Letters to the Editor

Clozapine and Venous Thromboembolism: Further Evidence

Sir: Although there are several reports of venous thromboembolic complications in patients on treatment with clozapine,[1–4] an association does not constitute proof of a causal relationship. The following history, however, may support causality.

Case report. Mr. A, a 28-year-old man with a 3-year history of schizophrenia (DSM-IV criteria), was admitted for evaluation of his unresponsiveness to several neuroleptics. He started with clozapine and received no other medication. Ten days later, he developed acute dyspnea and fever. At that time, he was taking clozapine, 225 mg/day, and his level of physical activity was normal: he did not stay in bed during the daytime and participated normally in the ward activities. The clinical suspicion of pulmonary embolism was confirmed by ancillary investigations (i.e., perfusion-ventilation lung scan, ventilation scan, arterial blood gases), and standard anticoagulant treatment was initiated promptly. He recovered well, from his psychosis as well as from the pulmonary embolism. Further investigation showed that he had no known risk factors for venous thromboembolism (VTE). He was not obese, he had not undergone a recent trauma, and his family history for VTE was negative. He had no medical disorder associated with an increased risk for VTE (e.g., inflammatory bowel disease, congestive heart failure, malignancy, myeloproliferative disorder). Laboratory investigations ruled out deficiencies of antithrombin III, proteins C and S, and the factor V Leiden mutation. Serious consideration was given to the possibility that the use of clozapine had caused the pulmonary embolism, but in view of this excellent response and the lack of good evidence for the relationship, his treatment with clozapine (400 mg/day) was continued. Oral anticoagulants (acenocoumarol) were stopped after 9 months.

Twenty-six months after discontinuation of his anticoagulant treatment, Mr. A was admitted for a new episode of chest pain and dyspnea. Perfusion-ventilation lung scanning revealed the presence of several new pulmonary emboli. Treatment with anticoagulants was resumed, and he recovered again. He has now been on treatment with clozapine (400 mg/day) and acenocoumarol for 4 years, and no new episodes of VTE have occurred. (Two years after the second episode, Mr. A.'s blood was examined for IgG and IgM antibodies against phospholipids; the negative results made an antiphospholipid syndrome unlikely.) The risks associated with long-term treatment with oral anticoagulants were explained to him, and a switch to another atypical neuroleptic was advised. However, he refused to stop his treatment with clozapine, because there is no guarantee that other drugs will be as effective and he is very concerned about a return of his auditory hallucinations.

A recognized approach to examine a presumed adverse reaction to a particular drug is discontinuation, which is usually followed by a disappearance of the reaction. A reappearance of the side effect upon re-administration of the drug provides evidence for a causal relationship. In the case of Mr. A, the resolution of the first episode of VTE was not due to the discontinuation of any drug, but was most likely the result of treatment with anticoagulants. The discontinuation of anticoagulants, however, can be regarded as equivalent to a reintroduction of clozapine. Although the interval between this discontinuation and the second episode was relatively long, the sequence of events suggests a causal relationship between clozapine and VTE. The history of Mr. A also illustrates that the continuation of clozapine treatment after the occurrence of a VTE carries a risk.

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

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Linezolid, a Monoamine Oxidase Inhibiting Antibiotic, and Antidepressants

Sir: The U.S. Food and Drug Administration recently approved linezolid for treating a variety of gram-positive cocci infections.[1] It is an oxazolidinone antimicrobial that has no known cytochrome P450 interactions, but it is a reversible, nonselective monoamine oxidase inhibitor (MAOI).[2] This latter effect raises important issues concerning its use with antidepressants.

Animal studies suggest that linezolid moderately potentiates the pressor effects of tyramine.[3] In clinical trials, transient enhanced pressor effects were seen with the coadministration of indirect-acting sympathomimetic agents such as phenylpropanolamine and pseudoephedrine, but the blood pressure variations were judged to be within the range of normal fluctuations and therefore not clinically significant.[2,4] The linezolid package insert warns against combining it with foods rich in tyramine, and to be aware of a potential interaction with adrenergic agents.[2]

The package insert also warns about the possibility of a serotonin syndrome from coadministration with serotonergic agents.[2] No serotonin syndrome–like effects were found in clinical trials when linezolid was combined with dextromethorphan,[2,4] a drug that may have serotonin reuptake–inhibiting properties as evidenced by its antagonism of tyramine effects on the unanesthetized cat nictitating membrane preparation.[5] While the effects of combining the selective serotonin reuptake inhibitors (SSRIs) with linezolid have not been studied, a recent case report suggests that a linezolid-sertraline combination caused a serotonin syndrome.[6]

Given that all available antidepressants facilitate serotonergic and/or adrenergic activity in varying degrees, treating depression in a patient who is also on linezolid can be a clinical challenge. We present what we believe to be the first reported case of successful pharmacotherapy of depression in a patient taking linezolid.

