

Mood-Stabilizing Effect of Twice-Weekly Administration of Fluoxetine in a Bipolar II Disorder Patient

Sir: Bipolar II disorder is a valid and reliable diagnosis^{1,2} and its prevalence in society is higher than was once assumed.³ Considering the fact that the main clinical presentation of bipolar II disorder is composed of depressive symptoms and the fact that the retrospective diagnosis of episodes of hypomania is often difficult,⁴ there has been an increased concern about the underdiagnosis of bipolar II disorder in clinical practice in recent years,^{5,6} and suggestions have been put forward in order to reach correct diagnosis.⁴ Nevertheless, treatment guidelines for bipolar disorders are mainly based on findings of research on bipolar I disorder patients, and most bipolar II disorder treatment algorithms are not grounded in strong experimental findings.⁷ Moreover, according to existing evidence, not only are the clinical pictures and courses of bipolar I disorder and bipolar II disorder different,³ there are also clear differences with regard to treatment response, such as a lower incidence of switch to hypomania with antidepressants⁸ and even a case report of the mood stabilizing effect of selective serotonin reuptake inhibitors in bipolar II disorder.⁹ Therefore, a case is presented here with the aim of introducing a new method of fluoxetine administration in the treatment of bipolar II disorder.

Case report. Mr. A was a 21-year-old single male student who had come to the Tehran Psychiatric Institute clinic with the complaint of anxiety and anger in April 2003. In the psychiatric assessment, no symptoms of a typical mood episode were identified. However, a thorough history revealed that Mr. A had experienced frequent cycles of hypomania (at least once per month, usually lasting for 2–5 days) and had also experienced, for the first time, an episode of major depression lasting about a month and ending only a few days before the assessment. Also, he had been under treatment with fluoxetine 10 mg/day for 10 days, and his depressive symptoms had decreased during this period. There was no history of major psychiatric disorders in Mr. A's first-degree relatives, but one of his cousins had bipolar II disorder (which was confirmed during clinical interview).

After a diagnosis of bipolar II disorder (based on DSM-IV-TR criteria), sodium valproate was prescribed, and its dosage was gradually increased to 600 mg/day (with a serum level of 52 µg/mL). Fluoxetine was also discontinued. With the relief of anxiety and anger, the situation of Mr. A was significantly improved. This improvement continued until the end of June, but at his next attendance in the month of July, it became evident that, after experiencing symptoms of depression, Mr. A had experienced mood elevation, as well as an increase in energy, libido, and appetite. The dosage of sodium valproate was increased to 800 mg/day (serum level 89 µg/mL) and Mr. A's mood improved in 1 week. In most of his monthly appointments until the end of March 2004, he would complain of heightened libido (without an apparent heightened mood) and unreasonable arguments with his parents.

In April 2004, Mr. A presented with symptoms of depressed mood, thoughts of death, hopelessness, decreased energy, change in sleep-wake pattern, and an increased appetite. Fluoxetine 10 mg/day was added to sodium val-

proate. After 3 weeks, even though thoughts of death had decreased, other depressive symptoms, in addition to hypersomnia, were present. The dosage of fluoxetine was increased to 20 mg/day, and the depression improved after several weeks. In June 2004, Mr. A again complained about elevated mood and increased libido and his behavior in seeking many girlfriends. Fluoxetine was discontinued; after 1 month his mood was normal, and the complaint of increased libido was resolved.

After failing some university courses, Mr. A presented with symptoms of depressed mood, decreased interests, lack of motivation, and sleep-wake cycle reversal in September 2004. Fluoxetine 20 mg/day was again added to sodium valproate. Monthly assessments thereafter indicated a relative improvement of the patient. However, Mr. A discontinued fluoxetine in January 2005 and presented with a relapse of depressive symptoms after 1 month. Depression was improved with the addition of fluoxetine to sodium valproate once more.

Improvement in depressive symptoms under the treatment with previous doses of fluoxetine and sodium valproate continued until December 2005. However, Mr. A always complained about periodic increases in libido, often associated with elevated mood. Since the discontinuation of fluoxetine helped to normalize the patient's libido but also led to a relapse in depression, in December 2005 a combination of 20 mg twice-weekly fluoxetine and 800 mg/day sodium valproate was begun. No subsequent change was made to Mr. A's drug regimen until about 1 year later (December 2006) and he was always totally compliant with a his drug regimen. No recurrence of hypomania or depression occurred during the follow-up of the patient.

Administration of sodium valproate in this patient reduced the episodes of hypomania but could not prevent depressive episodes. The addition of fluoxetine to sodium valproate would lead to an improvement in depression, but the frequent development of hypomanic symptoms would become troublesome. Also, discontinuation of fluoxetine was associated with a relatively early relapse of depression. Twice weekly administration of fluoxetine, with an appropriate serum level of sodium valproate for more than 1 year, led to the prevention of depressive and hypomanic episodes.

