

Treatment-Resistant Self-Mutilation, Tics, and Obsessive-Compulsive Disorder in Neuroacanthocytosis: A Mouth Guard as a Therapeutic Approach

Sir: The term *neuroacanthocytosis* describes a group of phenotypically and genetically heterogeneous disorders associated with choreatic movements, psychiatric abnormalities, and cognitive decline.^{1,2} Patients with neuroacanthocytosis may develop dementia,³ schizophrenia,^{4,5} obsessive-compulsive disorder (OCD),^{5,6} tourettism,⁷ and self-mutilation.⁸ We present the case of a patient with neuroacanthocytosis who developed treatment-resistant oral self-mutilation behaviors, phonic tics, OCD, and a severe lack of initiative (i.e., abulia). This syndrome responded to the regular use of a mouth guard, an unusual therapeutic approach for this complex psychiatric phenotype.

Case report. Mr. A, a 32-year-old white physical therapist, sought diagnostic evaluation at our center in a state of severe undernourishment. He had a 3-year history of progressive self-neglect, lack of initiative, and morbid adherence to rules and schedules. He persistently worried about missing the “correct time” for taking his meals and medication. The presence of complex vocal tics (including slurs, grunting, squeaking, and sucking sounds) and severe lip-biting behaviors was a major complaint, which was also disclosed during his mental status assessment. In a desperate attempt to avoid self-mutilation, Mr. A kept a scarf in his mouth several times a day.

Blood examinations disclosed acanthocytes and increased muscle creatine phosphokinase. Magnetic resonance imaging revealed atrophy of both caudate nuclei. Electromyography and nerve conduction studies evidenced a mononeuropathy multiplex of axonal type. Unfortunately, no chorein Western Blot testing² was available at the time of his evaluation.

Given the severity of Mr. A's oral self-injurious behaviors, this condition took relative precedence over other psychiatric symptoms and was considered a primary treatment target. Mr. A was initially treated with fluoxetine, up to 60 mg/day, for more than a year, along with quetiapine, 300 mg/day (for 8 weeks), clozapine, 200 mg/day (for 8 weeks), topiramate, 75 mg/day (for 6 weeks), and clonazepam, up to 6 mg/day (for 12 months), all employed as augmentation strategies for fluoxetine in a sequential fashion and after adequate periods of treatment. Unfortunately, though, Mr. A reported no significant improvement of his symptoms.

In an attempt to treat Mr. A's drug-resistant self-mutilation, a soft mouth guard was employed to prevent the destruction of perioral soft tissues. Surprisingly, not only did this strategy result in the remission of self-injurious behaviors but it also improved other psychiatric symptoms, including phonic tics, obsessive-compulsive symptoms, and lack of initiative. After using his mouth guard, Mr. A resumed several of his daily activities, such as getting in touch with his friends or even going to the beach. He displayed fewer phonic tics and became less preoccupied with daytime schedules.

The predilection of atrophy in the head of the caudate nucleus argues for a particular vulnerability of this part of the striatum in neuroacanthocytosis⁹ and is in agreement with the complex psychiatric syndrome presented by our patient. In fact, the disorders referred to in this report (i.e., impulsive aggres-

sion [self-mutilation], tics, OCD, and abulia) have each been linked to a dysfunctional medial striatum.¹⁰

It has been suggested that OCD in patients with neuroacanthocytosis may respond favorably to selective serotonin reuptake inhibitors.¹¹ Unfortunately, our case study suggests that this pattern of response may not be consistent, particularly when self-mutilation behaviors and tics dominate the clinical picture. Although the mouth-guard strategy was reported to be successful in the management of other disorders associated with oral self-mutilation (e.g., Lesch-Nyhan syndrome),¹² we are not aware of its previous use in neuroacanthocytosis.