Case report. Mr. A, a 67-year-old man, presented initially to his primary physician with a 3-month history of increasing sadness, anhedonia, decreased energy, loss of appetite and weight, insomnia, poor concentration, hopelessness, and passive death wish. His multiple medical problems included hypertension, status post-surgery for colon and prostate cancer, diabetes mellitus with retinopathy and nephropathy (serum creatinine = 2.3 mg/dL), and osteomyelitis in both feet that had necessitated a left below-knee amputation about 3 months earlier. He was taking a number of medications (see footnote* for a complete list), including linezolid, 600 mg b.i.d., which was essential to suppress the osteomyelitis in his remaining foot.

His primary physician started him on mirtazapine, 15 mg/day. A week later, the dose was increased to 30 mg/day, but this caused excessive sedation, and it was reduced to 15 mg again. At the same time, gabapentin, 300 mg h.s., was added to treat phantom limb pain, but 2 weeks after starting the latter medication, Mr. A became delirious, with confusion and prominent visual hallucinations. Given his compromised renal function, the delirium was attributed to the high levels of gabapentin. Gabapentin was discontinued, and the delirium resolved soon thereafter with no other symptoms suggestive of a serotonin syndrome. Serum gabapentin levels were not obtained at the time.

He first presented to us a week later, which was about 4 weeks after starting mirtazapine. Since he rejected the options of electroconvulsive therapy or cognitive-behavioral therapy, we continued him on mirtazapine treatment after discussing the potential for a linezolid-mirtazapine interaction. Three days later, the delirium recurred and resolved when the patient himself discontinued the mirtazapine. Nonetheless, he restarted the medication a few days later, as he was getting more depressed, this time without any recurrence of the delirium.

When we saw him in clinic a few days later, he was quite anxious and concerned about the recent delirium. Lorazepam was added to treat anxiety, and mirtazapine was stopped. Unfortunately, he became more depressed, and was hospitalized in the inpatient psychiatry unit. Alternative antidepressant options were explored, but none provided an assurance of safety in combination with linezolid. Consequently, it was thought reasonable to rechallenge him with mirtazapine, 15 mg, since he had taken it in the past without evidence of a serotonin syndrome. Vital signs and mental status were closely monitored. He tolerated the medication well and was discharged in a stable condition. Soon thereafter, he moved to a nearby city to enter an inpatient rehabilitation program for the visually impaired. Telephone follow-up with his family 3 months later revealed that his mood was substantially improved and that he was still tolerating mirtazapine. It should be noted that, throughout the period covered in this report, the patient remained on linezolid, 600 mg b.i.d.

The pharmacodynamics of mirtazapine are complex, and the resulting effect on causing or treating serotonin syndrome is far from clear. Mirtazapine significantly increases serotonergic 5-HT_{1A} and noradrenergic neurotransmission through its presynaptic α_2-autoreceptor and α_2-heteroreceptor antagonism, while blocking the 5-HT_2 and 5-HT_3 receptors. Its package insert contains a generic warning against combining it with MAOIs.[7] One case report described mirtazapine as effective in treating a serotonin syndrome, possibly because of its 5-HT_2 and 5-HT_3 receptor antagonism.[8] On the other hand, a more recent report published after we had treated this patient suggests that mirtazapine monotherapy can cause a severe serotonin syndrome, possibly due to its activation of the 5-HT_{1A} receptors.[9] 5-HT_3 antagonists, including mirtazapine, have also been thought to be contributory in the causation of serotonin syndrome.[10] Other case reports have implicated mirtazapine, in overdose and in combination with SSRIs, in causing a serotonin syndrome.[11–13] Mirtazapine was eventually continued in this patient because he had tolerated it well in the past and none of the other available antidepressants were thought to offer a significant advantage in this case. Furthermore, it was thought that the deliria were not due to serotonin syndrome and their resolution was coincidental to the use and discontinuation of mirtazapine. Finally, there was minimal potential for interaction through the cytochrome P450 enzyme system, since in vitro studies have not shown mirtazapine to be a potent inhibitor of any of those enzymes.[7]

The tyramine reaction and the serotonin syndrome are 2 potentially lethal complications of combining linezolid with adrenergic and serotonergic antidepressant medications. Further clinical experience is necessary to understand the magnitude of risk involved. While it is not possible to generalize from a single case, our experience with linezolid and mirtazapine suggests that this combination is safe.