Given that the elimination half-lives of fluoxetine and its metabolite norfluoxetine are 2 to 7 and 4 to 16 days, respectively,¹⁰ twice-weekly administration of this drug seems reasonable. Weekly administration of enteric-coated fluoxetine has been used for maintenance treatment of major depressive disorder^{11–15} and the maintenance therapy of panic disorder.¹⁶ Also, higher treatment compliance and lower drug side effects have been reported in patients taking weekly enteric-coated fluoxetine in comparison with those taking it daily.^{12,17} There is also a report of a bipolar I disorder patient in whom twice-weekly administration of fluoxetine has been used for treatment.¹⁸ In that instance, the patient was a 59-year-old woman under treatment with mood stabilizers and fluoxetine 10 mg/day who developed mania, and became euthymic after reducing the dosage of fluoxetine to 10 mg twice a week over an 18-day period.

In the present case, the twice-weekly administration of 20 mg of fluoxetine was effective in preventing depressive episodes and did not induce hypomania over a 1-year period, which suggests the effectiveness of this method of

fluoxetine administration as a mood stabilizing treatment in bipolar II disorder. Moreover, this case suggests the possibility of a dose-dependent effect of antidepressants on mood in patients with bipolar II disorder.

Dr. Shabani reports no financial affiliations or other relationships relevant to the subject of this letter.

REFERENCES

1. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from "unipolar" to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 1995;52:114–123
2. Coryell W, Endicott J, Maser JD, et al. Long-term stability of polarity distinctions in the affective disorders. *Am J Psychiatry* 1995;152:385–390
3. Berk M, Dodd S. Bipolar II disorder: a review. *Bipolar Disord* 2005;7:11–21
4. Benazzi F, Akiskal HS. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. *J Affect Disord* 2003;73:33–38
5. Ghaemi SN, Ko JY, Goodwin FK. "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Can J Psychiatry* 2002;47:125–134
6. Piver A, Yatham LN, Lam RW. Bipolar spectrum disorders: new perspectives. *Can Fam Physician* 2002;48:896–904
7. Amsterdam JD, Brunswick DJ. Antidepressant monotherapy for bipolar type II major depression. *Bipolar Disord* 2003;5:388–395
8. Goldberg JF, Ghaemi SN. Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression. *Bipolar Disord* 2005;7(suppl 5):3–12
9. Parker G, Tully L, Olley A, et al. SSRIs as mood stabilizers for bipolar II disorder? a proof of concept study. *J Affect Disord* 2006;92:205–214
10. Hurst M, Lamb HM. Fluoxetine: a review of its use in anxiety disorders and mixed anxiety and depression. *CNS Drugs* 2000;14:51–80
11. Schmidt ME, Fava M, Robinson JM, et al. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. *J Clin Psychiatry* 2000;61:851–857
12. Burke WJ, McArthur-Miller DA. Exploring treatment alternatives: weekly dosing of fluoxetine for the continuation phase of major depressive disorder. *J Clin Psychiatry* 2001;62(suppl 22):38–42
13. Burke WJ, Hendricks SE, McArthur-Miller D, et al. Weekly dosing of fluoxetine for the continuation phase of treatment of major depression: results of a placebo-controlled, randomized clinical trial. *J Clin Psychopharmacol* 2000;20:423–427
14. Dinan TG. Efficacy and safety of weekly treatment with enteric-coated fluoxetine in patients with major depressive disorder. *J Clin Psychiatry* 2001;62(suppl 22):48–52
15. Miner CM, Brown EB, Gonzales JS, et al. Switching patients from daily citalopram, paroxetine, or sertraline to once-weekly fluoxetine in the maintenance of response for depression. *J Clin Psychiatry* 2002;63:232–240
16. Emmanuel N, Ware MR, Brawman-Mintzer O, et al. Once-weekly dosing of fluoxetine in the maintenance of remission in panic disorder. *J Clin Psychiatry* 1999;60:299–301
17. Claxton A, de Klerk E, Parry M, et al. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. *J Clin Psychiatry* 2000;61:928–932
18. Megna JL, Devitt PJ. Treatment of bipolar depression with twice-weekly fluoxetine: management of antidepressant-induced mania. *Ann Pharmacother* 2001;35:45–47

Amir Shabani, M.D.
Mental Health Research Center
Tehran Psychiatric Institute
Tehran, Iran

Cryptococcal Meningitis With Acute Psychotic Confusion in a Sarcoid Patient

Sir: Cryptococcosis is a systemic fungal disease, usually caused by *Cryptococcus neoformans*, often transmitted by inhalation of dust or contaminated soil. The diagnosis of cryptococcal meningitis is difficult because of its various presentations. Non-HIV-contaminated patients may present brief mental confusion, coma, subacute or chronic meningitis, encephalitis, focal brain or spinal cord lesions, or mental changes.^{1–3} Sarcoidosis is an idiopathic granulomatous illness. While any organ may be involved, 90% of patients develop pulmonary disease. Sarcoidosis is associated with deficient cell-mediated immunity, because of sequestration of CD4 cells in sarcoid granulomas, anergy, and reversal of the CD4/CD8 ratio.⁴ Concurrent cryptococcal disease in sarcoid patients is not rare, even in the absence of immunosuppressive therapy, and it may be misdiagnosed as neurosarcoidosis.

Case report. Mr. A, a single, 27-year-old unemployed man, was admitted to the Medical Emergency Department at University Hospital Centre of Angers in November 2004, for nonspecific behavior disorders, which had been gradually worsening over a period of more than 1 year, and included, over the previous 24 hours, complete mutism, prostration, and two episodes of vomiting.