While the mouth guard might have relieved tic-related sensory phenomena,¹³ thereby reducing lip biting and phonic tics, we cannot exclude the possibility that resumption of normal activities was simply due to reduced social embarrassment ascribable to an alleviation of these symptoms. As noted, the mitigation of abnormal movements through the modulation of sensory input in tics and/or other basal ganglia disorders has been suggested to occur in the use of botulinum toxin for tics¹⁴ and restless legs syndrome¹⁵ and is argued to account for the phenomenon of *geste antagoniste* in the dystonia.¹⁶ Finally, the decrease of OCD and abulia suggests that these symptoms may constitute an epiphenomenon of the unbearable self-mutilation behaviors often found in neuroacanthocytosis.

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Leonardo F. Fontenelle, M.D., Ph.D.

Department of Psychiatry and Mental Health

Marco Antônio Araújo Leite, M.D.

Department of Clinical Medicine (Neurology)

Fluminense Federal University

Niterói-RJ, Brazil

The Continuum Hypothesis of Mood Disorders

Sir: The recent (November 2007) article by Laursen et al.¹ tested the continuum between mood and psychotic disorders. The authors state that, using “selected risk factors” (i.e., some family, environmental, and birth variables), “differences between the phenotypes were quantitative rather than qualitative”^(p1673) but that differences between genders and between “age-specific incidences” favored instead the Kraepelinian dichotomy^{2,3} (between “manic-depressive insanity,” including most DSM-IV-TR mood disorders, and “dementia praecox,” including several DSM-IV-TR psychotic disorders). The variables chosen are questionable. Among classic diagnostic validators,^{4–7} age at onset, boundaries between syndromes (i.e., bimodal distribution of distinguishing features), course, psychometric (multivariate) analyses, and, most of all, psychiatric family history (in this case, of bipolar, unipolar, psychotic disorders) figure prominently. The “environmental” variables used by the authors seem weak when compared with these classic validators, allowing one to question the authors’ speculations about the continuum/dichotomy hypotheses resulting from “quantitative” (and not “qualitative”) differences found.

The only variable close to the classic validators is “age-specific incidence of admission,” for which the greatest difference between unipolar and bipolar disorders was found.¹ On this basis, the continuum between mood and psychotic disorders was questioned, while there was a close similarity between unipolar disorder and schizophrenia in distributions of age-specific incidence of admission.¹ Paradoxically, the Kraepelinian dichotomy was questioned by using age at onset in this study,¹ which was similar between “manic-depressive insanity” and “dementia praecox” (most onsets between age 20 and 30 years).^{2,3}

At the end of the article, the authors’ speculations lead to the unipolar-bipolar division (a DSM-IV-TR division, not a Kraepelin one). This categorical distinction, championed by Angst and others in the 1960s, was mainly based on age at onset, recurrences, and differences in family history of mania.^{4,5} At that time, bipolar II disorder was not diagnosed. Recent reviews and research articles (e.g., references 8–20) have shown that the basic requirement of a clear boundary (i.e., bimodality) between unipolar major depressive disorder (MDD) and bipolar II disorder was not met by diagnostic validators such as age at onset, bipolar family history, and recurrences. A dose-response relationship was found between bipolar family history loading and number of hypomanic symptoms during depression (i.e., mixed depression) in bipolar II disorder and MDD.¹⁹ A significant subgroup of patients with mixed MDD had an age at onset and a

bipolar family history loading closer to those of bipolar disorders than to that of MDD.^{8–10,16} Furthermore, age at onset did not have the expected bimodal distribution between bipolar II disorder and MDD.¹⁷

An overlap between a significant proportion of MDD patients and bipolar II disorder patients was shown on the same classic diagnostic validators that had supported the splitting between bipolar I disorder and MDD.^{7–11,14,16,20} Co-occurrence of manic/hypomanic symptoms and depression (mixed depression) and of depressive symptoms in mania/hypomania (mixed mania/hypomania) by itself causes one to question any boundary between mood disorders.^{12,13,16,18,20} Mixed states (i.e., mania/hypomania and depression symptoms/syndromes co-occurring in the same episode) strongly support Kraepelin’s unitary view of “manic-depressive insanity.”

