

Letters to the Editor

Anger in Bipolar Depression

Sir: Koh et al.¹ reported that anger was more likely in depressive disorders than in anxiety and somatoform disorders, that anger was found in 30% to 40% of depressive disorders, and that comparative data were scarce among other mental disorders. My comment is that anger is even more likely in bipolar depression than in major depressive disorder (MDD).^{2,3} Finding a higher frequency of anger in bipolar depression has an important impact on the treatment of depression, because misdiagnosis of bipolar depression as MDD is high (at least 40%),⁴ and treatment of bipolar depression with antidepressants without concurrent mood stabilizers (and even with mood stabilizers) can induce mania/hypomania, mixed states, and rapid cycling.⁵ The importance for clinical practice of this finding is supported by the high frequency of bipolar II disorder in major depressive episode (MDE) outpatients (up to 60%) and in the community (11%, vs. 11% of MDD), found by improving the probing for past hypomania.³⁻¹⁴

Assessing hypomanic symptoms during MDE led to the finding of a high frequency (more than 50%) of bipolar II depressive mixed state (defined as an MDE plus some concurrent hypomanic symptoms not meeting full criteria for hypomania), in which anger was very common.^{2,3} Depressive mixed state in MDD was not uncommon (more than 20%), and these patients had a family history of bipolar disorders similar to that found in bipolar II disorder patients.³ These data suggest that assessment of past hypomania and of hypomanic symptoms during MDE should be done systematically.

My last updated sample of consecutive outpatients presenting for MDE treatment in a nontertiary care psychiatric setting (private practice) was assessed with the SCID-CV¹⁵ when patients were still psychoactive drug-free (bipolar II disorder patients: N = 281, mean \pm SD age = 41.7 \pm 13.9 years, female = 66.9%, and mean \pm SD Global Assessment of Functioning scale [GAF] score = 50.4 \pm 9.2; MDD patients: N = 202, mean \pm SD age = 47.3 \pm 15.3 years, female = 59.9%, and mean \pm SD GAF score = 51.1 \pm 9.2). Concurrent hypomanic symptoms were assessed. Frequency of anger (as defined in the SCID-CV question for irritability in bipolar disorders) was much higher in bipolar II MDE versus in MDD (61.2% vs. 35.6%; $\chi^2 = 31.8$, df = 1, p = .000) (study method details are reported elsewhere^{2,3,6,9,10}). These results are in line with the preliminary report by Perlis et al.¹⁶ showing that 62% of 29 bipolar disorder patients and 26% of 50 MDD patients had anger during MDE. These findings of the possible negative effects of antidepressant treatment on anger in bipolar depression^{5,11,17,18} suggest the need for improved diagnostic skills in distinguishing bipolar and depressive disorders.

Recognizing anger in MDE could also be a cross-sectional clinical marker of bipolar II depression (leading clinicians to better assessment of past hypomania). In the present sample, logistic regression of bipolar II disorder (dependent variable)

versus anger found the following: odds ratio = 2.8, z = 5.4, p = .000, 95% confidence interval = 1.9 to 4.1. The sensitivity and specificity of anger for predicting bipolar II disorder were 61.2% and 64.3%, respectively. Area under the receiver operating characteristic (ROC) curve was 0.62. This combination of relatively high sensitivity and specificity can make anger a useful marker of bipolar II. The association of anger with bipolar II was further tested by logistic regression of bipolar family history in first-degree relatives (dependent variable)¹⁹ versus anger, showing the following: odds ratio = 2.1, z = 3.1, p = .002, 95% confidence interval = 1.3 to 3.3. Family history is an important external validator.^{8,20} The study of anger in depression should be much improved, because of its higher association with bipolar disorders than with MDD and because of the related important treatment implications. Anger treatment in MDD also needs more studies.

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

REFERENCES

1. Koh KB, Kim CH, Park JK. Predominance of anger in depressive disorders compared with anxiety disorders and somatoform disorders. *J Clin Psychiatry* 2002;63:486-492
2. Benazzi F, Akiskal HS. Delineating bipolar II mixed states in the Ravenna-San Diego collaborative study: the relative prevalence and diagnostic significance of hypomanic features during major depressive episodes. *J Affect Disord* 2001;67:115-122
3. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. *J Affect Disord* 2003;73:113-122
4. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study [CME]. *J Clin Psychiatry* 2000;61:804-808
5. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: depression and anxiety. In: Hardman JG, Limbird LE, Goodman GA, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:447-483
6. 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
7. Angst J, Gamma A, Benazzi F, et al. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord* 2003;73:133-146
8. Akiskal HS. Classification, diagnosis and boundaries of bipolar disorders: a review. In: Maj M, Akiskal HS, López-Ibor JJ, et al, eds. *Bipolar Disorder*, vol 5. Chichester, UK: John Wiley & Sons; 2002: 1-52
9. Benazzi F. Prevalence of bipolar II disorder in outpatient depression: a 203-case study in private practice. *J Affect Disord* 1997;43:163-166
10. Benazzi F. Bipolar II depression in late life: prevalence and clinical features in 525 depressed outpatients. *J Affect Disord* 2001;66:13-18
11. 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
12. Angst J. Comorbidity of mood disorders: a longitudinal prospective

