

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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REFERENCES

1. Danek A, Jung HH, Melone MA, et al. Neuroacanthocytosis: new developments in a neglected group of dementing disorders. *J Neurol Sci* 2005;229-230:171-186
2. Dobson-Stone C, Velayos-Baeza A, Filippone LA, et al. Chorein detection for the diagnosis of chorea-acanthocytosis. *Ann Neurol* 2004;56(2):299-302
3. Danek A, Sheesley L, Tierney M, et al. Cognitive findings in patients with chorea-acanthocytosis. *J Int Neuropsychol Soc* 2003; 9:528
4. Bruneau MA, Lesperance P, Chouinard S. Schizophrenia-like presentation of neuroacanthocytosis. *J Neuropsychiatry Clin Neurosci* 2003;15(3):378-380
5. Miranda M, Castiglioni C, Frey BM, et al. Phenotypic variability of a distinct deletion in McLeod syndrome. *Mov Disord* 2007;22: 1358-1361
6. Lim SY. Oro-facial dyskinesias and obsessive compulsive disorder. *J Clin Neurosci* 2006;13(10):1018; discussion 1070
7. Saiki S, Hirose G, Sakai K, et al. Chorea-acanthocytosis associated with Tourettism. *Mov Disord* 2004;19(7):833-836
8. Walker RH, Liu Q, Ichiba M, et al. Self-mutilation in chorea-acanthocytosis: Manifestation of movement disorder or psychopathology? *Mov Disord* 2006;21(12):2268-2269
9. Henkel K, Danek A, Grafman J, et al. Head of the caudate nucleus is most vulnerable in chorea-acanthocytosis: a voxel-based morphometry study. *Mov Disord* 2006;21(10):1728-1731
10. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 2002;53(2): 647-654
11. Habermeyer B, Fuhr P, Hiss B, et al. Obsessive-compulsive disorder due to neuroacanthocytosis treated with citalopram: a case report. *Pharmacopsychiatry* 2006;39(5):193-194
12. Cusumano FJ, Penna KJ, Panossian G. Prevention of self-mutilation in patients with Lesch-Nyhan syndrome: review of literature. *ASDC J Dent Child* 2001;68(3):175-178
13. Miguel EC, do Rosario-Campos MC, Prado HS, et al. Sensory phenomena in obsessive-compulsive disorder and Tourette's disorder.

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- J Clin Psychiatry 2000;61(2):150–156
- Marras C, Andrews D, Sime E, et al. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001;56(5):605–610
 - Kushida CA. Botulinum toxin A: new hope for RLS? *J Clin Sleep Med* 2006;2(3):279–280
 - Lo SE, Gelb M, Frucht SJ. Geste antagonists in idiopathic lower cranial dystonia. *Mov Disord* 2007;22(7):1012–1017

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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.