Bipolar II disorder and mixed depression may bridge the gap between bipolar I disorder and MDD, supporting a continuum of mood disorders that is further supported by the grading of manic/hypomanic/depressive symptoms in the community and in the longitudinal course of bipolar I/II and MDD.^{7,21–25} On these stronger grounds, preliminary conclusions on the continuum of mood disorders could be reached.

Dr. Benazzi reports no financial affiliation or other relationship relevant to the subject of this letter.

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Franco Benazzi, M.D., Ph.D.
Hecker Psychiatry Research Center
University of California at San Diego
Collaborating Research Center
Forli, Italy

Dr. Laursen and Colleagues Reply

Sir: We thank Dr. Benazzi for his interesting comments on the findings in our article.¹ Psychiatric family history and course of the disorder are, as Dr. Benazzi states, among the more “classic” validators. In previous publications, using the same cohort, we have examined psychiatric family history as a risk factor. We found an overlap between bipolar disorder (ICD-8²: 296.19 or 296.39; ICD-10³: F30 or F31) and schizophrenia (ICD-8: 295 [excluding 295.79], ICD-10 F20) in that bipolar disorder in family members was a risk factor for developing schizophrenia and vice versa. Results suggested a genetic and/or environmental overlap, with schizoaffective disorder being an “intermediate” form.⁴ Furthermore, we have examined course/outcome, represented by mortality, after admission with severe mental disorders and found excess mortality in persons with the disorders. However, we also found differences in mortality rates in patients with bipolar disorder and schizophrenia.⁵ Those results could again suggest an overlap between bipolar disorder and schizophrenia.

Our intentions in the current article¹ were therefore to pursue the possible overlap by describing the incidence and overlap between schizophrenia and affective disorders and to compare other “environmental” risk factors in the same cohort using nation-based numbers. Comparisons of incidence and risk factors for disorders have often been made in different cohorts, but are very problematic due to, e.g., different age and gender com-

position and methodological differences. The Danish national registers are unique sources of information^{6,7} that allow the possibility of investigating several diseases in large cohorts over large time spans. However, register-based research, of course, has its limitations, one of them being the limited clinical information on each of the cases.

We hence agree that the variables chosen in the article are not the “classical” validators to examine overlap between disorders. We did, however, find that many patients had more than one of the disorders and that some risk factors were shared, again suggesting a possible overlap or even a continuum.

Our conclusion was therefore that results were not conflicting when held up against other models (such as the continuum model). However, with the variables available and the setup used in this particular article,¹ we did not find strong enough evidence to disregard the Kraepelinian dichotomization—*not* saying that the continuum model is not correct.

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The authors report no other financial affiliations or relationships relevant to the subject of this letter.

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Thomas Munk Laursen, M.Sc., Ph.D.

Trine Munk-Olsen, M.Sc., Ph.D.

National Centre for Register-Based Research
University of Aarhus
Aarhus, Denmark

Merete Nordentoft, M.P.H., Ph.D.

Department of Psychiatry
Bispebjerg Hospital
Copenhagen, Denmark

Preben Bo Mortensen, D.M.Sc.

National Centre for Register-Based Research
University of Aarhus
Aarhus, Denmark

Atomoxetine-Associated Hemospermia: A Case Report

Sir: Atomoxetine is the only nonstimulant medication approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. Since its approval in 2002, it has been widely prescribed and has been associated with a low overall incidence of adverse effects. The 4 most common adverse effects include dry mouth, insomnia, nausea, and erectile dysfunction.¹ The following case report describes a novel adverse effect associated with atomoxetine—hemospermia.

Case report. Mr. A, a 24-year-old man, was first noted to have problems with inattention, impulsiveness, and hyperactivity at age 4. He was officially given a diagnosis of ADHD in first grade and was prescribed methylphenidate. The patient derived variable benefit from methylphenidate, a benefit that seemed to wane over time. When he had difficulty adjusting to higher doses (up to 20 mg twice daily), his parents elected to discontinue the medication altogether. Fortunately, the patient was able to compensate for his ADHD symptoms without pharmacotherapy, eventually graduating from college with a 3.4 grade point average.