- study. *Br J Psychiatry* 1996;168(suppl 30):31–37
13. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998;50:143–151
 14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association; 2000
 15. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press; 1997
 16. Perlis RH, Smoller JW, Racette S, et al. A comparison of the prevalence and correlates of anger attacks in bipolar disorder. In: *Syllabus and Proceedings Summary of the 155th annual meeting of the American Psychiatric Association*; May 20, 2002; Philadelphia, Pa. *Scientific and Clinical Report Session 7*, No. 20:9–10
 17. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. *Psychiatr Clin North Am* 1999;22:517–534
 18. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. *Psychiatr Clin North Am* 1999;22:547–564
 19. Weissman MM, Wickramaratne P, Adams P, et al. Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry* 2000;57:675–682
 20. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry* 1970;126:983–987

Franco Benazzi, M.D.
Outpatient Psychiatry Center
Ravenna and Forli, Italy

Dr. Koh Replies

Sir: We tried to include patients with major depressive disorder or dysthymic disorder in the depressive disorder group for our study¹ and to exclude patients with bipolar disorder on the basis of the DSM-IV criteria. However, we are not sure how many of them would become bipolar or have a diagnosis of bipolar depression in a follow-up observation.

With respect to the relationship between hostility and depression, hostility is considered a manifestation of depressive disorder, especially when the disorder is attended by mixed bipolar features.² Thus, as Dr. Benazzi mentioned, it is possible that bipolar depression patients are likely to have more anger than major depressive disorder patients. However, unfortunately, I have not found a study on the comparison of anger in the 2 disorders. Nonetheless, I agree with Dr. Benazzi that great care should be exercised in diagnosing major depression and the risk of misdiagnosis of bipolar depression as major depression should be always considered in research.

I thank Dr. Benazzi for his comment.

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

REFERENCES

1. Koh KB, Kim CH, Park JK. Predominance of anger in depressive disorders compared with anxiety disorders and somatoform disorders. *J Clin Psychiatry* 2002;63:486–492
2. Akiskal HS. Mood disorders: introduction and overview. In: Sadock BJ, Sadock VA, eds. *Comprehensive Textbook of Psychiatry*. 7th ed. New York, NY: Lippincott Williams & Wilkins; 2000:1284–1298

Kyung Bong Koh, M.D., Ph.D.
Yonsei University College of Medicine
Seoul, Korea

Possible Antidepressant-Associated Activation of Mania and Psychosis in the Mentally Retarded: Four Case Reports

Sir: In some individuals, antidepressants can activate manic and psychotic behavior. Individuals with a history of mania and psychosis are uniquely vulnerable to this behavior.¹ When the use of antidepressants in the mentally retarded is considered, evidence of a major Axis I disorder may be difficult to determine. In the literature on use of antidepressants in the mentally retarded, there are a number of reports of pathologic behavioral activation suggesting underlying manic or psychotic disorders that were not initially apparent.^{2–4} We report here 4 consecutive cases over a 4-month period that demonstrate worsening manic or psychotic behavior associated with antidepressant use in mentally retarded individuals. In 3 of 4 instances, there was a previous history of manic or psychotic behavior. Therefore, in the mentally retarded, as in the rest of the adult population, care should be taken in the use of antidepressants in individuals with a possible history of mania or psychosis.

Case 1. Ms. A, a 22-year-old single white woman with a history of bipolar disorder, most recent episode manic, severe with psychotic features (DSM-IV), and Down's syndrome, was admitted from supervised living secondary to increased psychotic and aggressive behavior. She had been spitting at staff, breaking objects, and screaming at "people inside." Her medications at admission included carbamazepine, 400 mg/day; citalopram, 20 mg/day; and ziprasidone, 100 mg/day (citalopram and ziprasidone were recent additions). At admission, these medications were discontinued, and she was started on treatment with lithium and perphenazine, which were titrated up to daily doses of 900 mg and 48 mg, respectively. Ms. A was discharged 10 days later on treatment with these medications with no aggressive behavior, increased cooperation, and greatly decreased responses to internal stimuli.

