Letters to the Editor

Treatment of Preexisting Diabetes With Olanzapine

Sir: The treatment of diabetes in patients with schizophrenia can be a challenge for both clinicians and patients. In recent years, novel ("atypical") antipsychotics have become the preferred pharmacologic intervention, both to control symptoms and because of their apparent ability to improve social functioning and quality of life. Among these, both clozapine[1–4] and olanzapine[3,5–10] have been associated with the emergence or worsening of abnormalities of carbohydrate and lipid metabolism. We report on 2 patients who developed type 2 diabetes mellitus while taking clozapine and were subsequently treated with olanzapine.

Case 1. Mr. A is a 43-year-old white man with a 25-year history of schizophrenia, paranoid type. In 1992, he was given clozapine, after 16 years of treatment with 5 different conventional antipsychotics. After 4 years of clozapine treatment, he had gained 40 pounds (18 kg) and began to complain of polyuria, polydipsia, fatigue, and blurred vision. A fasting blood glucose test showed 181 mg/dL (normal range, 70–115 mg/dL). The consultant endocrinologist diagnosed type 2 diabetes mellitus and prescribed an 1800-calorie/day diet with concurrent exercise. No oral hypoglycemic agents or insulin were prescribed. During the next 2 years, Mr. A was unable to follow either his diet or exercise regimen, and he gradually began to exhibit more severe metabolic compromise. The treating psychiatrist attempted to convert Mr. A to risperidone. However, during the cross-titration, Mr. A developed akathisia and refused further risperidone treatment. Clozapine was subsequently increased back to 400 mg/day, and risperidone was discontinued. The endocrinologist prescribed glimepiride, 8 mg q.a.m., and Mr. A was intermittently compliant with this medication. On admission to our facility, his fasting plasma glucose concentration was 222 mg/dL, glycosylated hemoglobin (HbA_{1c}) level was 9.6% (normal range, < 6.5), total serum cholesterol level was 325 mg/dL (normal range, < 200 mg/dL), and serum triglyceride level was 642 mg/dL (normal range, < 200 mg/dL). His weight was 247 pounds (111.2 kg) with a body mass index (BMI) of 35.5. His Positive and Negative Syndrome Scale (PANSS)[11] total score was 67. During the next 6 weeks, Mr. A was successfully cross-titrated to olanzapine, 15 mg/day, and maintained a total PANSS score of 65. He also agreed to further endocrinologic follow-up and was prescribed metformin, 500 mg b.i.d., in addition to the glimepiride. Three months after clozapine discontinuation, Mr. A's fasting plasma glucose concentration was 148 mg/dL, HbA_{1c} level was 7.4%, total serum cholesterol level was 227 mg/dL, and serum triglyceride level was 218 mg/dL. His weight has decreased to 229 pounds (103.1 kg) with a BMI of 32.9. He is actively engaged in both his schizophrenia and diabetes treatment, which consists of (1) taking prescribed oral diabetes medications and antipsychotic, (2) mall walking 3 times per week, and (3) following dietary recommendations more closely.

Case 2. Mr. B is a 28-year-old white man with a 10-year history of schizophrenia, paranoid type. Mr. B was placed on treatment with clozapine in 1993 and effectively managed on clozapine, 350 mg/day. During the next 2 years, his weight increased 30 pounds (13.5 kg), and he began to complain of polydipsia, polyuria, and fatigue. A fasting blood glucose test was obtained and showed 212 mg/dL. The consultant endocrinologist diagnosed type 2 diabetes mellitus. Mr. B was placed on troglitazone, 400 mg/day, along with a diet and exercise regimen. When troglitazone was withdrawn from the market, the patient was placed on treatment with 70/30 insulin (70/30 mixture of isophane insulin suspension and regular insulin), 56 U q.a.m. and 44 U with dinner. Mr. B's psychiatrist also tried risperidone as an alternative antipsychotic therapy. During cross-titration, Mr. B developed impotence and galactorrhea. Assessment of serum prolactin level was performed and showed 56.4 ng/mL. Risperidone was discontinued, and clozapine was increased to 350 mg/day. On admission to our facility, Mr. B's fasting plasma glucose concentration was 319 mg/dL, HbA_{1c} level was 10.4%, total serum cholesterol level was 236 mg/dL (high-density lipoprotein [HDL] = 96 mg/dL, low-density lipoprotein [LDL] = 140 mg/dL), and serum triglyceride level was 1652 mg/dL. His weight was 201 pounds (90.5 kg) with a BMI of 27.3. Mr. B's PANSS total score was 52. Over the next 6 weeks, Mr. B was successfully cross-titrated to olanzapine, 20 mg/day, and maintained a total PANSS score of 48. He admitted to difficulty in self-administering his insulin and was changed to metformin, 500 mg/day, and glyburide, 5 mg/day. Three months after clozapine discontinuation, Mr. B's fasting plasma glucose concentration was 135 mg/dL, HbA_{1c} level was 7.8%, total serum cholesterol level was 179 mg/dL (HDL = 40 mg/dL; LDL = 139 mg/dL), and serum triglyceride level was 407 mg/dL. His weight has decreased to 192 pounds (86.4 kg) with a BMI of 26.1. He is taking his prescribed oral diabetes medications and antipsychotic while following dietary recommendations.