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Olanzapine-Sertraline Combination in Schizophrenia With Obsessive-Compulsive Disorder

Sir: Schizophrenia patients with obsessive-compulsive disorder (OCD) are generally characterized by poor treatment response. Addition of serotonin reuptake inhibitors (SRIs) including clomipramine and fluvoxamine has been found efficacious in ameliorating OCD symptoms in schizophrenia.[1,2] To date, there is no report of sertraline combined with antipsychotic agents for this comorbidity or of switching to a second SRI after failure to respond to the first-line SRI-antipsychotic combination. Sertraline has been well tolerated as an adjuvant treatment in schizophrenia patients.[3] We present a case of successful addition of sertraline to olanzapine in a father and son diagnosed with schizophrenia and OCD.

Case 1. Mr. A, Jr., 23 years old, was hospitalized for a first psychotic episode, lasting 8 months, characterized by delusions of persecution, auditory hallucinations, and first-rank Schneiderian symptoms. He met DSM-IV criteria for schizophrenia disorder, paranoid type. Three years prior to occurrence of initial schizophrenia symptoms he exhibited repetitive ego-dystonic preoccupation with symmetry, accompanied by checking and touching rituals. He met DSM-IV criteria for OCD. Paroxetine (60 mg/day for 12 weeks) led to partial resolution of symptoms (Yale-Brown Obsessive Compulsive Scale [YBOCS][4] score decreased from 20 to 16). During hospitalization, psychotic symptoms remitted with olanzapine (up to 20 mg/day, within 5 weeks). No signs of OCD were noted during the acute psychotic episode with pervasive delusions. Four weeks after resolution of psychosis, OCD symptoms reemerged. Addition of fluvoxamine (300 mg/day for 12 weeks) had no effect (YBOCS scores range, 21–19) and was associated with troublesome sedation. Sertraline was given instead, in daily doses up to 150 mg, and within 4 weeks there was substantial improvement of OCD (YBOCS score = 6). The combination of olanzapine and sertraline was well tolerated. At 6-month follow-up the patient remained in remission of both psychosis and OCD.

Case 2. Mr. A, Sr., 55 years old, had been diagnosed with DSM-IV schizophrenia, paranoid type, at age 30. During his current hospitalization, he was successfully treated with olanzapine (7.5 mg/day). While in remission, he revealed obsessive preoccupation with his bodily wastes accompanied by checking compulsions (YBOCS score = 16). Similar OCD symptoms had emerged in his early adulthood and resolved spontaneously. Notably, 10 months before hospitalization he also developed panic attacks. Paroxetine (40 mg/day) and alprazolam (up to 3 mg/day) were added to ongoing olanzapine therapy but discontinued after 4 months due to lack of improvement (YBOCS score = 18). Considering his son's robust response to sertraline, it was given at 150 mg/day with olanzapine (7.5 mg/day), and both OCD and panic attacks remitted within 10 weeks (YBOCS score = 7) and remained in remission at 6-month follow-up.

We demonstrated therapeutic efficacy and tolerability of sertraline with olanzapine in 2 OCD-schizophrenia patients. The similar specific beneficial responses to sertraline-olanzapine treatment may indicate a possible pharmacogenetic component in OCD-schizophrenia comorbidity. The beneficial effect of add-on sertraline after failure of first-line SRI treatment (fluvoxamine, paroxetine) that was revealed in our 2 cases is consistent with the observation of preferential response to specific SRIs in OCD patients without schizophrenia.[5] Preclinical findings that combinations of atypical antipsychotics and SRIs have substantially different profiles of serotonin reuptake inhibition[6] also support our observations. Larger controlled studies are warranted to confirm whether adjuvant sertraline will expand our therapeutic options for treating OCD in schizophrenia.