Case 2. Mr. B, a 37-year-old single white man with a history of major depressive disorder with psychotic features (DSM-IV) and mental retardation, presented from the medical unit at our hospital. He presented to the medical emergency room with multiple self-induced hematomas and epistaxis secondary to nasal trauma. He had hit multiple staff members over a 3-month period prior to admission. Mr. B's outpatient psychiatrist had made multiple medication changes including starting venlafaxine and ziprasidone 1½ weeks prior to admission. On the medical unit, results of a workup, including computed tomographic scan of the head, were negative. He was transferred to the psychiatry unit on treatment with olanzapine, 20 mg/day; haloperidol, 5 mg/day; venlafaxine, 75 mg/day; and ziprasidone, 120 mg/day. We discontinued all medications except olanzapine, which we continued at 20 mg/day. After 3 days, Mr. B exhibited neither aggressive behavior nor the serious self-injurious behavior with which he had been admitted.

Case 3. Mr. C, an 18-year-old single white man, was admitted secondary to hitting his roommate and breaking the window of a police car. He carried a diagnosis of mental retardation and intermittent explosive disorder (DSM-IV). At presentation, he complained of hearing voices calling his name. He had been discharged 2 weeks prior to this admission. The previous admission was also due to aggressive behavior. At that time, sertraline was discontinued, but apparently restarted on an outpatient basis, and Mr. C presented again with similar complaints. Sertraline was again discontinued, and, after 3 days, the patient was discharged on treatment with his other outpatient medications, which included haloperidol, 17 mg/day; clonazepam, 3 mg/day;

and bupropion, 2 mg/day. The patient exhibited no aggressive behavior on the unit and denied psychotic symptoms at discharge.

Case 4. Mr. D, a 32-year-old single white man with a diagnosis of psychosis not otherwise specified (DSM-IV) and mental retardation, presented from a structured facility because he exhibited aggressive behavior toward his roommates and increased agitation. On initial interview, he complained of auditory hallucinations and was irritable and mildly disorganized. His admission medications included sertraline, 75 mg/day; olanzapine, 15 mg/day; and valproic acid, 2000 mg/day. At admission, we discontinued sertraline and increased the olanzapine dose to 20 mg/day. With this regimen, the patient became more organized and markedly less irritable, and his auditory hallucinations subsided. He was discharged back to the structured facility. Of note, 1 year prior to this admission, Mr. D had been admitted with psychosis in the setting of recent addition of fluoxetine.

There are prior reports of pathologic activation of behavior with the use of antidepressants in this population.⁵ In a study by Troisi et al.,² 9 of 16 patients with mental retardation who were treated with fluoxetine demonstrated increased aggression during treatment. Bodfish and Madison³ conducted a study to determine the effectiveness of a selective serotonin reuptake inhibitor (fluoxetine) for the treatment of compulsive behavior in adults with mental retardation. Primary target behaviors were aggression and self-injurious behavior. They noted that 9 of 16 patients showed no improvement. In fact, 6 of the 9 patients had an increase in these target behaviors. In a study by Gordon et al.,⁴ irritability, temper outbursts, and aggression were noted in 8 of 12 patients treated with desipramine.

The common link in the cases presented here was the marked improvement noted in psychotic or manic symptoms and agitated behavior with the discontinuation of the antidepressant (and, in some cases, addition/dose increase of a neuroleptic). Similar findings were reported by Preda et al.¹ in 2001 in a group of adult patients without mental retardation but with a history of mania or psychosis. We feel that the above cases indicate a need for caution when prescribing antidepressants to individuals with mental retardation, since it may be more difficult to identify an Axis I disorder in these individuals.

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

REFERENCES

1. Preda A, MacLean RW, Mazure CM, et al. Antidepressant-associated mania and psychosis resulting in psychiatric admissions. *J Clin Psychiatry* 2001;62:30-33
2. Troisi A, Vicario E, Nuccetelli F, et al. Effects of fluoxetine on aggressive behavior of adult inpatients with mental retardation and epilepsy. *Pharmacopsychiatry* 1995;28:73-76
3. Bodfish JW, Madison JT. Diagnosis and fluoxetine treatment of compulsive behavior disorder of adults with mental retardation. *Am J Ment Retard* 1993;98:360-367
4. Gordon CT, State RC, Nelson JE, et al. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry* 1993;50:441-447
5. Santosh PJ, Baird G. Psychopharmacotherapy in children and adults with intellectual disability. *Lancet* 1999;354:231-240

Neayka Sahay, M.D.
Etienne Muscat, M.D.
Malcolm B. Bowers, Jr., M.D.
Yale University
New Haven, Connecticut

A Case of Risperidone-Induced Priapism

Sir: Priapism is a rare but serious adverse effect of psychotropic drugs¹ that is attributed to the blockade of α -adrenergic receptors in the corpora cavernosa.² Among psychotropics, antipsychotics, most often typical antipsychotics, are common causative agents.¹ We report a case of priapism associated with risperidone, an atypical antipsychotic.

