

## A Case of Pulmonary Thromboembolism and Rhabdomyolysis During Therapy With Mirtazapine and Risperidone

**Sir:** Mirtazapine may be combined with antipsychotic drugs to treat depressive disorders complicated by psychosis.<sup>1</sup> Mirtazapine is an effective and safe drug in this setting.<sup>2</sup> We describe severe and life-threatening rhabdomyolysis and pulmonary thromboembolism in a patient receiving mirtazapine and risperidone.

**Case report.** In 2005, Mr. A, a nonobese 40-year-old man (body mass index = 26 kg/m<sup>2</sup>), developed a syndrome consistent with schizophrenia. He was treated with high doses of risperidone (8 mg); after he subsequently developed a hypokinetic-rigid syndrome, biperiden (2 mg) was added. However, it soon became apparent that the psychosis was followed by a major depressive episode (his Hamilton Rating Scale for Depression [HAM-D]<sup>3</sup> score was 30), and mirtazapine (45 mg) was added.

Outpatient treatment failed, and he was admitted to our psychiatric day clinic (serum levels: risperidone was 5.1 µg/L and 9-OH-risperidone was 47.7 µg/L during therapy with risperidone 7 mg/day). Mirtazapine was increased to 60 mg and risperidone reduced to 3 mg daily. The patient improved, but 6 weeks after starting this combination therapy, he developed acute aching in his left leg and respiratory problems. These led to his admission to a medical hospital, where pulmonary embolism and rhabdomyolysis (creatinine kinase level = 4795 U/L) were diagnosed. No hemostatic defect (no abnormalities were found in antithrombin III level, protein C activity, protein S antigen level, or activated protein C resistance) and no evidence for smoking, autoimmune activities, or malignant diseases were detected. During treatment with heparin followed by warfarin, Mr. A recovered. In parallel to the medical therapy, we replaced mirtazapine with reboxetine and replaced risperidone with aripiprazole and achieved a remission of the major depressive episode (his HAM-D score decreased by 24 points to 6). We successfully initiated vocational rehabilitation, and the patient was discharged in a euthymic state 8 weeks after the thromboembolism.

Venous thromboembolism is considered a severe adverse effect of antipsychotic therapy<sup>4</sup> about which we do not have a clear picture regarding predisposing risk factors and biological mechanisms. Thioridazine and clozapine in particular seem to carry a high risk for venous thromboembolism.<sup>5,6</sup> Two cases with pulmonary thromboembolism during treatment with risperidone have been reported,<sup>7</sup> as well as a further 2 cases with rhabdomyolysis during treatment with risperidone,<sup>8</sup> 2 more in combined treatment with risperidone and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors,<sup>9,10</sup> and 1 during monotherapy with mirtazapine.<sup>11</sup>

Ours is the first report on the coincidence of rhabdomyolysis and thromboembolism during combined therapy with risperidone and mirtazapine. A malignant neuroleptic syndrome and a central serotonin syndrome can definitely be ruled out, and a careful examination was unable to define any medical cause for the mentioned complications. Therefore, a causal attribution to the psychotropic medication seems to be likely. The pathomechanism, however, remains unclear and might involve pharmacodynamic interactions and changes of blood vessel and thrombocyte function. We recommend awareness regarding

these complications and clinical drug monitoring, including creatine kinase monitoring, if patients receive the combination of risperidone and mirtazapine.

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**Mathias Zink, M.D.**  
**Udo Knopf, M.D.**  
**Sotiria Argiriou**  
**Anna Kuwilsky**

Central Institute of Mental Health  
Department of Psychiatry and Psychotherapy  
University of Heidelberg  
Mannheim, Germany

## Repetitive Transcranial Magnetic Stimulation for Maintenance Treatment of Depression: A Case Report

**Sir:** Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a new and innovative method for treating neuropsychiatric diseases. Whereas acute antidepressant effects of prefrontal rTMS have been demonstrated in numerous studies,<sup>1,2</sup> there is almost no reported experience in using rTMS as a maintenance therapy in affective disorders. One session of rTMS per week has been proposed as a treatment schedule for maintenance therapy, and successful outcome results with this treatment schedule were reported in a patient with recurrent depression<sup>3</sup> and in 3 patients with bipolar depression.<sup>4</sup> However, clinical observations in acute phase treatment as well as animal

studies suggest that effects of rTMS accumulate in an additive manner when daily stimulations are administered,<sup>5</sup> potentially offering a new way for rTMS maintenance therapy.