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Two Cases of Alcohol Craving Curbed by Topiramate

Sir: Anticonvulsants have been previously reported to reduce alcohol craving among alcoholics.[1,2] There have been reports of possible relapse prevention benefit with the use of various anticonvulsants.[1–3] Alcohol craving may be mediated by various receptor mechanisms including γ-aminobutyric acid (GABA) and glutamate.[4] In addition, glutamate receptor changes may play a role in chronic alcoholism.[5] The anticonvulsant topiramate has been postulated to act by a variety of mechanisms including GABA potentiation and glutamate inhibition.[6] The author reports 2 cases in which the addition of topiramate significantly reduced alcohol craving and resulted in an "altered" taste for alcohol.

Case 1. Ms. A, a 52-year-old female veteran with a history of DSM-IV bipolar II disorder, posttraumatic stress disorder (PTSD), panic disorder, and alcohol abuse, had undergone unsuccessful trials of numerous antidepressants and mood stabilizers for management of her psychiatric conditions. During the above trials the patient did not abstain from alcohol and she frequently stopped taking various medications secondary to side effects. In an effort to manage her bipolar II disorder, topiramate was added to her medication regimen in June 2000. The patient initially noted a substantial decrease in alcohol craving. She stated "alcohol tasted very sweet and I couldn't drink anymore." She was able to abstain from alcohol despite living with an alcoholic sister. The patient denies substantial alcohol craving, and she has not consumed alcohol for over 2 years. Her current medication regimen includes topiramate, 100 mg t.i.d.; lorazepam, 1 mg t.i.d.; bupropion SR, 150 mg t.i.d.; and diphenhydramine, p.r.n., for insomnia. The patient also informed her 53-year-old alcoholic brother how she has abstained from alcohol using topiramate. Her brother obtained topiramate from a friend who is a physician. The patient's brother also abstained from alcohol for several months. He stopped topiramate and relapsed to alcohol abuse. He was lost to follow-up.

Case 2. Mr. B, a 54-year-old male Vietnam combat veteran with a long history of DSM-IV bipolar disorder, PTSD, and alcohol dependence, had undergone unsuccessful trials of multiple mood stabilizers, antipsychotics, and anticonvulsants to manage his various psychiatric illnesses. He had been maintained on a regimen of olanzapine, gabapentin, and carbamazepine when topiramate was added to reduce mania. Carbamazepine was tapered at the patient's request. Prior to the addition of topiramate, the patient noted a strong alcohol craving despite a medication regimen that included gabapentin and carbamazepine. Gabapentin and carbamazepine have been previously described to reduce alcohol craving.[2,3] The patient's current medication regimen is as follows: topiramate, 100 mg t.i.d.; olanzapine, 10 mg q.i.d.; gabapentin, 300 mg q.i.d.; temazepam, 30 mg q.h.s.; fluoxetine, 40 mg q.d.; and lorazepam, 1 mg b.i.d. This patient also noted a substantial decrease in alcohol craving and an "altered taste" of alcohol with the addition of topiramate to his medication regimen. Prior to the addition of topiramate he intermittently consumed "nonalcoholic beer." The patient noted that even the taste of this low alcohol–containing beverage was substantially altered. He has remained abstinent from all forms of alcohol including "nonalcoholic" beer for the past 2 years.

There are many confounding variables with these 2 patients. Both patients have required a complex regimen of medications, which partially controlled various psychiatric symptoms. Both patients continue to experience some PTSD symptoms, but the mood disorder has been essentially under control. In both cases, topiramate significantly reduced the craving for alcohol and led to an "altered taste" of alcohol-containing beverages. Neither patient was able to abstain from alcohol prior to the addition of topiramate. A larger trial of individuals without psychiatric comorbidity is needed to better define the role of topiramate in the management of alcoholism. In addition, alcoholism is a very common condition among bipolar patients.[7] Topiramate may play a unique role in the management of both bipolar illness and alcoholism.

Dr. Komanduri reports no financial or other relationship relevant to the subject matter of this letter.

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Quetiapine and QTc Issues: A Case Report

Sir: The issues associated with QTc interval prolongation have resurfaced again and have resulted in more electrocardiogram (ECG) screenings associated with the prescription of antipsychotics. We describe a case to bring attention to the importance of manual checking when the ECG printout suggests a prolonged QTc interval.