After college, Mr. A took a job as a scientific research assistant in a high-profile laboratory, where he no longer felt able to compensate for his symptoms of ADHD. He noted increased forgetfulness, inattention, fidgety behavior, and distractibility. He was prescribed atomoxetine in 2006. Once he reached the target dosage of 80 mg daily (after about 4 weeks), the patient reported significant improvement in job performance with heightened attention and concentration. However, he also noted the emergence of a rather distressing adverse effect, hemospermia. He discontinued atomoxetine after 6 weeks of treatment, and the hemospermia rapidly resolved.

The patient's ADHD symptoms continued, so he was prescribed 30 mg of extended-release dextroamphetamine/amphetamine within 3 days, which caused heart palpitations; this treatment was discontinued after about 2 weeks. Approximately 2 weeks later, he was given a trial of 300 mg extended-release bupropion, which had no effect on his symptoms. Bupropion was discontinued after 8 weeks. After much deliberation, he decided to restart atomoxetine immediately after cessation of bupropion treatment. Once again, his ADHD symptoms improved dramatically, but the hemospermia returned. Urologic consultation was obtained, and infectious and inflammatory etiologies for the hemospermia were ruled out. The patient's prostate was nontender and of normal size.

Quickly thereafter, the patient discovered that his symptoms of hemospermia could be controlled if he waited at least 11 hours after his morning dose of atomoxetine to engage in sexual activity. This behavioral modification allowed him to stay on atomoxetine treatment while virtually eliminating the hemospermia.

To the best of my knowledge, this is the first report of atomoxetine-associated hemospermia in the literature. Hemospermia (also called hematospermia) is traditionally defined as the macroscopic presence of blood in the semen, typically recognized during the terminal orgasmic phase of sexual activity. It is a relatively rare condition that tends to be benign and self-limiting in the majority of cases,² yet it can be quite distressing to affected patients and their sexual partners.

The pathophysiologic link between atomoxetine and hemospermia is speculative. However, given existing data support for the role of increased norepinephrine as a possible mediator in

erectile dysfunction,³ it is likely that selective norepinephrine reuptake inhibition from atomoxetine is the culprit for hemospermia as well. In the case described, the patient demonstrated an ability to overcome the hemospermia by waiting to engage in sexual activity until well beyond atomoxetine's 5.2-hour average half-life.⁴ This suggests that perhaps once-daily, early-morning dosing of atomoxetine, combined with restricting sexual activity until beyond 2 half-lives of the medication, eliminates the threat of atomoxetine-related hemospermia.

Dr. Raj reports no financial affiliation or other relationship relevant to the subject of this letter.

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Y. Pritham Raj, M.D.

Departments of Internal Medicine and Psychiatry
Oregon Health & Science University
Portland, Oregon

Parkinsonism and Akathisia With Quetiapine: Three Case Reports

Sir: Quetiapine, a dibenzothiazepine derivative produced by altering the structure of the clozapine molecule, has been shown to have low to moderate affinity for the D₁, D₂, 5-HT_{1A}, and 5-HT_{2A} receptors and moderate to high affinity for the α₁- and α₂-adrenergic receptors.¹ Due to this receptor profile, quetiapine has been claimed to have a low incidence of extrapyramidal side effects. Large controlled trials have also shown that quetiapine is associated with placebo-level extrapyramidal side effects and akathisia in schizophrenia and bipolar disorder.^{2,3} However, evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness suggests that there is no difference in the incidence of extrapyramidal side effects and akathisia between quetiapine, olanzapine, and risperidone.⁴ A few case reports of akathisia, dystonia, and tardive dyskinesia with quetiapine have been published over the years^{1,5-8}; however, there is no literature in relation to parkinsonism with quetiapine. We report 2 cases of parkinsonism and 1 case of akathisia with quetiapine.