On the basis of these considerations, we propose a treatment schedule with 1 week of daily rTMS per month and report the first results of this treatment schedule in a patient suffering from recurrent major depression.

**Case report.** Ms. A, a 60-year-old woman with a 7-year history of recurrent major depressive disorder (DSM-IV), was referred for a course of rTMS in February 2004. At that time, the patient had experienced her 12th depressive episode. Within the course of the disease, recovery from depressive episodes was increasingly slow and incomplete. Psychosocial stressors contributing to the onset or course of depressive episodes could not be identified despite repeated extensive exploration. Antidepressant medication based on current treatment guidelines, including a variety of distinct antidepressant drugs for adequate duration (at least 12 weeks) such as amitriptyline (100 mg/day), tranylcypromine (60 mg/day), reboxetine (8 mg/day), venlafaxine (300 mg/day), and escitalopram (60 mg/day) as well as augmentation strategies with mood stabilizers such as valproate (1000 mg/day), lamotrigine (200 mg/day), and lithium carbonate (900 mg/day), failed to relieve her depression decisively.

By the time Ms. A was referred for rTMS, her major depressive episode had lasted for 6 months and was characterized by severely depressed mood, recurrent suicidal ideation, anhedonia, insomnia, anxiety, decreased appetite, somatic symptoms, and diurnal variation with depression regularly worse in the morning. Since the current severe episode did not respond to drug treatment, rTMS was considered as an alternative. Prior to this treatment attempt, antidepressant medications, including venlafaxine (150 mg/day), escitalopram (50 mg/day), lithium (225 mg/day), and lamotrigine (100 mg/day), were kept stable for 2 weeks and remained unchanged during rTMS treatment. The patient underwent 15 rTMS sessions (Medtronic MagPro, figure-of-eight coil MCF-B65; Medtronic, Minneapolis, Minn.) during 3 weeks at the following stimulation parameters: left dorsolateral prefrontal cortex, 20 Hz, 90% of motor threshold intensity (resulting in a stimulation intensity of 60% of maximal stimulator output), 2000 stimuli/day (40 trains of 2.5 seconds each with an interstimulus interval of 25 seconds), 5 treatment sessions/week. Depressive symptoms started to decrease after 1 week of rTMS and almost completely disappeared toward the end of rTMS treatment (21-item-Hamilton Rating Scale for Depression [HAM-D]<sup>6</sup> score pre-rTMS = 30; post-rTMS score = 3).

Despite maintenance therapy with escitalopram (60–80 mg/day), lithium (225 mg/day), and lamotrigine (200 mg/day), Ms. A relapsed twice during the following 7 months. After both relapses, rTMS treatment with identical stimulation conditions as applied initially resulted in total remission of the depressive episodes (May 2004: HAM-D score pre-rTMS = 27, post-rTMS score = 3; September 2004: HAM-D score pre-rTMS = 26; post-rTMS score = 4).

Due to this convincing clinical effect, we offered rTMS maintenance treatment after the second relapse. On the basis of physiologic considerations of additive efficacy of daily rTMS,<sup>5</sup> we decided to administer 5 sessions of daily rTMS every fifth week. With this treatment schedule, the patient remained free of any further depressive episodes during a follow-up period of 12 months up to the time of this report. HAM-D scores obtained at every treatment week ranged between 0 and 3 points. This relapse-free period is unique in the disease history of the patient and cannot be explained by changes in psychosocial or environmental factors.

We are aware of the limitations of these data, which derive from open treatment in just 1 patient. Nevertheless, the presented case suggests that rTMS administered in a specific temporal pattern provides a promising maintenance treatment in recurrent depression.