Although these are only 2 cases, both of relatively short duration, several points emerge. First, the monitoring of de novo onset of type 2 diabetes may be of great importance in individuals receiving the newer antipsychotics.[12] Second, we have previously described the safety of switching patients from clozapine to olanzapine.[13] Metabolic changes have generally not been considered during switching of medications, but were critically important in these cases and should be further explored in controlled switching studies. Third, significant consideration should be given to changes in antipsychotic medication because of the emergence of diabetes. The factors to consider when altering medications should include the psychiatric status of the individual, quality of life, and potential effects on compliance. Although poorly controlled diabetes poses an increased risk for an array of metabolic, vascular, and infectious complications,

methods for the treatment and prevention of these complications are quite well evolved. Fourth, while the seriousness of diabetes mellitus must not be underestimated, its management need not be an insuperable task because of comorbid psychiatric problems. Last, it is important to be alert to any potential interactions between psychotropic and antidiabetic medications.

Financial disclosure: Ms. Littrell is a consultant for Eli Lilly, Janssen, and Pfizer; has received grant/research support from Eli Lilly, Janssen, Pfizer, and Abbott; and has received honoraria from and is a speakers/advisory board member for Eli Lilly, Janssen, Pfizer, Abbott, and Novartis. Dr. Petty is a consultant for Eli Lilly and Janssen; has received grant/research support from Eli Lilly, Janssen, and Abbott; has received honoraria from Eli Lilly, Janssen, Abbott, and AstraZeneca; and is a speakers/advisory board member for Eli Lilly, Janssen, and AstraZeneca. Mss. Peabody and Hilligoss are speakers/advisory board members for Eli Lilly and Company. Dr. Johnson has received grant/research support from Eli Lilly, Janssen, and Abbott and is a speakers/advisory board member for AstraZeneca.

References

1. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108–111
2. Hägg S, Joelsson L, Mjörndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294–299
3. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new-onset diabetes. Biol Psychiatry 1998;44:778–783
4. Colli A, Cocciolo M, Francobandiera F, et al. Diabetic ketoacidosis associated with clozapine treatment. Diabetes Care 1999;22:176–177
5. Fertig MK, Brooks VG, Shelton PS, et al. Hyperglycemia associated with olanzapine [letter]. J Clin Psychiatry 1998;59:687–689
6. Lindenmayer JP, Patel R. Olanzapine-induced ketoacidosis with diabetes mellitus [letter]. Am J Psychiatry 1999;156:1471
7. Paizis M, Cavaleri S, Schwartz ME, et al. Acute-onset diabetic ketoacidosis during olanzapine treatment in a patient without pretreatment obesity or treatment-associated weight gain. Primary Psychiatry 1999;12:37–38
8. Ober SK, Hudak R, Rusterholtz A. Hyperglycemia and olanzapine [letter]. Am J Psychiatry 1999;156:970
9. Gatta B, Rigalleau V, Gin H. Diabetic ketoacidosis associated with olanzapine treatment. Diabetes Care 1999;22:1002–1003
10. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000;34:865–867
11. Kay SR, Opler LA, Fiszbein A, The Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health System; 1986
12. Goldstein L, Henderson DC. Atypical antipsychotic agents and diabetes mellitus. Primary Psychiatry 2000;7:65–68
13 Littrell KH, Johnson CG, Hilligoss NM, et al. Switching clozapine responders to olanzapine. J Clin Psychiatry 2000;61:912–915