Case report. Mr. A, a 32-year-old man, presented to our outpatient services with a 12-year illness characterized by vague, circumstantial, and metaphorical thinking; multiple obsessive ruminations; lack of confidants; ideas of reference and persecution; and brief psychotic episodes. A DSM-IV³ diagnosis of schizotypal personality disorder was made, and flupenthixol (up to 3 mg/day) was prescribed. He remained better and stable over 5 years of follow-up, but had 4 brief psychotic (delusional) episodes.

The patient presented with a 1-week psychotic episode in December 2001. In view of recurrent psychotic episodes and mild extrapyramidal symptoms, flupenthixol was changed to risperidone, 4 mg/day. Over the next 2 months, in view of partial response, the patient's risperidone dose was increased to 5 mg/day. Almost 2 weeks after the last dose increase, Mr. A woke up in the middle of the night with a persistent, painful penile erection. He presented to the hospital services almost 36 hours later. Priapism was diagnosed, and risperidone treatment was immediately stopped. Aspiration of venous blood followed by intracavernosal injection of epinephrine with subsequent bilateral Winters shunt were performed, resulting in partial detumescence. The patient presented the next day with recurrence of priapism; corporeal aspiration with intracavernosal epinephrine injection achieved almost complete detumescence. However, for the next 4 days, the patient had episodes of rigid erection that subsided without surgical intervention. Results of investigations, i.e., a complete hemogram, sickling test, penile Doppler study, and penile biopsy, were within normal limits.

Detailed reevaluation revealed that no additional medications were ever taken. Also, since starting risperidone treatment, Mr. A had experienced recurrent, prolonged, nonpainful penile erections (unassociated with sexual stimulation) that would subside spontaneously. After 2 weeks, he was started on treatment with flupenthixol, 1 mg/day, and has been maintaining well for 14 weeks. Absence or presence of impotence cannot be commented on, as the patient did not engage in sexual intercourse.

That this case manifested risperidone-induced priapism can be concluded from the following factors: temporal relationship of sustained erections after initiation of risperidone, absence of sustained erections after risperidone discontinuation, and absence of any other causative factor. Interestingly, priapism manifested after a change to an antipsychotic of a different class (flupenthixol to risperidone) and a subsequent dose increase of the latter drug.⁴ This could possibly be due to higher α_1 -adrenergic blockade affinity of risperidone.⁵ However, atypical antipsychotics are infrequently associated with priapism. We performed a MEDLINE search using the keywords *priapism*, *atypical antipsychotics*, and *risperidone* and could find reports of only 3 priapism cases linked to risperidone.¹

The patient reported that he had been experiencing prolonged erections during the 2 months he took risperidone, a phenomenon commonly reported in priapism.^{1,4} However, the lack of reporting and inquiry about prolonged erections (after antipsychotic initiation) by the patient and the doctor, respectively, led to development of potentially serious morbidity.^{1,4}

Hence, there is a need for greater awareness of this phenomenon among physicians.

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

REFERENCES

1. Compton MT, Miller AH. Priapism associated with conventional and atypical antipsychotic medications: a review. *J Clin Psychiatry* 2001;62:362–366
2. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. *Arch Gen Psychiatry* 1989;46:275–284
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994
4. Thompson JW Jr, Ware MR, Blashfield RK. Psychotropic medication and priapism: a comprehensive review. *J Clin Psychiatry* 1990;51:430–433
5. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry* 1999;60(suppl 10):5–14

Pankaj Relan, M.D.
Nitin Gupta, M.D.
Surendra K. Mattoo, M.D.

Postgraduate Institute of Medical Education and Research
Chandigarh, India

Paroxetine-Induced Somnambulism

Sir: Somnambulism is classified as a parasomnia¹ and has been reported with the use of classical antidepressants.^{2,3} However, to our knowledge, there have been no reports of somnambulism associated with the use of selective serotonin reuptake inhibitors. We herein report a case of somnambulism induced by paroxetine.

Case report. Ms. A, a 61-year-old Japanese woman, presented with a 1-year history of anxiety, difficulty falling asleep, nervousness, and mild depression. She reported no personal or familial history of epilepsy, panic disorder, somnambulism, or other parasomnias. Results of general physical and neurologic examinations, as well as electrocardiogram and routine blood and urine tests, showed no significant changes from normal. Magnetic resonance brain imaging and electroencephalogram results were also within normal range. The patient started daily treatment with 10 mg of paroxetine in the evening. After 2 weeks, Ms. A's dose of paroxetine was increased to 20 mg/day.

One week later, Ms. A presented with sleepwalking almost every night. Her sleepwalking was witnessed by her husband. At assessment, her sleep pattern was as follows: she went to bed at 9 p.m. and awakened at 5 a.m. She fell asleep within 10 to 30 minutes. She arose from bed once a night in the first few hours of sleep and walked through the house, sometimes attempting to leave the home through the door. Typically, these episodes lasted approximately 15 minutes. When awakened by her husband during an episode, Ms. A would be confused for a few minutes and would have no memory of the event. The patient was advised to gradually reduce the medication dosage to 10 mg/day for 2 weeks and then discontinue it. Her sleepwalking ceased immediately when she stopped taking paroxetine. At follow-up 2 months later, her recovery had been maintained.