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**Berthold Langguth, M.D.**

**Michael Landgrebe, M.D.**

**Marc Zowe, M.D.**

**Maria Gerst, M.D.**

**Göran Hajak, M.D., Ph.D.**

**Peter Eichhammer, M.D., Ph.D.**

Department of Psychiatry, Psychotherapy and Psychosomatics  
University of Regensburg  
Regensburg, Germany

#### Open Study of Creatine Monohydrate in Treatment-Resistant Posttraumatic Stress Disorder

**Sir:** Creatine-containing compounds play an important role in brain energy homeostasis and may have a beneficial effect on brain functioning.<sup>1–3</sup> Accumulated evidence suggests the possible involvement of altered cerebral energy metabolism in the pathophysiology of posttraumatic stress disorder (PTSD).<sup>4</sup> Oral creatine supplementation may increase brain creatine level and modify brain high-energy phosphate metabolism in hypoactive brain areas in subjects with treatment-resistant PTSD.

**Method.** The study was an open, 4-week clinical trial examining the effect of creatine monohydrate added to ongoing psychotropic treatment in PTSD patients. Male and female patients aged 18 to 65 years with chronic PTSD (according to DSM-IV-TR criteria) who had received psychotropic treatment for at least 6 weeks (selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors) without a clinically relevant therapeutic response were included in the study. Patients with alcohol or drug abuse or any clinically significant unstabilized medical condition were excluded. The study was approved by the local institutional review board.

The following scales were used at baseline and at 2 and 4 weeks of the study: the Clinician Administered PTSD Scale (CAPS),<sup>5</sup> the Hamilton Rating Scales for Depression (HAM-D)<sup>6</sup> and Anxiety (HAM-A),<sup>7</sup> the Clinical Global Impressions scale (CGI),<sup>8</sup> the Sleep Quality Scale,<sup>9</sup> and the Sheehan Disability Scale (SDS).<sup>10</sup>

All patients were treated with creatine monohydrate for 4 weeks (3 g daily in the first week and then 5 g daily for another 3 weeks). Ongoing psychotropic treatment was not altered during the study as there was no clinical need. Statistical analysis included 1-way repeated-measures analyses of variance. All data are presented as mean  $\pm$  SD.

**Results.** Ten patients (8 men, 2 women; age range: 43–61 years) participated in the study. Scores on all scales except the SDS and HAM-A improved mildly yet significantly during the study. The CGI scores improved from  $4.75 \pm 0.7$  at baseline to  $4.63 \pm 0.7$  and  $4.37 \pm 0.9$  at 2 and 4 weeks of creatine supplementation, respectively ( $p = .035$  at 4 weeks). All CAPS parameters mildly improved during the study: intrusiveness scores improved the most, and avoidance, the least. Total CAPS score was reduced from  $75.6 \pm 11$  at baseline to  $70.1 \pm 10$  at 2 weeks and  $69.8 \pm 9$  at 4 weeks of creatine consumption (8% improvement,  $p = .003$  at 4 weeks). HAM-D score was reduced from  $24.1 \pm 5$  at baseline to  $20.4 \pm 6$  at 4 weeks of creatine consumption (16% improvement,  $p = .006$ ). One patient complained of transient weakness at 2 weeks of treatment.

Total CAPS, HAM-D, and HAM-A scores for patients with comorbid DSM-IV-TR major depressive disorder ( $N = 6$ ) showed greater numerical improvement compared with scores for patients who had no psychiatric comorbidity. The differences were not of statistical significance, probably due to the small sample size.

This preliminary open study of creatine monohydrate demonstrates a modest beneficial effect of this drug on sleep, depressive, and PTSD symptomatology in treatment-resistant PTSD patients. That creatine supplementation also had a beneficial effect on sleep is intriguing, as sleep disturbances are common in PTSD patients and the use of benzodiazepines for such disturbances may carry the risk of abuse and dependence.