Mr. A used to have a moderate consumption of cannabis but stopped it when he was diagnosed with sarcoidosis in May 2004 (microscopic lesions of lymphadenopathy were typical, containing noncaseating epithelioid cell granulomas). Tuberculosis and brucellosis had been excluded. Mr. A had not been treated with steroids. He exhibited progressive social and professional withdrawal and showed increasing negligence of his personal hygiene, evoking a diagnosis of early schizophrenia. Since September 2004, Mr. A had suffered with neck pain, episodes of generalized contractures in the limbs (which resolved spontaneously), and insomnia. On November 1, 2004, his psychotic-like behavior disorders had resulted in his first hospitalization in a psychiatry department, although no specific diagnosis was made. He remained in bed and continually complained of diffuse pain. He did not have any hallucinations or delusional ideas, but his affective contact was strange, and his answers poor and sometimes inappropriate. Medical (including neurologic) examinations and standard blood tests revealed no abnormalities, except for a blood C-reactive protein (CRP) level of 38 mg/dL, attributed to sarcoidosis. An emergency brain computed tomography (CT) scan found no abnormalities. Urinary screening for drugs was negative. Twenty-four hours after being admitted to the hospital, he became asymptomatic and was discharged.

When Mr. A was admitted a second time, on November 10, 2004, he had a fever of 38.7°C and confusion, with disorientation in time and space. His answers were short and poor. He was hyperactive, with a mood disorder, alternating rapidly between euphoria and apathy. He complained of abdominal pain and had a distended bladder. On examination, he was found to have binocular diplopia and meningeal signs. Blood tests showed hyponatremia (127 mmol/L) and an inflammatory syndrome, with increased white blood cells (20,000 cells/mL), a blood CRP level of 59 mg/mL, and a high level of angiotensin convertase (44 U/L). There was hypogammaglobulinemia (IgG of 645 ng/dL). A lumbar puncture was performed, following another brain CT scan, which showed clear cerebrospinal fluid (CSF), increased CSF protein (1.14 g/dL), low CSF glucose

(<0.1 mmol/L), and 70 nucleated cells (78% polynuclear neutrophils, 12% lymphocytes). A diagnosis of cryptococcal infection was confirmed by the presence of *Cryptococcus neoformans* on direct microscopy (staining with Chinese ink) and culturing. HIV-1 and -2 serologies were negative, despite the low CD4 lymphocyte count (228 cells/mL). The other serologies performed on the CSF specimen (herpes simplex virus, chicken pox/herpes zoster virus, cytomegalovirus, and Epstein-Barr virus) were also negative. A brain magnetic resonance imaging (MRI) scan showed contrast being taken up in the meninges and signs of meningitis, but no dilatation of the ventricles or any abscess. This MRI scan allowed a diagnosis of neurosarcoidosis to be excluded. Immediate treatment was started with IV amphotericin B, which was very quickly effective, with a complete disappearance of the confusion, the mood disorder, the hyperactivity, and the behavior disorders. The treatment was continued by mouth for 4 months. The improvement continued throughout the regular follow-up, which lasted 1 year. His social reinsertion was shown by his quickly finding a job and friends.

We here report the case of a young adult with sarcoidosis who presented with fluctuating acute cryptococcal meningitis and psychotic confusion. He also presented with progressive social withdrawal over 1 year and nonspecific behavior disorders that were misinterpreted as the early phase of hebephrenic schizophrenia. A search of the literature for related case reports was conducted on MEDLINE, with *cryptococcosis*, *psychosis*, *confusional meningitis*, and *sarcoidosis* as keywords.

Sarcoidosis is considered an independent risk factor for cryptococcal infection due to the immunosuppression generally associated with it.^{4,5} The most frequent manifestations of cryptococcosis in sarcoid patients are fever (69%), headache (54%), meningismus (54%), nausea and vomiting (31%), anorexia (23%), and decreased level of consciousness (23%).⁶ The principal differential diagnosis is neurosarcoidosis with overlapping clinical and laboratory features. However, cranial nerve palsies (especially of the facial and optic nerves) are more common in neurosarcoidosis (72%) than in cryptococcal meningitis (11%). Neurosarcoid patients less frequently present with signs suggesting infectious meningitis: only 12% have meningismus, 19% fever, and 24% headache. The CSF profile is similar in neurosarcoidosis and cryptococcal meningitis, but hypoglycorrhachia is much more common in cryptococcal meningitis.^{6,7}

Cryptococcal meningitis with confusional psychosis before meningeal signs are present is rare in non-HIV-infected patients⁸ and usually mimics mood disorders (hypomania).^{9,10} This type of pseudopsychiatric history may be due to meningeal cryptococcosis with normal pressure hydrocephalus.¹¹ Laboratory investigation of the CSF, such as an Indian ink smear and fungal cultures, to detect the infective organism, and the latex agglutination test to detect the streptococcal antigen, are invaluable aids for making the correct diagnosis.¹² The test of choice for the diagnosis in HIV-negative patients is CSF cryptococcal antigen titer, which is positive in 97% of cases. Eighty-seven percent of HIV-negative patients with cryptococcal meningitis also have a positive serum cryptococcal antigen.⁴ For our patient, both acute meningitis and chronic social isolation were successfully treated with specific antifungal treatment. During the 1-year follow up, we noted a sustained improvement of all his mental functions.