Somnambulism consists of a series of complex types of behavior that are initiated during slow-wave sleep (SWS) (stages

3 and 4)⁴ and reflects impairment in the normal mechanisms of arousal from sleep, resulting in partial arousals during which motor behaviors are activated without full consciousness. Drug-induced somnambulism may represent a physiologic state during SWS that mimics primary somnambulism.⁴ For Ms. A, an increase in paroxetine dose was accompanied by the clinical appearance of somnambulism. Oswald and Adam⁵ reported that paroxetine, 30 mg, increased SWS and decreased REM sleep in healthy individuals. Therefore, somnambulism following paroxetine use might be attributed to a physiologic alteration of SWS.

In contrast to most antidepressant drugs, nefazodone, a potent blocker of postsynaptic serotonin receptors as well as a serotonin reuptake inhibitor, does not suppress REM sleep or increase REM latency in patients with major depressive disorder.⁶ Nefazodone also tends to decrease SWS in healthy individuals.⁷ These studies suggest that nefazodone might reverse somnambulism in depressed patients.

Although a case of night terrors and somnambulism that improved with paroxetine treatment has been reported,⁸ Van Sweden et al.⁹ pointed out that the diagnosis in that case was thought to be nocturnal panic attacks rather than somnambulism. No clear relationship has yet been established between somnambulism and paroxetine.

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

REFERENCES

1. American Sleep Disorders Association. *The International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual*. Rochester, Minn: American Sleep Disorders Association; 1997
2. Huapaya LVM. Seven cases of somnambulism induced by drugs. *Am J Psychiatry* 1979;136:985–986
3. Ferrandiz-Santos JA, Mataix-Sanjuan AL. Amitriptyline and somnambulism [letter]. *Ann Pharmacother* 2000;34:1208
4. Charney DS, Kales A, Soldatos CR, et al. Somnambulistic-like episodes secondary to combined lithium-neuroleptic treatment. *Br J Psychiatry* 1979;135:418–424
5. Oswald I, Adam K. Effects of paroxetine on human sleep. *Br J Clin Pharmacol* 1986;22:97–99
6. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. *Biol Psychiatry* 1998;44:3–14
7. Sharpley AL, Williamson DJ, Attenburrow MEJ, et al. The effects of paroxetine and nefazodone on sleep: a placebo controlled trial. *Psychopharmacology* 1996;126:50–54
8. Lillywhite AR, Wilson SJ, Nutt DJ. Successful treatment of night terrors and somnambulism with paroxetine. *Br J Psychiatry* 1994;164:551–554
9. Van Sweden B, van Erp MG, Mesotten F, et al. Night terrors [letter]. *Br J Psychiatry* 1994;164:834–835

Toshiro Kawashima, M.D., Ph.D.
Shigeto Yamada, M.D., Ph.D.
Saga Medical School
Saga, Japan

Olanzapine Elevation of Serum Creatine Kinase

Sir: We describe a causal finding of a clinically asymptomatic case of serum creatine kinase (CK) increase in a 54-year-old man treated with olanzapine.

Case report. The patient, a health care professional, was admitted to the emergency room after a sudden episode of dyspnea

Table 1. Comparison of Clinical Cases of Serum Creatine Kinase (CK) Increase in Patients Treated With Olanzapine

Characteristic	Our Case	Meltzer et al ^{3*}	Marcus et al ^{4**}		
			Case 5	Case 6	Case 7
Age, y	54	39	42	33	21
Gender	Male	Male	Male	Male	Male
Olanzapine dose	10 mg/d	10 mg/d	20 mg/d	?	?
Other medications	Alprazolam	No	No	No	No
History of neuroleptic malignant syndrome	No	No	No	No	No
Other pathologies	No	No	No	No	No
Physical, neurologic examination, and electrocardiogram	Normal	Normal	Normal	Normal	Normal
Recent history of neuroleptic malignant syndrome, myocardial infarction, infection, trauma, excessive physical activity, intramuscular injections, cocaine abuse	No	No	No	No	No
Psychotic outbreak	No	No	No	No	No
Biochemistry (serum urea and creatine) and blood count	Normal	Normal	Normal	Normal	Normal
Serum CK (normal range, 20–204 IU/L)	5851	4000	15,000	8150	8920
Discontinuation of treatment	Yes (during 1 wk, then continued with 5 mg/d of olanzapine)	Yes	Yes	Yes	No
Normalization of serum CK	Serum CK = 4330 IU/L after 12 h	8 d	6 d	3 d	7 d

*Case report.