REFERENCES

- Laursen TM, Munk-Olsen T, Nordentoft M, et al. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort. *J Clin Psychiatry* 2007 Nov;68(11):1673–1681
- Kraepelin E. Dementia praecox and paraphrenia. In: *Text Book of Psychiatry*. 8th ed. Barclay RM, trans. Edinburgh, Scotland: E & S Livingstone; 1919:226
- Kraepelin E. Manic-depressive insanity and paranoia. In: *Text Book of Psychiatry*. 8th ed. Barclay RM, trans. Edinburgh, Scotland: E & S Livingstone; 1921:168
- Goodwin FK, Jamison KR. *Manic-Depressive Illness*. 2nd ed. New York, NY: Oxford University Press; 2007
- Winokur G, Tsuang MT. *The Natural History of Mania, Depression, and Schizophrenia*. Washington, DC: American Psychiatric Press; 1996
- Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry* 2003;160:4–12
- Angst J. The bipolar spectrum. *Br J Psychiatry* 2007 Mar;190:189–191
- Benazzi F. Bipolar disorder—focus on bipolar II disorder and mixed depression. *Lancet* 2007 Mar;369(9565):935–945
- Benazzi F. Is there a continuity between bipolar and depressive disorders? *Psychother Psychosom* 2007;76(2):70–76
- Benazzi F. Mood patterns and classification in bipolar disorder. *Curr Opin Psychiatry* 2006 Jan;19(1):1–8
- Cassano GB, Rucci P, Frank E, et al. The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. *Am J Psychiatry* 2004 Jul;161(7):1264–1269
- Swann AC, Gerard Moeller F, Steinberg JL, et al. Manic symptoms and impulsivity during bipolar depressive episodes. *Bipolar Disord* 2007;9:206–212
- Bauer MS, Simon GE, Ludman E, et al. “Bipolarity” in bipolar disorder: distribution of manic and depressive symptoms in a treated population. *Br J Psychiatry* 2005;187:87–88
- Akiskal HS, Akiskal KK, Lancrenon S, et al. Validating the bipolar spectrum in the French National EPIDEP Study: overview of the phenomenology and relative prevalence of its clinical prototypes. *J Affect Disord* 2006;96:197–205
- Suppes T, McElroy SL, Altshuler LL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Bipolar Treatment Network: a sex-specific phenomenon.

- Arch Gen Psychiatry 2005;62:1089–1096
16. Benazzi F, Akiskal HS. How best to identify a bipolar-related subtype among major depressive patients without spontaneous hypomania: superiority of age at onset criterion over recurrence and polarity? *J Affect Disord* 2008 Apr;107(1–3):77–88
 17. Benazzi F. Does age at onset support a dimensional relationship between bipolar II disorder and major depressive disorder? *World J Biol Psychiatry* 2007;8:105–111
 18. Benazzi F. Challenging the unipolar-bipolar division: does mixed depression bridge the gap? *Prog Neuropsychopharmacol Biol Psychiatry* 2007 Jan;31(1):97–103
 19. Akiskal HS, Benazzi F. The DSM-IV and ICD-10 categories of recurrent [major] depressive and bipolar II disorders: evidence that they lie on a dimensional spectrum. *J Affect Disord* 2006;92:45–54
 20. Ghaemi SN, Baldessarini RJ. The manic-depressive spectrum and mood stabilization: Kraepelin's ghost. *Psychother Psychosom* 2007; 76:65–69
 21. Angst J, Gamma A, Benazzi F, et al. Toward a re-definition of sub-threshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord* 2003;73: 133–146
 22. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007;64:543–552
 23. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002;59:530–537
 24. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003;60:261–269
 25. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry* 1998;55:694–700

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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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REFERENCES

1. Laursen TM, Munk-Olsen T, Nordentoft M, et al. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort. *J Clin Psychiatry* 2007 Nov;68(11): 1673–1681
2. World Health Organization. *Klassifikation af sygdomme; Udvidet dansk-latinsk udgave af verdenssundhedsorganisationens internationale klassifikation af sygdomme. 8 revision, 1965* [Classification of Diseases: Extended Danish-Latin Version of the World Health Organization International Classification of Diseases, 8th revision, 1965]. 1st ed. Copenhagen, Denmark: Danish National Board of Health; 1971
3. World Health Organization. *WHO ICD-10: Psykiske lidelser og adfærdsmæssige forstyrrelser. Klassifikation og diagnosekriterier* [WHO ICD-10: Mental and Behavioural Disorders. Classification and Diagnostic Criteria]. Copenhagen, Denmark: Munksgaard Danmark; 1994
4. Laursen TM, Labouriau R, Licht RW, et al. Family history of psychiatric illness as a risk factor for schizoaffective disorder: a Danish register-based cohort study. *Arch Gen Psychiatry* 2005 Aug;62(8): 841–848
5. Laursen TM, Munk-Olsen T, Nordentoft M, et al. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 2007 Jun;68(6):899–907
6. Frank L. Epidemiology: when an entire country is a cohort. *Science* 2000 Mar;287(5462):2398–2399
7. Frank L. Epidemiology: the epidemiologist's dream: Denmark. *Science* 2003 Jul;301(5630):163

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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.