This case underlines the necessity of making a careful search for subtle systemic and neurologic signs, in order to exclude organic brain syndromes, before embarking on psychiatric treatment for apparent psychosis. In particular, cryptococcal

meningitis in sarcoid patients should be excluded before neurologic disturbances by obtaining CSF samples, even when MRI findings suggest neurosarcoidosis.^{4,13}

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

REFERENCES

- Petrini B, Karlsson M, Lindqvist L. Cryptococcal meningitis should be suspected in diffuse cerebral symptoms or indistinct meningitis. *Lakartidningen* 1992;89:2584–2586
- Mitchell DH, Sorrell TC, Allworth AM, et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. *Clin Infect Dis* 1995;20:611–616
- Revest M, Decaux O, Frouget T, et al. Cryptococcal infections in non-HIV infected patients. Study of four cases and review of literature [in French]. *Rev Med Interne* 2006;27:203–208
- Ross JJ, Katz JD. Cryptococcal meningitis and sarcoidosis. *Scand J Infect Dis* 2002;34:937–939
- Botha RJ, Wessels E. Cryptococcal meningitis in an HIV negative patient with systemic sarcoidosis. *J Clin Pathol* 1999;52:928–930
- Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in HIV-negative patients in the era of effective azole therapy. *Clin Infect Dis* 2001;33:690–699
- Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis: diagnosis and management. *QJM* 1999;92:103–117
- Sa'adah MA, Araj GF, Diab SM, et al. Cryptococcal meningitis and confusional psychosis. *Tropical Geographical Medicine* 1995;47:224–226
- Tan WK, Ungvari GS, Leing CM, et al. Cryptococcal meningitis mimicking primary mania in a young female. *Gen Hosp Psychiatry* 2005;27:298–303
- Johnson FY, Naragi S. Manic episode secondary to cryptococcal meningitis in a previously healthy adult. *P N G Med J* 1993;36:59–62
- Thienhaus OJ, Khosla N. Meningeal cryptococcosis misdiagnosed as a manic episode. *Am J Psychiatry* 1984;141:1459–1460
- Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. *Infectious Society of America. Clin Infect Dis* 2000;30:710–718
- Gibold X, Husson A, Corbain V, et al. Cryptococcosse neuroméningée révélée par une baisse de l'acuité visuelle chez un patient atteint de neurosarcoidose et porteur d'une dérivation ventriculoatriale [Cryptococcal meningitis disclosed by visual loss in HIV negative patient with ventriculo-atrial shunting]. *Rev Med Interne* 2006;27:330–332

Jean-Louis Goeb, M.D.

Service de Psychiatrie de l'Enfant et de l'Adolescent
Centre Hospitalier Régional et Universitaire
Lille, France

Virginie Leon, M.D.

Centre de Santé Mentale Angevin,
Sainte Gemmes sur Loire, France

Géraldine Kechid, M.D.

Service de Psychiatrie de l'Enfant et de l'Adolescent
Centre Hospitalier Régional et Universitaire
Lille, France

Transcultural Issues in Asperger's Disorder: A Comparison of 2 Cases

Sir: Much controversy exists regarding the definition of Asperger's syndrome or disorder, both in clinical practice and in research studies. Furthermore, there is not yet agreement that Asperger's disorder is indeed a mental disorder requiring long-term support from mental health services. However, it is becoming an increasingly prevalent concept that is applied loosely to

a variety of a mental disorders ranging from schizophrenia to personality disorders.

We present 2 cases of Asperger's syndrome that demonstrate the effect of culture and ethnicity on presentation and management.

Case 1. Mr. A, who is of Asian ethnicity, is 26 years old; he presented to us for treatment at the age of 21. He is the youngest of 4 siblings, and his family history is unremarkable. His motor development and communicative milestones were normal. The family moved from Bangladesh to Britain when Mr. A was 5 years of age. He started immersing his feet in bowls of water at the age of 8 for prolonged periods of time, stating that he felt comfortable and calm. This behavior continued unchanged despite recurrent severe fungal and bacterial infections that required medical intervention. Even while he was in the hospital due to his foot infections, his behavior continued unchanged.

The patient left school at the age of 13 and never acquired useful work experience. He was subjected to racist bullying, but denied feeling traumatized by it. Currently, he lives at home and is constantly preoccupied with decorating his room. His search for symmetry was noted during his admission to the hospital and was evident when he was observed tidying up his bed and using a variety of toothpastes and toothbrushes. Although Mr. A's behavior and mood marginally improved with a combination of clomipramine 75 mg/day and amisulpride 100 mg/day during a hospital stay, his adherence to medication was poor when he was living in the community.

Mr. A always maintains good eye contact. There is no evidence of a mood disorder or ego-dystonic obsessions, nor of a paranoid process, delusions, or hallucinations. His IQ is judged to be within normal range. He lives with his family, with no noteworthy interactions with his mother, brother, or sister.

Mr. A fulfills the DSM-IV criteria for Asperger's disorder. He failed to develop peer relationships appropriate to developmental level and lacked social and emotional reciprocity. He exhibits restricted repetitive and stereotyped behavior that is abnormal in intensity and focus.