**Prospective study to characterize the serum creatine kinase increase in patients treated with novel antipsychotics.

Symbol: ? = unknown.

with minimal disturbance, following a mildly physical walking effort, that disappeared spontaneously after a few minutes. During admittance, his pulse, blood pressure, and temperature were within normal limits, and no mental or neurologic signs nor muscular rigidity or pain was noticed. He also denied any toxic drug ingestion or intense physical exercise during the previous 48 hours. Because of the dyspnea, a thorax radiography and an electrocardiogram were ordered, and no abnormality was found. A further echocardiogram also showed a normal pattern and function, but thoracic computer tomography revealed an interstitial fibrotic pattern compatible with a primary diagnosis of pulmonary fibrosis, which was confirmed at a later date by appropriate studies. Since this was the first time the patient had been treated at the hospital, no previous analytical and clinical data were available. The patient's history revealed that he was taking olanzapine, 10 mg q.h.s., and alprazolam, 0.25 mg t.i.d., both of which had been started in the past after a psychotic outbreak. The blood biochemistry performed at the time of admission showed normal electrolyte, renal, liver, and hematologic values but a striking increase of serum CK to 5851 IU/L, which is about a 20-fold increase above the upper limit of the range of normal laboratory values (normal range, 20–204 IU/L). The biochemistry was repeated 12 hours later, with the dose of olanzapine suspended, and the serum CK level remained elevated but lower (4330 IU/L) than in the first analysis. The serum CK-MB values, the isoenzyme cardiac muscle form of serum CK, were 60 IU/L in the first analysis and 43 IU/L 12 hours later (normal range, 0–25 IU/L). The patient was released from the emergency room 24 hours after his admittance.

This analytic profile and the prescribed medication could lead to the impression of a neuroleptic malignant syndrome. A neuroleptic malignant syndrome was considered immediately prior to the patient's release, but was soon rejected because it was not in accordance with the patient's clinical status. However, the possibility of a relationship between olanzapine therapy and the increased serum CK emerged from the serum CK decay observed in the second blood chemistry. To challenge this hypothesis, the patient was contacted, and a new serum CK analysis was performed 1 year later. At that time, the patient was on olanzapine treatment at half the original dose, i.e., 5 mg q.h.s., because of medical reasons. The serum CK chemistry value was 348 IU/L, and the patient reported no systemic or

organ-specific symptoms. The application of the Naranjo Adverse Drug Reaction Probability Scale¹ (NADRPS) to the serum CK analysis at 1 year after his emergency room visit and to the 2 prior blood chemistries yielded a value of 6, which is indicative of a probable relationship between the adverse increase in serum CK level and olanzapine therapy, although the contribution of psychotic outbreaks unknown to treatment providers cannot be excluded.²

Given the NADRPS analysis and the data in the literature^{3–5} about other individual cases of serum CK elevation associated with olanzapine (Table 1), the suggested hypothesis presented here seems reinforced. A particular caution on the increasing use of this antipsychotic drug is warranted and constitutes, in our opinion, enough reason to be expectant and to advise on performing regular serum CK surveillance analysis on this set of patients.

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

REFERENCES

1. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reaction. *Clin Pharmacol Ther* 1981;30:239–245
2. Manor Y, Hermesh H, Valevski A, et al. Recurrence pattern of serum creatine phosphokinase levels in repeated acute psychosis. *Biol Psychiatry* 1998;43:288–292
3. Meltzer HY, Cola PA, Parsa M. Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. *Neuropsychopharmacology* 1996;15:395–405
4. Marcus EL, Vass A, Zislin J. Marked elevation of serum creatine kinase associated with olanzapine therapy. *Ann Pharmacother* 1999;33:697–700
5. Jarventausta K, Leinonen E. Neuroleptic malignant syndrome during olanzapine and levomepromazine treatment. *Acta Psychiatr Scand* 2000;103:231–233

Ezequiel Martí-Bonmatí, Pharm.D.
Eva San Valero-Carcelén, M.D.
María Pilar Ortega-García, Pharm.D.
Ricardo Rubini-Puig, M.D.
 University General Hospital
 Valencia, Spain

A Case Report of Hypomania Following Vagus Nerve Stimulation for Refractory Epilepsy

Sir: One of the adverse effects of antidepressant treatments is the induction of a transition from depression to mania or hypomania, particularly in bipolar patients.^{1,2} Mood improvements in patients undergoing vagus nerve stimulation (VNS) for refractory epilepsy were noted in early clinical trials.³ Since then, the efficacy of VNS for treatment-resistant depression has been investigated.⁴⁻⁶ We report a case in which the mood-elevating properties of VNS led to a hypomanic state in an individual receiving VNS for refractory epilepsy.