Case 1. Ms. A, a 14-year-old girl, presented in April 2007 with an acute-onset illness of 4 weeks' duration that was not preceded by any stressors, was continuous and fluctuating in nature, and was characterized by overcheerfulness, overactivity, grandiosity, incoherent speech with singing, occasional fearfulness, auditory hallucinations, visual hallucinations, reduced sleep, and increased appetite. Initially, she was treated with risperidone 1 mg/day and alprazolam 0.5 mg/day (both in tablet form), with which she showed significant improvement in all symptoms over a 1-week period. Her family stopped the medi-

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Rahul Bharadwaj, M.D.
Sandeep Grover, M.D.

Department of Psychiatry
Postgraduate Institute of
Medical Education and Research
Chandigarh, India

Transcranial Magnetic Stimulation: Clinical Applications Beyond Depression

Sir: Janicak et al.¹ in their recent study have provided clear and excellent evidence in support of the use of transcranial magnetic stimulation for the treatment of major depressive disorder. The results of the study support the results of a recent study by Anderson et al.,² who showed that transcranial magnetic stimulation is more effective than sham treatment for the treatment of patients with depression. Interestingly, transcranial magnetic stimulation is increasingly being used for the management of various neurologic disorders as well as psychiatric disorders besides depression.

Transcranial magnetic stimulation has been shown to be effective in the management of panic disorder in patients with underlying major depression.³ Repetitive transcranial magnetic stimulation improves auditory hallucinations in patients with schizophrenia⁴ and is also effective in improving movement scores as well as depression scores in patients with neurologic disorders such as Parkinson's disease.⁵ Repetitive transcranial magnetic stimulation is also effective in the treatment of levodopa-induced dyskinesias in patients with Parkinson's disease.⁶

Recent studies support the application of transcranial magnetic stimulation in the management of Tourette syndrome. For instance, Mantovani et al.⁷ reported 2 cases, both of whom were treated with repetitive transcranial magnetic stimulation of the supplementary motor area. At the end of 2 weeks of treatment, both patients demonstrated significant improvement on the Yale Global Tic Severity Scale, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Yale-Brown Obsessive Compulsive Scale.

Repetitive transcranial magnetic stimulation over the parietal and temporal lobes is also effective in improving symptoms of tinnitus.⁸ Centonze et al.⁹ in a recent study have shown that transcranial magnetic stimulation is effective in decreasing spasticity in patients with multiple sclerosis. Repetitive sub-threshold transcranial magnetic stimulation applied at 10 Hz also significantly decreases pain scores in patients with chronic neuropathic pain.¹⁰

Clearly, transcranial magnetic stimulation is a major development in the field of psychiatry as well as neurology. Hopefully, the next few years will see more extensive and larger studies to expand the role of transcranial magnetic stimulation in the management of other neurologic and psychiatric disorders besides depression.

Dr. Kapoor is no longer affiliated with the University of Illinois at Chicago. Dr. Kapoor reports no financial or other relationship relevant to the subject of this letter.

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Shailendra Kapoor, M.D.
University of Illinois at Chicago
Chicago, Illinois

Dr. Rado and Colleagues Reply

Sir: We agree with Dr. Kapoor's assessment regarding the growing number of psychiatric and neurologic disorders for which transcranial magnetic stimulation (TMS) is proving

useful. Of note, the recently published study of TMS was the largest (N = 302) randomized, sham-controlled trial to demonstrate efficacy in patients with major depression.¹ Further, the treatment modality was well tolerated by a majority of patients, with a low incidence of side effects and a low discontinuation rate.² Patients with acute bipolar mania and posttraumatic stress disorder have also experienced a reduction in their symptoms following TMS treatment.^{3,4}

TMS has also shown utility in substance dependence. For example, Camprodon et al.⁵ demonstrated a decrease in cocaine craving in addicted patients following 1 session of TMS. Administration of TMS has also been associated with decreased nicotine craving and cigarette smoking.^{6,7}

We predict that larger, well-designed studies will better characterize the potential role of TMS for various neuropsychiatric disorders.

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Jeffrey T. Rado, M.D.
Sheila Dowd, Ph.D.

Philip G. Janicak, M.D.
Rush University Medical Center
Chicago, Illinois