Case 2. Mr. B, who is of white ethnicity, is 27 years old; he presented to us for treatment at the age of 23. He is an only child who has normal birth and developmental histories. He was noted to have marked difficulties in peer interactions from an early age. He left home and enrolled in a university course that he was unable to conclude; for the past 12 years, he has been preoccupied with writing and amassing factual information about different topics. Mr. B always arrives at the clinic carrying his theses. His eye-to-eye gaze is markedly impaired, and he is socially isolated (always living with his father). He became preoccupied with changing the internal and external decoration of the house, but never concluded the job.

Mr. B's mental state remained stable for years, and he did not engage in mental health services. There was no evidence of significant paranoid or psychotic process over the years, but the patient did have 2 lengthy admissions to a psychiatric hospital. Mr. B fulfills the DSM-IV criteria for Asperger's disorder.

Asperger's syndrome is a Western concept characterized by impaired social interaction, restricted interests, and behaviors that is different from autism. Hans Asperger's original description of "autistic psychopathy" refers to stable personality disorder marked by social isolation.¹ The condition was not widely known to the English-speaking world until 1981, when Lorna Wing published a series of cases showing similar symptoms.² Wing's codification of the syndrome blurred the differences between Kanner's description of autism³ and Asperger's syn-

drome because of her inclusion of a small number of girls and mildly mentally retarded children, and the whole concept of Asperger's disorder became diluted and imprecise for clinical practice.

Despite the inclusion of the syndrome in the ICD-10 and DSM-IV, its nosologic status is rather uncertain. The criteria used to identify the 2 cases, DSM-IV,⁴ are widely available and used by different disciplines in identifying cases with Asperger's disorder. However, there is well-documented variation in beliefs concerning the diagnosis of autism and the use of different criteria in the West.⁵

There are some similarities in the described cases. Both patients are young men who are socially isolated and who have failed to develop meaningful peer relationships. They share obsessional behavior aimed at decorating their own living environments. Neither case displays any evidence of a mood disorder, and their longitudinal clinical histories do not suggest the presence of a psychotic process.

The influence of the patients' cultural backgrounds is evident in the specific manifestations of their restricted, repetitive, stereotyped behavior, which is central to the diagnosis. The second case is typical of the Western concept of an adult case of Asperger's syndrome. He normally avoids eye contact, often carrying masses of paperwork related to factual information he has collected about a particular subject. His educational background is probably relevant to his behavior, and many people with Asperger's syndrome are expected to continue with their education, especially if they grow up in a middle-class, protective environment.

The educational background of the Asian patient is remarkably different. He received some education in his native country and was subjected to racist bullying in his early teens, which contributed to an early conclusion of his academic development. However, the behavior of immersing the feet in water started at least 4 years earlier and might be relevant to his Muslim cultural background. Washing of the feet is required before every prayer among Sunni Muslims, and this could represent a behavior learned or observed at home. Although both of the individuals described now receive regular monitoring by social services, delivery of appropriate social support to the ethnic minority patient was previously not met by the available services.

The concept of Asperger's syndrome is rather vague and becoming increasingly diluted, and it is being applied publicly to socially isolated people. Acquiring the label of Asperger's syndrome probably confuses eligibility for services and may complicate the delivery of appropriate psychiatric services to many individuals, especially in the non-indigenous populations of a country. It might be that these people are essentially cases of stable personality disorder who are socially isolated, as outlined originally by Hans Asperger.¹

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

REFERENCES

1. Asperger H. "Autistic psychopathy" in childhood. In: Frith U, trans ed. *Autism and Asperger Syndrome*. Cambridge, UK: Cambridge University; 1991:37-92
2. Wing L. Asperger's syndrome: a clinical account. *Psychol Med* 1981;11:115-129
3. Kanner L. Autistic disturbances of affective contact. *Nerv Child* 1943;2:217-250
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American

Psychiatric Association; 1994

5. Sturmeijer P, Sevin JA. Defining and assessing autism. In: Matson JL, ed. *Autism in Children and Adults: Etiology, Assessment and Intervention*. Pacific Grove, Calif: Brooks/Cole; 1994:13–36

Sudad Jawad, M.D., F.R.C.P.I., F.R.C.Psych.
The Links Centre
Isaac O'Homba, M.B.
Whitchurch Hospital
Cardiff, Wales

Remission of Panic Disorder With Mirtazapine Augmentation of Paroxetine: A Case Report

Sir: Paroxetine is a selective serotonin reuptake inhibitor (SSRI) antidepressant with proven efficacy in the short- and long-term treatment of panic attacks with or without agoraphobia.¹ Mirtazapine is a noradrenergic and specific serotonergic antidepressant that acts by antagonizing the adrenergic α_2 -autoreceptors and α_2 -heteroreceptors, as well as by blocking serotonin 5-HT₂ and 5-HT₃ receptors. It enhances, therefore, the release of norepinephrine and 5-HT_{1A}-mediated serotonergic transmission. It has also shown efficacy and good tolerability in panic attacks, without sexual side effects, in at least 2 open-label clinical trials.^{2,3}

In depression, remission is considered to be the treatment gold standard. Rates of remission following treatment with only 1 antidepressant are usually only between 35% and 45%.⁴ In a double-blind clinical study by Tremblay,⁴ antidepressant drugs with complementary mechanisms of action on serotonin and norepinephrine were combined from treatment initiation to potentially accelerate the response and increase the remissions within a standard treatment period of 6 weeks. The combination of an SSRI and mirtazapine 30 mg/day was compared to each antidepressant alone at the same dose. The combination group showed a significantly higher remission rate (Hamilton Rating Scale for Depression [HAM-D]-17 score of < 7) and a faster onset of action compared to monotherapy. The remission rate of 52% was more than double that of an SSRI alone at 25%. In monotherapy nonresponders, the addition of the other antidepressant produced a rapid improvement.⁴