Case report. Ms. A is a 26-year-old woman with diagnoses of intermittent explosive disorder, impulse control disorder, adjustment disorder, borderline personality disorder, and possible bipolar disorder according to DSM-IV criteria and a medical history, since 12 years of age, of complex partial seizures of left temporal origin that often secondarily progress to generalized tonic-clonic seizures. Over the years, her seizures have been partially controlled with phenobarbital, phenytoin, carbamazepine, and gabapentin, and she has never received mood stabilizers. Two years prior to her admission, she had a vagus nerve stimulator implanted and since then has taken only phenobarbital, 180 mg/day.

The patient's VNS settings were as follows: output current, 1.50 mA; signal frequency, 30 Hz; pulse width, 250 μ sec; on time/off time, 30 seconds/5.0 minutes. Her output current was increased from 1.00 mA to 1.50 mA 2 months prior to admission in an attempt to better control her seizures. At admission, Ms. A was hyperactive, with pressured speech, tangential thinking, positive suicidal ideation, and labile mood, and was assessed to be hypomanic according to the Young Mania Rating Scale (YMRS)⁷ (score 21/60). She refused a trial of divalproex sodium, and, over the course of her 8-day admission, her mood remained labile and she was often energized and agitated, with pressured and verbose speech. Her affect was never sad or constricted. She was discharged when she denied suicidal ideation and was assessed as not being a threat to herself or others.

At follow-up, Ms. A's seizures had increased in rate and were characterized by more frequent secondary generalization with postictal speech difficulties. Her VNS settings were adjusted to output current, 1.50 mA; signal frequency, 15 Hz; pulse width, 250 μ sec; on time/off time, 21 seconds/1.8 minutes. The VNS adjustments were empirical, taking into account the patient's seizure frequency and comfort. The patient's score on a repeat YMRS assessment, recorded after these adjustments, was 8/60.

While it is possible that our patient's hypomania occurred independently of VNS, we speculate that the VNS treatment resulted in her hypomania and that her underlying psychiatric conditions increased her susceptibility to this side effect. The fact that the VNS output current was increased 2 months prior to admission lends support to that speculation, as does the observation that the patient was psychiatrically stable for at least 6 months prior to the increase in VNS output current.

Although VNS has proved to be useful for treating refractory epilepsy, clinicians should be aware of coexisting mood disorders in epileptic patients and monitor all patients for signs of hypomania following activation of the VNS device. If such manic symptoms develop, VNS adjustment or addition of a mood-stabilizing agent may be indicated.

Dr. Thompson has received financial support from Cyberonics. Mr. Klein and Drs. Jean-Baptiste and Bowers report no financial affiliation or other relationship relevant to the subject matter of this letter.

REFERENCES

- Henry C, Sorbara F, Lacoste J, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. *J Clin Psychiatry* 2001;62:249-255
- Sachs GS, Koslow CL, Ghaemi SN. The treatment of bipolar depression. *Bipolar Disord* 2000;2:256-260
- Elger G, Hoppe C, Falkai P, et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res* 2000;42:203-210
- Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry* 2000;47:276-286
- Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001;25:713-728
- Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry* 2002;51:280-287
- Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry* 1978;133:429-435

Joshua P. Klein, B.A.

Michel Jean-Baptiste, M.D.

James L. Thompson, M.D.

Malcolm B. Bowers, Jr., M.D.

Yale University School of Medicine
New Haven, Connecticut

Three Case Reports of Modafinil Use in Treating Sedation Induced by Antipsychotic Medications

Sir: Atypical and typical antipsychotics have been associated with a high rate of sedation. Sedation usually occurs with the initiation of treatment, and tolerance usually develops within a few months of treatment. Sedation is associated with high-dose, low-potency agents. Of the atypical antipsychotics, sedation has been reported most frequently with clozapine use, followed by olanzapine, risperidone, and sertindole.¹ Using the lowest effective dose or changing the medication regimen to a nighttime dose may help to manage sedation.² Stimulants have been used successfully in the treatment of sedation in patients using antipsychotics, but can lead to worsening of movement disorders or exacerbation of psychosis.³ We report 3 patients from the Thought Disorders Program at West Virginia University Hospital whose sedation has been successfully managed with modafinil. Diagnoses for all patients are based on DSM-IV criteria.

Case 1. Mr. A is a 32-year-old man diagnosed with schizophrenia. Mr. A's medication regimen includes clozapine, 400 mg at bedtime; divalproex sodium, 500 mg twice daily; and atorvastatin, 10 mg/day. Mr. A frequently complained that clozapine was causing him to miss out on daily activities because he was sleeping approximately 14 hours per day. Trials of various antipsychotics and attempts to reduce the dose of clozapine proved unsuccessful, with the reoccurrence of psychosis. Modafinil, 200 mg every morning, was prescribed beginning in September 2001. After a 2-week trial, Mr. A reported that he was sleeping only 10 hours per day. According to the patient, modafinil treatment resulted in increased time awake and improved quality of life, and he was considering returning to work. He reported that he was more motivated for participation in both school and band activities. Modafinil worked well to allay the sedation caused by clozapine. The patient stated that he

was more wakeful and productive throughout the day and experienced no adverse effects from the medication.