REFERENCES

- Adler L, Dietrich A, Reimherr FW, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. *Ann Clin Psychiatry* 2006 Apr-Jun;18(2):107-113
- Ahmad I, Krishna NS. Hemospermia. *J Urol* 2007 May;177(5):1613-1618
- Seftel A. Cavernous and systemic plasma levels of norepinephrine and epinephrine during different penile conditions in healthy men and patients with erectile dysfunction [abstract]. *J Urol* 2002 Aug;168(2):866
- Atomoxetine Full Prescribing Information. Indianapolis, Ind: Eli Lilly and Co; 2008. Available at: <http://pi.lilly.com/us/strattera-pi.pdf>. Accessed Nov 2, 2007

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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 α_1 - and α_2 -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-

cation, thinking that the patient had recovered. Following the stoppage of medication, a relapse of symptoms occurred, with the patient requiring admission.

Mental status examination at the admission revealed increased psychomotor activity, overcheerfulness, incoherent speech, echolalia, echopraxia, and auditory hallucinations of discussions about the patient. The DSM-IV diagnosis of mania with psychotic symptoms made at the initial admission was kept. Results of investigations in the form of hemogram, liver and renal function tests, thyroid function tests, electrocardiogram (ECG), and chest x-ray were normal. The patient was initially treated with risperidone 1 mg/day, which was increased to 2 mg/day. With this, she developed marked rigidity of the limbs, tremors of the hands, sialorrhea, masking of facies, and a decreased arm swing, without much improvement in psychopathology. Risperidone treatment was stopped, and quetiapine (in tablet form) was started in a dose of 25 mg/day and increased over a 2-week period to 150 mg/day. Over these 2 weeks, parkinsonian symptoms decreased and disappeared. As Ms. A's psychiatric symptoms continued, the dose of quetiapine was increased to 200 mg/day after 1 week. At 200 mg/day, tremors of the hand and cogwheel rigidity reappeared. Over the period, the parkinsonian symptoms worsened, and there was a decrease in arm swing and masking of facies. However, her psychotic symptoms responded to quetiapine 200 mg/day. Trihexyphenidyl was started at 2 mg/day. Within 1 week, rigidity, tremors, and masking of facies disappeared.

Case 2. Ms. B, a 37-year-old housewife, presented in May 2007 with an insidious-onset illness of 5 years' duration that had no precipitating factor and had a continuous and fluctuating course characterized by suspiciousness, bizarre delusions, blunted affect, formal thought disorder, poor interaction with family members, decreased interest in household work, posturing, staring, and decreased sleep, self-care, and appetite. She had been treated in the past with amoxapine, paroxetine, olanzapine, venlafaxine, clozapine, imipramine, and haloperidol in varying combinations. She also had a 4-year history of generalized tonic-clonic seizures, with the last seizure 2 years before, for which she was being treated with phenytoin 300 mg/day (in tablet form).

At the index presentation, she was being treated with haloperidol 10 mg/day (in tablet form) and was found to have tremors of the hands and cogwheel rigidity in the upper extremities along with frank psychotic symptoms. A DSM-IV diagnosis of undifferentiated schizophrenia, seizure disorder, and drug-induced parkinsonism was made. On investigations, no abnormality was detected in hemogram, liver and renal function tests, or ECG. Her electroencephalogram (EEG) showed intermittent sharp and slow waves suggestive of interictal generalized seizure disorder. In liaison with the neurologist, phenytoin 300 mg/day was continued and haloperidol was stopped.