In one study⁵ of obsessive-compulsive disorder, i.e., an anxiety disorder, the SSRI-plus-mirtazapine group achieved a reduction of at least 35% in Yale-Brown Obsessive Compulsive Scale score and a "much improved" or "very much improved" rating on the Clinical Global Impressions-Improvement (CGI-I)⁶ scale from the fourth week, while the SSRI-plus-placebo group obtained these results only from the eighth week. The number of responders was higher in the combination group at the fourth week of treatment.⁵ In panic disorder, complete absence of panic attacks and a CGI-I score of 1 are considered to be indication of remission.⁷

To my knowledge, this letter is the first report of a combination strategy, i.e., augmentation of paroxetine with mirtazapine, in order to achieve remission in a patient with panic disorder.

Case report. Mr. A, a 28-year-old man, presented for his first interview in February 2006 and was diagnosed with DSM-IV panic disorder. He reported a frequency of 7 panic attacks per week, and his initial Hamilton Rating Scale for Anxiety (HAM-A)⁸ score was 25. He was treated with 20 mg/day of paroxetine, which was increased to 60 mg/day in the third week

of treatment. After 12 weeks of continuous treatment, the patient reported a decrease in frequency of panic attacks, his HAM-A score decreased more than 50%, and his CGI-I score was 2.

Although he was better, he still complained of panic attacks and anticipatory anxiety; therefore, mirtazapine 15 mg/day was added to his regimen and increased to 30 mg/day after the first week of combination treatment. After just 2 weeks of combination treatment with paroxetine 60 mg/day and mirtazapine 30 mg/day, the patient was free of panic attacks, his HAM-A score was less than 7, and his CGI-I score was 1. The combination treatment was well tolerated.

Our case report suggests that simultaneous activation of noradrenergic and serotonergic reuptake and specific serotonergic receptor transmission might be needed to achieve full remission of panic disorder. Further controlled clinical trials and genotyping are needed to identify partial responders who may benefit from the combination strategy at the beginning of their treatment.

Dr. Pavlovic reports no financial or other relationships relevant to the subject of this letter.

REFERENCES

1. Dannon PN, Iancu I, Cohen A, et al. Three year naturalistic outcome study of panic disorder patients treated with paroxetine. *BMC Psychiatry* 2004;4:16
2. Sarchiapone M, Amore M, De Risio S, et al. Mirtazapine in the treatment of panic disorder: an open-label trial. *Int Clin Psychopharmacol* 2003;18:35–38
3. Carli V, Sarchiapone M, Camardese G, et al. Mirtazapine in the treatment of panic disorder. *Arch Gen Psychiatry* 2002;59:661–662
4. Tremblay P. Combining mirtazapine (Remeron) with other antidepressants improves remission rates in patients with unipolar depression. Presented at the 55th annual conference of the Canadian Psychiatric Association; November 3–6, 2005; Vancouver, British Columbia, Canada
5. Pallanti S, Quercioli L, Bruscoli M. Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study. *J Clin Psychiatry* 2004;65:1394–1399
6. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
7. Bandelow B. Defining response and remission in anxiety disorders: toward an integrated approach. *CNS Spectr* 2006;11(suppl 12):21–28
8. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–55

Zoran Milan Pavlovic, M.D.
Private Practice
Belgrade, Serbia

A Case of Genital Self-Mutilation in an Elderly Man

Sir: Genital self-inflicted wounds are generally categorized as self-mutilating behavior or partial suicides. Although genital self-mutilation occurs in all racial groups, cultures, and religions, the vast majority of reported incidents occur in single, male Caucasians in their 20s or 30s.¹

This case highlights the beliefs that precipitated genital self-mutilation in an elderly man.

Case report. Mr. A, a 72-year-old married man, was admitted in August 2006 with a history of genital self-mutilation at home in an attempt to bleed and die. The patient was pre-morbidly well adjusted with no past suicide attempts or any major psychiatric or medical illness. There was no evidence of sexual conflicts over past experiences and no history of previous self-injury or family history of psychiatric illness. The patient tried to castrate himself, believing this to be lethal. Using a knife, he incompletely amputated his penis at its base and thereby expected to bleed himself to death. He was rescued, and reconstructive surgery was performed. During his recuperation in the hospital, he was assessed by a psychiatrist. Mental status examination revealed no cognitive deficits. The patient had no depression or psychosis, and his only reason for committing the act was a genuine wish to die, precipitated by a dispute among his children related to property and finances. Due to this ongoing dispute the patient preferred to die rather than witness the growing animosity between his children. There was no evidence of any physical, sexual, or psychological abuse of the patient by his family. The patient continued to harbor thoughts of self-castration and was determined to repeat the act if the conflict between his children was not resolved.