Case 2. Mr. B is a 25-year-old man with the diagnoses of schizophrenia and mood disorder not otherwise specified. Mr. B was started on risperidone treatment in July 2000. He complained of sleeping too much and after a short trial was switched to olanzapine. Mr. B did not respond as well to olanzapine, and risperidone, 6 mg at bedtime, was again prescribed. Mr. B reported that he was sleeping 14 hours per day and had no motivation. In October 2001, Mr. B was started on modafinil, 200 mg in the morning. He reported a significant reduction in sleep from 14 hours to 9 to 10 hours per day. The patient stated that he felt better about himself and denied any adverse effects associated with modafinil.

Case 3. Mr. C is a 25-year-old man with the dual diagnosis of schizophrenia with cannabis abuse and nicotine dependence and a history of seizure disorder. Mr. C has been a patient of the Thought Disorders Clinic since 1995. His medication regimen in August 2000 consisted of fluphenazine, 2.5 mg twice daily; olanzapine, 5 mg in the morning and 10 mg in the evening; and divalproex sodium, 1000 mg at bedtime. The patient complained of excessive sleepiness in the morning, and his medication regimen was changed to all doses being received at bedtime. The patient continued to complain of daytime somnolence and sleeping 12 to 14 hours per day. Soon after a brief hospitalization in June 2001, Mr. C's medication regimen was changed to fluphenazine decanoate, 37.5 mg i.m. every 2 weeks; olanzapine, 20 mg at bedtime; divalproex sodium, 1000 mg at bedtime; and citalopram, 40 mg/day. At a Thought Disorders Program visit in fall 2001, Mr. C was started on modafinil, 200 mg every morning, for excessive sleepiness. He reported a decrease in total sleep time of 2 to 3 hours per night. He denied problems associated with the treatment.

Modafinil is primarily metabolized by the liver, but appears to have no significant drug-drug interactions with the atypical antipsychotics. Modafinil is a reversible inhibitor of the enzyme cytochrome P450 2C19. The most common adverse effects associated with modafinil use are headache, nausea, rhinitis, and insomnia. In premarketing trials, there is 1 report of a healthy male volunteer who developed psychotic symptoms after taking multiple doses of modafinil, 600 mg.⁴ Narendran et al.⁵ report 1 patient with schizophrenia whose psychotic symptoms appar-

ently worsened in response to the addition of modafinil, 200 mg 4 times daily. The 3 patients in our report had no exacerbation of psychotic symptoms with a daily dose of 200 mg. Modafinil is U.S. Food and Drug Administration–approved for the treatment of narcolepsy.⁴

In a recent study, Hofer and colleagues⁶ found sedation to be the second most frequently reported antipsychotic-induced adverse effect. Additionally, sedation negatively affected the attitudes of patients in regard to their medications. The authors hypothesized that sedation led to noncompliance, which fosters poor patient outcomes. Our clinical experience mimics these findings. Many patients are bothered by antipsychotic-induced sedation, and some will not tolerate it.

To our knowledge, these are the first literature reports of the use of modafinil to treat antipsychotic-induced sedation. In the cases described above, the cause of the patients' excessive sedation was believed by both the practitioners and the patient to be a result of antipsychotic medication. These findings support the need for further investigation into the use of modafinil for patients in whom antipsychotic-induced sedation is intolerable.

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

REFERENCES

1. Casey DE. Side effect profile of new antipsychotic agents. *J Clin Psychiatry* 1996;57(suppl 11):40–45
2. Lader M. Some adverse effects of antipsychotics: prevention and treatment. *J Clin Psychiatry* 1999;60(suppl 12):18–21
3. Miller SC. Methylphenidate for clozapine sedation. *Am J Psychiatry* 1996;150:1231–1232
4. Provigil (modafinil). Physicians' Desk Reference. 56th ed. Montvale, NJ: Medical Economics; 2002:1193–1196
5. Narendran R, Young CM, Valenti AM, et al. Is psychosis exacerbated by modafinil? [letter] *Arch Gen Psychiatry* 2002;59:292–293
6. Hofer A, Kemmler G, Eder U, et al. Attitudes toward antipsychotics among outpatient clinic attendees with schizophrenia. *J Clin Psychiatry* 2002;63:49–53

Eugene H. Makela, Pharm.D., B.C.P.P.
Karla Miller, Pharm.D.
William D. Cutlip II, M.D.
 West Virginia University
 Morgantown, West Virginia