Case report. Ms. A, a 50-year-old woman, was hospitalized with a DSM-IV diagnosis of schizoaffective disorder, depressive type. She had a past history of 6 psychiatric hospitalizations, and her mother had a diagnosis of schizophrenia. She had a 28-pack-per-year history of smoking, but denied using any other drugs. Her medical history included morbid obesity, obstructive sleep apnea (OSA), hypercholesterolemia, congestive heart failure (CHF), hypertension, asthma, and chronic obstructive pulmonary disease (COPD).

At admission to the hospital, the patient was experiencing auditory hallucinations and delusions of reference. Her medications included citalopram, 40 mg/day; quetiapine, 300 mg at bedtime; fluticasone propionate inhaler, 2 puffs twice daily; theophylline, 200 mg twice daily; ipratropium bromide multi-

dose inhaler, 2 puffs twice daily; furosemide, 20 mg daily; amlodipine, 5 mg/day; and perindopril, 8 mg/day.

One day after Ms. A's quetiapine dosage was increased to 100 mg in the morning and 300 mg at bedtime, she was noted to have a prolonged QTc interval measuring 612 ms as seen on the ECG printout. She had no complaints of shortness of breath or palpitations, but she had chest pain. A manual check of the ECG revealed a QTc interval of 480 ms, suggesting the presence of an artifact. No electrolyte abnormalities had been found.

A cardiology consultation was followed by 5 serial ECGs, each done daily, and an echocardiogram. The cardiologist felt that the chest pain was noncardiac in nature and that the patient had a systolic ejection murmur over the aortic area. The ECGs revealed normal sinus rhythm. The QTc intervals measured 427 ms, 421 ms, 407 ms, 408 ms, and 411 ms, respectively. Subsequent ECGs performed in the office of Ms. A's family physician revealed a QTc interval of 433 ms 2 months after the patient's discharge from the hospital. Five months after discharge from the hospital, a single ECG indicated a QTc interval of 455 ms, while the others at that time indicated 398 ms and 396 ms. None of the other ECGs had such a significant discrepancy on manual checking. No ECG had been done at admission, as it was not a routine practice for psychiatric hospitalizations unless ordered by the emergency room physician or the admitting psychiatrist. Ms. A's last ECG at the same hospital in 1996 revealed normal sinus rhythm, with a QTc interval of 409 ms. Her echocardiogram revealed mild concentric left ventricular hypertrophy with diastolic dysfunction and an ejection fraction of 60%. The patient's calcium (9.4 mg/dL), magnesium (2.1 mg/dL), phosphorus (81 mg/dL), and potassium (3.8 mEq/L) levels were all within normal limits.

The patient's quetiapine dose was increased gradually to a total of 800 mg/day in divided doses, followed by augmentation with fluphenazine, 2.5 mg at bedtime, resulting in substantial decrease in psychotic symptoms. At discharge from the hospital, the patient was taking fluphenazine, 2.5 mg/day; quetiapine, 300 mg in the morning and 500 mg at bedtime; citalopram, 40 mg/day; and her medical medications. Her QTc interval at discharge was 411 ms.

Atypical antipsychotics are not free from cardiovascular side effects,[1,2] and ECG abnormalities such as QTc prolongation have been reported with quetiapine overdose. In one case, QTc interval increased to 537 ms in a patient who ingested 2000 mg of quetiapine in overdose while also taking risperidone.[3,4] Most antipsychotic agents are known to cause QTc prolongation, some significantly more than others.[5] There is a recent report of QTc prolongation with ziprasidone in the elderly.[6]

Our patient was an obese middle-aged woman who had multiple medical problems, including a history of CHF, COPD, and OSA. A strict temporal relationship cannot be established in this patient because of her multiple medical problems, obesity, age, and female gender and the ECG artifact. When manually checked, the ECG of interest revealed a QTc interval of 480 ms. In reviewing the patient's medical record, we found only 1 other ECG, done 5 months later, that was noted to be borderline, with a QTc interval of 455 ms. No other ECGs revealed a prolonged or borderline QTc interval on the basis of the printout or a manual check. The cardiology consultation did not suggest that we stop the antipsychotic, but recommended daily ECGs.

