and has participated in speakers/advisory boards for AstraZeneca and Eli Lilly. Dr. Kupfer has been a consultant for Servier Amerique and has participated in speakers/advisory boards for Pfizer, Eli Lilly, Forest, and Hoffman-LaRoche. Drs. Mammen and Pilkonis report no financial affiliation or other relationship relevant to the subject matter of this letter.

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