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

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**Daniela Amital, M.D.**

**Tali Vishne, M.D.**

**Suzana Roitman, M.D.**

**Moshe Kotler, M.D.**

Ness-Zionna Mental Health Center,  
Sackler Faculty of Medicine  
Tel Aviv University  
Ness-Ziona, Israel

**Joseph Levine, M.D.**

Department of Psychiatry and the Stanley Research Center  
Faculty of Health Sciences  
Ben Gurion University of the Negev  
Beersheva, Israel

#### Long-Term Outcome of Vagus Nerve Stimulation in Rapid-Cycling Bipolar Disorder

**Sir:** The phenomenon of rapid cycling in patients with bipolar disorder has been identified as a marker for high risk of recurrence and resistance to conventional drug treatment.<sup>1</sup> New anticonvulsants are promising agents for the treatment of bipolar disorders, but they are heterogeneous with regard to their efficacy, target symptoms, and adverse event profiles.<sup>2</sup>

Vagus nerve stimulation (VNS) therapy is delivered with a device (NCP System; Cyberonics, Houston, Tex.) and has received U.S. Food and Drug Administration approval for adjunctive long-term treatment of chronic or recurrent depression for patients who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments. A recent study did not yield definitive evidence of short-term efficacy for adjunctive VNS in major depression.<sup>3</sup> In contrast, long-term data suggested that VNS is associated with clinically meaningful antidepressant effects.<sup>4</sup> To date, there is no investigation of the effect of VNS on rapid cycling in patients with bipolar disorder.

**Case report.** Ms. A, a 60-year-old woman, was diagnosed with bipolar II disorder with rapid cycling according to DSM-IV criteria.<sup>5</sup> The patient had no history of drug, alcohol, or substance abuse. She was diagnosed with breast carcinoma in 1990; underwent surgery, chemotherapy, and radiation in the same year; and has been relapse free since then. In the 5 years before implantation (in 2003) of a vagus nerve stimulator, she had a mean (SD) of 8.8 (1.7) depressive, 1.6 (1.0) mixed, and 7.6 (1.0) hypomanic episodes per year. In the 12 months after VNS implantation, Ms. A had 5 depressive, 2 mixed, and 7 hypomanic episodes. After beginning VNS therapy, mean (SD) duration of her depressive episodes decreased from 9.2 (5.1) weeks to 4.6 (3.1) weeks, whereas duration of mixed and hypomanic episodes remained nearly unchanged. After implantation of the stimulator, mean severity of depressive symptoms (measured with the 21-item Hamilton Rating Scale for Depression<sup>6</sup>) decreased from 24.8 (7.3) in the year before implantation to 16.9 (6.1) in the year after implantation. At the request of

the patient, pharmacologic treatment consisting of valproic acid, 1000 mg, and paroxetine, 40 mg, remained unchanged throughout the 12 months prior to and 12 months after VNS implantation.

This case represents the first, and thus far the only, patient with rapid-cycling bipolar disorder who has been treated with VNS reported in the literature. During VNS treatment, there was a notable decrease in the severity and duration of depressive symptoms. As the only change in therapy during the 12 months prior to and 12 months after VNS implantation was the addition of VNS, it seems likely that the clinical improvement of depressive symptoms was associated with the VNS. However, since total number and severity of hypomanic episodes were not influenced by VNS, this case suggests that this stimulation therapy may preferentially aim at depressive symptoms. Future long-term investigations should also address the use of VNS in a larger sample of rapid-cycling bipolar patients.

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**Malek Bajbouj, M.D.**  
**Heidi Danker-Hopfe, Ph.D.**  
**Isabella Heuser, M.D., Ph.D.**  
**Ion Anghelescu, M.D.**

Department of Psychiatry  
 Charité—Universitätsmedizin Berlin  
 Benjamin Franklin Campus  
 Berlin, Germany

#### QTc and Metabolic Parameters

**Sir:** My colleagues and I have been interested in QTc interval prolongation, torsade de pointes, and antipsychotic drugs for some time.<sup>1–9</sup> The article by Mackin and Young<sup>10</sup> in the November 2005 issue of the *Journal* has sufficient limitations both in its own right and as a model for a larger study to stimulate the following comments:

- In the Introduction, Mackin and Young assert a need to examine “the relationship between QTc interval, antipsychotic use, and metabolic dysfunction.”<sup>10(p1387)</sup> The

authors do not mention plasma or serum potassium concentrations and are seemingly unaware that low potassium states are far and away the most common cause of QTc interval prolongation.<sup>11</sup>