This case illustrates 3 important points: (1) Psychiatrists and other physicians should always do a manual check of the ECG to verify that the printout from the machine is accurate. It takes only a short time. In the case of this patient, the presence of a U wave led to an inaccurate reading by the machine. Once the U wave resolved, the QTc interval was within normal range on the basis of both the printout and a manual check. (2) Although the QTc issue has been linked mostly to the new atypical antipsychotic ziprasidone, psychiatrists and primary care physicians need to be vigilant with all antipsychotics. In the Pfizer 054 study,[5] risperidone, olanzapine, and haloperidol demonstrated the least propensity to cause significant prolongation of the QTc interval. (3) All risk factors listed, such as cardiac problems, obesity, age, treatment with multiple medications, female gender, and machine artifact, should be considered in addition to the antipsychotic as a possible etiology of a prolonged QTc interval. This case suggests that primary care physicians and psychiatrists should remain vigilant and open-minded on this issue and avoid stereotyping one antipsychotic or another. Each situation should be dealt with on a case-by-case basis. It is important to perform a manual check and not depend on the ECG printout alone. Guidelines should be developed with regard to ECG abnormalities in patients taking antipsychotic as well as other psychotropic medicine with which such issues might arise.

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

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The Efficacy and Safety of Bilateral rTMS in Medication-Resistant Depression

Sir: Repetitive transcranial magnetic stimulation (rTMS) may be useful for the treatment of medication-resistant depressed patients, and it may be a safer alternative to electroconvulsive therapy (ECT).[1,2] Favorable results have been obtained primarily by applying repetitive, high-frequency stimulation (usually 10–20 Hz) over the left dorsolateral prefrontal cortex (DLPFC).[1,2] However, several investigators[3,4] have obtained significant improvement by stimulating the right DLPFC with low-frequency stimulation (1 Hz).

Because both left-sided and right-sided stimulation have produced significant, albeit modest improvements, we postulated that greater efficacy might be attained by stimulating both left and right DLPFCs. To our knowledge, this strategy has not been tried previously. There is theoretical support for using bilateral stimulation. Because studies in healthy controls indicate that the right prefrontal cortex mediates negative emotions such as sadness, whereas the left prefrontal cortex mediates positive emotions,[5,6] depression could be alleviated by the application of fast and slow rTMS, which facilitate and inhibit cortical excitability, respectively. Thus, fast rTMS could be applied to the left DLPFC and slow rTMS to the right DLPFC.

Using parameters established previously for fast and slow rTMS, we describe our findings from an open study of 10 medication-resistant patients with major depressive disorder who received fast rTMS to the left DLPFC followed immediately by slow rTMS to the right DLPFC.

Ten consecutively referred medication-resistant outpatients with a DSM-IV diagnosis of major depression and a 21-item Hamilton Rating Scale for Depression (HAM-D)[7] score of ≥ 16 were scheduled to receive at least 9 rTMS sessions (maximum = 10 sessions) over a 2-week period. The mean age of the sample was 45 years (range, 27–68 years), equally divided between men and women. They had a mean depression history of 14 years (range, 3–31 years), and subjects had previously received an average of 8 antidepressants, mood stabilizers, or antipsychotic agents; 3 had previously received ECT. All of the subjects were taking at least 1 antidepressant medication at the time of study. While the modal number of rTMS in the literature is 10,[1] our decision to aim for 9 treatments was based on practical difficulties patients had in attending 10 sessions over a consecutive 2-week period. Moreover, several studies found substantial clinical responses after 5 sessions,[1,8,9] although some studies suggest that maximal effects may require 20 sessions.[1,10,11] During each session, 20 trains of 1.5 seconds at 20 Hz and 100% motor threshold were administered over the left DLPFC followed by 2 trains of 60 seconds at 1 Hz and 100% motor threshold over the right DLPFC. Depression, cognition, and side effects were assessed at baseline and at every other session prior to stimulation.

Seven of 10 subjects completed the study; all subjects completed at least 7 sessions. Using an intent-to-treat design, last assessment carried forward, a repeated-measures analysis of variance indicated a significant decline in the mean HAM-D scores from 21.9 at baseline to 15.7 at follow-up ($F = 3.25$, $df = 4$, $p < .02$). Four of 10 subjects showed a ≥ 50% decline on the HAM-D, with a strong trend for those under age 50 (Fisher exact test; $df = 1$, $p = .076$). There were no adverse events or changes in cognitive status as measured by the Mini-Mental State Examination.[12]

Improvement on the HAM-D scores was similar to results reported for unilateral treatment.[1,2] Thus, serial bilateral treatment may afford no added benefits. Nevertheless, controlled trials with larger samples may be worthwhile because younger subjects responded more robustly, bilateral rTMS appears to be safe, and there is theoretical support for using bilateral rTMS.