A week after haloperidol was stopped, the parkinsonian symptoms disappeared, and Ms. B was started on treatment with quetiapine 50 mg/day in tablet form, which was gradually increased to 500 mg/day over 4 weeks with increments of 50 mg every 3 to 5 days. At a dose of 500 mg/day, her psychotic symptoms improved. However, within 1 week of receiving 500 mg of quetiapine, she complained of subjective restlessness, which was worse on rest and was relieved by moving her legs while sitting or by walking. She was rated on the Barnes Akathisia Rating Scale and received a score of 2 (mild akathisia). Propranolol 40 mg/day was started, with which her restlessness resolved.

Case 3. Ms. C, a 24-year-old housewife, presented in March 2007 with an acute-onset illness of 3 months' duration that had no precipitating factor and had a continuous course character-

ized by decreased interaction, decreased speech followed by mutism, posturing, rigidity, unprovoked aggression, decreased sleep and appetite, and poor self-care. A DSM-IV diagnosis of catatonic schizophrenia was made. Results of investigations in the form of hemogram, liver and renal function tests, ECG, noncontrast computed tomography of the brain, EEG, and lipid profile were normal. She was initially treated with risperidone tablets (started at a dose of 2 mg and increased to 3 mg after 5 days) and electroconvulsive therapy.

Two weeks after starting risperidone, Ms. C was noted to have cogwheel rigidity, tremors of the hands, constipation, and pedal edema, which persisted despite a dose reduction to 2.5 mg and the addition of trihexyphenidyl 4 mg/day. Treatment with risperidone was then stopped, and treatment with quetiapine tablets was started at a dose of 50 mg/day and increased at 50-mg/day increments every week to a dose of 250 mg/day. Over the next 10 days, parkinsonian side effects and pedal edema decreased. When the patient was receiving a quetiapine dose of 200 mg/day, the parkinsonian side effects disappeared completely. However, within 1 week of Ms. C's receiving a 250-mg/day quetiapine dose, rigidity and tremors appeared again. The dose of quetiapine was decreased to 200 mg/day, with which the parkinsonian symptoms disappeared.

Various mechanisms such as higher 5-HT_{2A}/D₂ receptor antagonism, fast dissociation of quetiapine from D₂ receptors,⁹ and ability to normalize striatal tyrosine hydroxylase¹⁰ have been proposed as mechanisms by which quetiapine produces the lower incidence of extrapyramidal side effects among antipsychotics. However, recent reports have shown that akathisia, dystonia, and dyskinesia can occur with quetiapine^{1,5-8} and suggest the presence of other pathophysiologic mechanisms.

Risk factors for the development of extrapyramidal side effects with neuroleptic use include age (younger age for dystonia and older age for parkinsonism), male gender, history of extrapyramidal symptoms with past neuroleptic use, presence of affective symptoms, use of high-potency neuroleptic medications, high dose of medication, and parenteral administration.¹¹ In our cases, the following vulnerabilities for extrapyramidal symptoms existed: presence of affective symptoms (first case) and history of extrapyramidal symptoms with neuroleptic use (all cases). Further, development of extrapyramidal symptoms with lower doses of quetiapine may also be due to low levels of cytochrome P450 3A4 enzymes, which metabolize quetiapine, in these subjects.

These cases demonstrate 2 important facts. First, quetiapine can cause parkinsonism and akathisia, and second, the propensity to develop these side effects is guided not only by the type of antipsychotic but also by risk factors for the development of extrapyramidal symptoms. Hence, in the presence of vulnerability factors, the target dose of antipsychotics should be achieved by gradual titration and close monitoring for the development of these side effects.