Mr. A firmly believed that amputation of his penis would result in his death. He felt justified in indulging in this act of self-mutilation because he thought that the source of life was related to the penis. A similar act by a 24-year-old man to attain salvation (*Moksha*, defined as "liberation from the cycle of death and rebirth and all the suffering and limitation entailed in embodied worldly existence") has been reported.² There are case reports of 3 Chinese men who believed that in severing the penis, death was inevitable.³ These men expressed surprise and dismay at finding themselves still alive. In Chinese, 1 term for penis is *Ming Gon*, meaning "life root" or "life source."³ The Greeks and Romans had adorned images of the penis on their pottery and household items and considered the symbol to be potent for fertility and longevity. The eponym "Klingsor syndrome" has been proposed for acts of genital self-mutilation involving religious delusions.⁴ Religious and biblical delusions have been associated with auto-castration in schizophrenia.⁵

Our patient had no religious delusions but had a belief associating death with amputation of the penis. This belief was culturally accepted and shared by many of his family members. This case highlights the need to recognize cultural and religious beliefs in patients with regard to self-castration.

Dr. Tharoor reports no financial or other relationships relevant to the subject of this letter.

REFERENCES

1. Stunell H, Power RE, Floyd M Jr, et al. Genital self-mutilation. *Int J Urol* 2006;13:1358–1360
2. Bhatia MS, Arora S. Penile self-mutilation. *Br J Psychiatry* 2001;178:86–87
3. Yang JG, Bullard MJ. Failed suicide or successful male genital self-amputation? *Am J Psychiatry* 1993;150:350–351
4. Schweitzer I. Genital self-amputation and the Klingsor syndrome. *Aust N Z J Psychiatry* 1990;24:566–569
5. Greilshheimer H, Groves JE. Male genital self-mutilation. *Arch Gen Psychiatry* 1979;36:441–446

Hema Tharoor, D.P.M., D.N.B., M.N.A.M.S.
Department of Psychiatry
Kasturba Medical College
Kasturba Hospital
Udupi, Karnataka, India

Onset of Paranoid Delusions After Addition of Topiramate for Seizure Disorder Treatment: A Case Report

Sir: Incidence of psychosis during initial clinical trials of topiramate was reported as 0.8%, not significantly different from placebo.¹ Auditory hallucinations, aggressive and suicidal thoughts, and paranoid delusions have been infrequently reported after initiation of topiramate.^{1,2} Although studies indicate that topiramate is generally well tolerated, neuropsychiatric side effects have been reported, including cognitive disturbances, confusion, psychomotor slowing, concentration problems, memory difficulties, depression, and mood disturbances.³ I present a case of a young man with traumatic brain injury and seizure disorder who developed sudden onset of paranoid delusions after initiation of topiramate.

Case report. Mr. A is a 23-year-old man brought to the emergency room in 2006 by his parents. His family was concerned because he had suffered a recent change in behavior after his medications were changed. According to the family, he was accusing them of making a murder pact against him, and he was accusing his father of walking around and thinking of stabbing him with a knife.

During evaluation, Mr. A reported that he was convinced that his parents and sibling were conspiring against him and were planning to kill him by stabbing. He reported that he had to protect himself from everyone around him, and he appeared to be grossly suspicious of his surroundings, with evidence of psychomotor agitation. He reported that he did not feel safe going back home because of fear that he would be murdered. He was admitted to the hospital for psychiatric care.

Collateral reports from the parents indicated that the patient had suffered a closed head injury 10 years before and, since then, had been treated for grand mal seizures. His medication regimen included carbamazepine and lamotrigine. The family reported that his seizures were only partially controlled on the above regimen and, therefore, topiramate 100 mg/day was initiated 10 days previously by his neurologist. The family reported that after 1 week of adding topiramate to his regimen, the patient started to talk about his family being "after him," and he started to isolate himself in his room, stating that he would be murdered by his family. No previous patient history of psychiatric symptoms or family history of psychiatric illness was given by the family, and they reported good pre-morbid functioning of the patient, including maintaining a full-time job. The family reported that because of concerns that the new medication might be causing these symptoms, they discontinued the patient's topiramate 2 days before his arrival at the emergency department.

Risperidone 1 mg daily was initiated for paranoid delusions. Carbamazepine and lamotrigine were continued for seizure disorder, but topiramate was not reinitiated because of concerns that it might be a factor instigating the patient's psychiatric symptoms. The patient's carbamazepine level was observed to be within the therapeutic range. A computed tomographic scan of the patient's head revealed no new changes as compared with previous studies.

Mr. A's symptoms resolved rapidly after topiramate was discontinued and risperidone was initiated. Within 48 hours of hospitalization, Mr. A denied any suspicions that his family was planning to kill him. His affect became brighter, and he started to interact with his milieu without any suspicion. He was able to discuss his paranoia and the fact that his former thoughts had no

value or validity and were irrational. He was continuously observed for the next 2 days for symptom recurrence, during which time family visits and meetings were held. Mr. A did not exhibit any paranoid symptoms and related to his family and surroundings without any inhibitions. After consultation with the family and the outpatient psychiatric clinic, it was decided to continue risperidone at present and to taper the medication over the next 8 weeks.

In this case, the most likely explanation of the patient's psychiatric symptoms appears to be the addition of topiramate to his medication regimen. Although he has a history of traumatic brain injury and seizures, he did not suffer from any psychiatric symptoms for 10 years after his brain injury and maintained good social and occupational functioning. His symptoms appeared within 1 week after initiation of topiramate and were rapidly resolved after discontinuation of topiramate and initiation of risperidone. Such sudden onset and resolution of symptoms and their correlation with initiation and discontinuation of topiramate make topiramate-induced symptoms the most likely explanation in this case.