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

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Racial Differences in Use of Antipsychotics Among Patients With Bipolar Disorder

Sir: Fleck and colleagues[1] recently reported on the differences in prescribing practices in black versus white patients with new-onset bipolar disorder. As part of our ongoing interest in prescribing practices, we examined psychotropics prescribed at our facility at the time of discharge for 535 hospitalized patients with a diagnosis of bipolar disorder.[2] Our findings regarding antipsychotic use in this population support these authors' call for further study of clinical decision making in patients with bipolar disorder. Compared with whites, both blacks and Hispanics were significantly more likely to have antipsychotics prescribed (92.0% and 85.0%, respectively, vs. 62.2%). In a logistic regression analysis, race made an independent contribution to use of an antipsychotic. The variables in this analysis included age (< 20 years, 20–64 years, > 64 years; each vs. all others), race (white, black, Hispanic; each vs. all others), bipolar type (bipolar I manic, bipolar I depressed, bipolar I mixed, bipolar II; each vs. all others), concurrent diagnosis of anxiety disorder, concurrent diagnosis of adjustment disorder, concurrent diagnosis of substance dependence, concurrent diagnosis of substance abuse, and any concurrent diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) were used to identify the variables that were predictive: white (OR = 0.289, CI = 0.157 to 0.533), diagnosis of bipolar I manic (OR = 2.594, CI = 1.508 to 4.458), diagnosis of substance de-

pendence (OR = 0.319, CI = 0.189 to 0.541), any concurrent diagnosis (OR = 3.165, CI = 1.786 to 5.608), diagnosis of anxiety disorder (OR = 0.233, CI = 0.096 to 0.566), and diagnosis of substance abuse (OR = 0.445, CI = 0.255 to 0.777). Among patients for whom antipsychotics were prescribed, there was no difference in type of antipsychotic (atypical vs. conventional). Atypicals were prescribed for 86.9% of whites (5.3% of these also received a conventional antipsychotic), 89.1% of blacks (6.5% also received a conventional), and 85.3% of Hispanics.

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

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Drs. Fleck and Strakowski Reply

Sir: We are pleased that Ms. Szarek and Dr. Goethe are also examining the influence of ethnicity on antipsychotic prescribing practices for patients with bipolar disorder. Their large-scale study indicated that white patients were 3.5 times less likely to receive antipsychotics at hospital discharge relative to minority patients (African American and Hispanic). Additionally, a primary diagnosis of bipolar I disorder, manic, increased prescriptions for antipsychotics by 2.5 times, independent of ethnicity.[1]

These retrospective findings are in line with our prospective results indicating that African American patients received antipsychotics for a significantly greater percentage of follow-up time during the 2-year period since first hospitalization. Our findings suggest that excess prescriptions for antipsychotics are not restricted to acute care but likely extend into early-course maintenance treatment for bipolar disorder.[2]

Where our 2 studies diverge is in how conventional antipsychotics were prescribed. Szarek et al.[1] reported no ethnicity differences in the percentage of patients receiving conventional agents at hospital discharge, while we found that African Americans were more than twice as likely as whites to receive conventional agents at some time during follow-up (38% vs. 15%, respectively).[2] This discrepancy suggests that although African Americans are more likely to receive antipsychotics while hospitalized, community-based physicians may be more likely than inpatient-attending psychiatrists to prescribe less-preferred conventional agents. Further research will be needed to test this prediction empirically.

Over-reliance on antipsychotics may be related to the disproportionately increased diagnosis of schizophrenia in African American patients with affective psychosis. Recent results from our site indicate that ethnicity-blinded clinicians do not find an increased incidence of schizophrenia spectrum disorders in African American men presenting with either psychosis or affective psychosis.[3,4] These results highlight the impact ethnicity may have on the assessment of psychosis and assignment of schizophrenia. To counteract this influence, affective symptoms should be carefully and continually assessed in minority patients who present with psychosis. As we improve our understanding of the influence ethnicity has on clinical assessment, we can minimize the potential for misdiagnosis and ineffective or increased antipsychotic treatment in minority patients.

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