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

REFERENCES

1. Habermeyer B, Rabovsky K, Jentsch C, et al. Cervical dystonia due to interaction of valproic acid and quetiapine. *J Clin Psychopharmacol* 2007 Aug;27(4):396-397
2. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 1997 Aug;42(4):233-246
3. Nasrallah HA, Brecher M, Paulsson B. Placebo-level incidence of

- extrapyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. *Bipolar Disord* 2006 Oct;8(5 pt 1):467–474
4. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry* 2007 Mar;164(3):415–427
 5. Catalano G, Grace JW, Catalano MC, et al. Acute akathisia associated with quetiapine use. *Psychosomatics* 2005 Jul–Aug;46(4):291–301
 6. Desarkar P, Sinha VK. Quetiapine-induced acute dystonia and akathisia. *Aust N Z J Psychiatry* 2006 Jun–Jul;40(6–7):607–608
 7. Ghelber D, Belmaker RH. Tardive dyskinesia with quetiapine. *Am J Psychiatry* 1999 May;156(5):796–797
 8. Ghaemi SN, Ko JY. Quetiapine-related tardive dyskinesia. *Am J Psychiatry* 2001 Oct;158(10):1737
 9. Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 2002 Feb;47(1):27–38
 10. Zhang Y, Xu H, He J, et al. Quetiapine reverses altered locomotor activity and tyrosine hydroxylase immunoreactivity in rat caudate putamen following long-term haloperidol treatment. *Neurosci Lett* 2007 Jun;420(1):66–71
 11. American Psychiatric Association. Practice Guidelines for the Treatment of Schizophrenia. In: Practice Guidelines for the Treatment of Psychiatric Disorders. Washington DC: American Psychiatric Association; 2000:299–412

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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.

REFERENCES

1. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry* 2008 Feb;69(2):222–232
2. Anderson IM, Delvai NA, Ashim B, et al. Adjunctive fast repetitive transcranial magnetic stimulation in depression. *Br J Psychiatry* 2007 Jun;190:533–534
3. Mantovani A, Lisanby SH, Pieraccini F, et al. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of panic disorder (PD) with comorbid major depression. *J Affect Disord* 2007 Sep;102(1–3):277–280
4. Stanford AD, Sharif Z, Corcoran C, et al. rTMS strategies for the study and treatment of schizophrenia: a review. *Int J Neuropsychopharmacol* 2008 Feb;11:563–576
5. Epstein CM, Evatt ML, Funk A, et al. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. *Clin Neurophysiol* 2007 Oct;118(10):2189–2194
6. Wagle-Shukla A, Angel MJ, Zadikoff C, et al. Low-frequency repetitive transcranial magnetic stimulation for treatment of levodopa-induced dyskinesias. *Neurology* 2007 Feb;68(9):704–705
7. Mantovani A, Leckman JF, Grantz H, et al. Repetitive transcranial magnetic stimulation of the supplementary motor area in the treatment of Tourette syndrome: report of two cases [letter]. *Clin Neurophysiol* 2007 Oct;118(10):2314–2315
8. Khedr EM, Rothwell JC, Ahmed MA, et al. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. *J Neurol Neurosurg Psychiatry* 2008 Feb;79(2):212–215
9. Centonze D, Koch G, Versace V, et al. Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. *Neurology* 2007 Mar;68(13):1045–1050
10. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, et al. Motor cortex rTMS in chronic neuropathic pain: pain relief is associated with thermal sensory perception improvement. *J Neurol Neurosurg Psychiatry* 2008 Jan 25 [epub ahead of print]

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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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REFERENCES

1. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007 Dec;62(11):1208–1216
2. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry* 2008 Feb;69(2):222–232
3. Michael N, Erfurth A. Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. *J Affect Disord* 2004 Mar;78(3):253–257
4. Khurshid KA, Janicak PG. Treating neuropsychiatric disorders other than depression using transcranial magnetic stimulation. *Psychiatr Ann* 2005;35(2):147–158
5. Camprodon JA, Martinez-Raga J, Alonso-Alonso M, et al. One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug Alcohol Depend* 2007 Jan;86(1):91–94
6. Eichhammer P, Johann M, Kharraz A, et al. High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. *J Clin Psychiatry* 2003 Aug;64(8):951–953
7. Johann M, Wiegand R, Kharraz A, et al. Transcranial magnetic stimulation for nicotine dependence [in German]. *Psychiatr Prax* 2003 May;30(suppl 2):S129–S131

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