Dr. Mahmood reports no financial or other relationships relevant to the subject of this letter.

REFERENCES

1. Khan A, Faught E, Gilliam F, et al. Acute psychotic symptoms induced by topiramate. *Seizure* 1999;8:235–237
2. Kober D, Gabbard GO. Topiramate-induced psychosis [letter]. *Am J Psychiatry* 2005;162:1542
3. Zesiewicz TA, Tullidge A, Tidwell J, et al. Topiramate-induced psychosis in patients with essential tremor: report of 2 cases. *Clin Neuropharmacol* 2006;29:168–169

Ahsan Mahmood, M.D.
Department of Psychiatry
University at Buffalo,
The State University of New York
Buffalo, New York

Effective Treatment of Fibromyalgia Comorbid With Premenstrual Dysphoric Disorder With a Low Dose of Venlafaxine

Sir: Fibromyalgia and premenstrual dysphoric disorder (PMDD) are common psychosomatic disorders in women. Fibromyalgia is characterized by chronic widespread pain, and tenderness at specific muscle-tendon sites. Estimates of lifetime prevalence are 3.4% for women and 0.5% for men.¹ We report the case of a 39-year-old woman with both conditions treated successfully with only 75 mg daily of venlafaxine, a dosage much lower than that used in previously published studies. To our best knowledge, no instances of fibromyalgia comorbid with PMDD have been reported.

Case report. Ms. A, a 39-year-old married Asian woman, had a history of marked pain and tenderness in the neck, shoulders, hands, and occipital and sacral areas for more than 10 years. The symptoms would worsen before menstruation. She visited various orthopedic outpatient clinics repeatedly, and high daily doses of nonsteroidal anti-inflammatory agents were prescribed. Other medical conditions included peptic ulcers, duodenal polyps, chronic pharyngitis, migraine, and irritable

bowel syndrome. PMDD was diagnosed by DSM-IV research criteria and the Prospective Record of the Impact and Severity of Menstrual Symptomatology (PRISM) calendar for 2 menstrual cycles after other psychiatric diagnoses and possible organic contributions were ruled out in the premenstrual syndrome specialty clinic at Chang-Gung Hospital, Taoyuan, Taiwan.^{2,3}

Ms. A sought help from the departments of gastroenterology, gynecology, rheumatology, rehabilitation, and neurology of Chang-Gung Hospital; the diagnosis of fibromyalgia without active pain symptoms and impaired occupational function was confirmed. She received treatment of physical rehabilitation, acupuncture, local steroid injections, yoga, and Chinese qi training, with little improvement.

Venlafaxine 75 mg was prescribed with PRISM calendar recording and assessment of pain severity with a visual analog scale. Ms. A reported that the pain was decreased at least 50% after 4 weeks' treatment. Further improvement was reported in the following 8 months. The severity of PMDD decreased 72%, as assessed with the PRISM calendar.

The average dosage of venlafaxine for fibromyalgia is 75 mg to 225 mg daily. In this case, a low dosage had significant effectiveness. A randomized, controlled trial of 90 patients with fibromyalgia found that venlafaxine (75 mg daily) was not significantly different from placebo.⁴ Venlafaxine at a higher dosage was found useful in 2 small, open-label studies.⁵

Venlafaxine for PMDD has had some clinical trials.^{6,7} The average dosage in one double-blind, placebo-controlled study in the West was 75 to 112.5 mg daily.⁶ To our best knowledge, this is the first report to discuss the role of antidepressants in fibromyalgia comorbid with PMDD. The presenting case improved markedly with a dosage of 75 mg daily. I conclude that both fibromyalgia and PMDD impair women's mental health significantly, and more clinical trials of antidepressants are needed.

Dr. Hsiao reports no financial affiliations or other relationships relevant to the subject of this letter.

REFERENCES

1. Wolfe F, Cathey MA. Prevalence of primary and secondary fibrositis. *J Rheumatol* 1983;10:965–968
2. Hsiao MC, Liu CY. Effective open-label treatment of premenstrual dysphoric disorder with venlafaxine. *Psychiatry Clin Neurosci* 2003;57:317–321
3. Hsiao MC, Liu CY, Chen KC, et al. Characteristics of women seeking treatment for premenstrual syndrome in Taiwan. *Acta Psychiatr Scand* 2002;106:150–155
4. Zijlstra TR, Barendregt PJ, van de Laar MA. Venlafaxine in fibromyalgia: results of a randomized, placebo-controlled, double-blind trial [abstract]. *Arthritis Rheum* 2002;46 (suppl 19):S105
5. Dwight MM, Arnold LM, O'Brien H, et al. An open clinical trial of venlafaxine treatment of fibromyalgia. *Psychosomatics* 1998;39:14–17
6. Cohen LS, Soares CN, Lyster A, et al. Efficacy and tolerability of premenstrual use of venlafaxine (flexible dose) in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol* 2004;24:540–543
7. Freeman EW, Rickels K, Yonkers KA, et al. Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2001;98:737–744

Mei-Chun Hsiao, M.D.
Department of Psychiatry
Chang-Gung Hospital and Chang-Gung University
School of Medicine
Taoyuan, Taiwan