- In the Method section, the authors claim that they “randomly recruited 103 patients.”<sup>10(p1387)</sup> What method of randomization was used?
- Mackin and Young did not measure plasma or serum potassium concentrations. In a prospective study assessing the potential effects of metabolic parameters on the QTc interval, this is an important missing piece.
- The authors said that one of them made the QTc interval measurements. In a PubMed search, I could find no articles by either author on electrocardiographic interpretation. Would the authors please describe their training and experience in electrocardiographic interpretation? If no training or experience is present, I suggest the authors seek training from Marek Malik, M.D., in the Department of Cardiac and Vascular Sciences at St. George’s Hospital Medical School, London.<sup>12</sup>
- Mackin and Young<sup>10</sup> used Bazett’s formula to determine their QTc interval measurements but did not use his methods as described in his 1920 article.<sup>13</sup>
- The authors did not separate QTc interval measurements by sex even though they acknowledge that women tend to have longer QTc interval measurements than men. I assume they did not separate these electrocardiographic measurements by sex so that they could use a larger N in their statistical analyses. That is quite a price to pay for more statistical power.

In summary, I hope the authors will reanalyze their data and report their findings in a response to this letter.

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

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**W. Victor R. Vieweg, M.D.**

Department of Psychiatry and Internal Medicine  
Medical College of Virginia Campus,  
Virginia Commonwealth University  
Richmond, Virginia

### Drs. Mackin and Young Reply

**Sir:** We thank Dr. Vieweg for his comments regarding our recent article.<sup>1</sup>

Dr. Vieweg is correct to state that serum potassium concentration has an important bearing on cardiac repolarization, a fact about which we are well aware. There are also a number of other risk factors for cardiac repolarization abnormalities that have been reviewed elsewhere.<sup>2</sup> Our study was designed specifically to investigate the relationship between QTc prolongation and metabolic parameters, in the absence of any similar data in this patient group. This is an important area of investigation given the reports that patients with severe mental illness are at increased risk of cardiovascular<sup>3</sup> and metabolic<sup>4</sup> disease.

Although we agree that investigating the relationship between serum potassium, metabolic parameters, and QTc prolongation would have been of considerable interest, serum potassium levels were not available, and therefore such analysis is not possible. We agree with Dr. Vieweg's assertion that serum potassium concentration would be important "in a prospective study assessing the potential effects of metabolic parameters on the QTc interval," but our study is cross-sectional in design, the limitations of which are clearly described in the discussion of our results. We are currently analyzing data from a prospective study of this group of patients, and we hope to report these findings in the near future.

We are surprised by Dr. Vieweg's suggestion that we seek training in electrocardiographic interpretation, based on his inability to find any article "by either author on electrocardiographic interpretation" in a PubMed search. We believe the implication that an assessment of an individual investigator's expertise in any methodology can be based on the results of a PubMed search is fundamentally flawed. The investigator who performed QTc interval measurements has had extensive training and experience in this methodology. Indeed, a number of important electrocardiographic studies, using similar methodology, are in progress or have been completed<sup>5–7</sup> in the University

of Newcastle upon Tyne. We are, therefore, of the opinion that the expertise for the execution of such studies is available locally.

Dr. Vieweg points out that in our current study we used Bazett's formula to calculate the QTc interval, "but did not use his methods as described in his 1920 article." We did indeed use Bazett's formula, but the passage of time has brought with it advances in technology (such as digitizing tablets) that were not available to Bazett; hence, our methodology may be different. However, the technique employed in our study is valid and has been described previously.<sup>7</sup>

Finally, we would wish to point out that the preliminary nature of our study is reflected both in its title and in the discussion of our results. We maintain that our data are novel, and the concluding statement from our article stands: "In order to increase our understanding of the causes of increased mortality in patients with severe mental illness, and to clarify the interplay between psychiatric medication and metabolic factors, future studies should measure cardiac electrophysiology as well as markers of metabolic disease."<sup>1(p1390)</sup>

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**Paul Mackin, M.B., B.S., Ph.D., M.R.C.Psych.**  
**Allan H. Young, M.B., Ch.B., Ph.D., F.R.C.Psych.**  
School of Neurology, Neurobiology, and Psychiatry  
University of Newcastle upon Tyne  
Newcastle upon Tyne, United Kingdom