Kimberly H. Littrell, M.S., A.R.N.P.
Richard G. Petty, M.D., M.R.C.P., M.R.C.Psych. (UK)
Carol D. Peabody, M.S., C.C.R.C.
Nicole M. Hilligoss, M.S., C.R.C.
Craig G. Johnson, M.D.
The Promedica Research Center
Tucker, Georgia

Psychotic Symptoms Presented in Familial Creutzfeldt-Jakob Disease, Subtype E200K

Sir: Creutzfeldt-Jakob disease is a rare but fatal neurologic disease. It may manifest with psychiatric symptoms as an initial presentation, which makes the differential diagnosis very difficult because of lack of specific clinical symptoms and image findings in the early stage of Creutzfeldt-Jakob disease.

We report on a familial Creutzfeldt-Jakob disease E200K patient who presented with coexistent psychosis and confusion as prominent features in the early phase of the disease. The familial Creutzfeldt-Jakob disease group was confirmed by special immunostaining, and a mutation was found in the PrP gene, codon 200, in which glutamate (E) was replaced by lysine (K)—E200K.

Case report. Ms. A is a 48-year-old, widowed Ecuadorian woman without past psychiatric history, living with her children, 2 sons and 1 daughter. She had been doing well until 1 week prior to admission, when she started to talk incoherently and act strangely. She was telling her family that she had won 25 million dollars from *Sweepstakes Magazine* and was going to buy houses for them in New Jersey. She barricaded herself in the bathroom, put towels into the toilet, and spread shampoo on her legs. She believed that her dead husband was alive and waiting for her somewhere.

On assessment of initial mental status, Ms. A was poorly groomed and was constantly moving around and breaking things into small pieces with her hands. Her speech was normal. Her mood was anxious, and her affect, blunted. She was very tangential with loosening of association and had grandiose delusions. She reported hearing God's voices, "very soft and slow." She denied visual hallucinations, depression, and suicidal ideation. She was oriented to place and person but not to time. Her attention and concentration were decreased, with impaired short-term memory. Ms. A's Mini-Mental State Examination (MMSE) score was 19/30. Computed tomographic scan of the head revealed a small, old lacunar infarct in the left lentiform nucleus. There was no brain atrophy.

Ms. A was admitted to the psychiatric unit with the diagnosis of psychosis not otherwise specified, rule out brief psychotic disorder (DSM-IV criteria). She was placed on treatment with haloperidol, 5 mg p.o. b.i.d.; benztropine, 1 mg p.o. b.i.d.; and lorazepam, 0.5 mg p.o. b.i.d. and 1 mg p.o. q.h.s. The patient remained confused, psychotic, and disorganized in the first week after admission. At the end of the first week, stiffness in her extremities appeared in the clinical picture. Ms. A's MMSE score also dropped to 16/30. Benztropine was increased to 2 mg, p.o. b.i.d., and lorazepam was decreased to 0.5 mg, p.o. b.i.d. and q.h.s. One day after the change of the dosages, the patient was seen by a nurse to have a "seizure lasting less than a minute" and then fell. A few days later, the patient fell again. Stiffness, tremor, and cogwheel rigidity became prominent. Neurologic consultation was called, and the diagnoses of extrapyramidal syndrome and rule out neuroleptic malignant syndrome were made. Haloperidol was discontinued. At the end of the third week, Ms. A's MMSE score dropped to 13/30. The primary diagnosis was changed to delirium.

All medications were subsequently discontinued. At the end of the first month of hospitalization, "seizures" with typical myoclonic jerks were noticed by the treating physician. When an electroencephalograph (EEG) was done, "consistent seizures" were found, and the patient was transferred to the neurology department.

Ms. A stayed in the neurology department for about 3 weeks. She experienced 52 seizures in spite of being treated with several antiseizure medications. The patient was diagnosed with partial complex seizure and encephalopathy, with strong suspicion of Creutzfeldt-Jakob disease and vaculitis. Extensive medical workup was done during the first 2 weeks Ms. A was in the neurology department, including magnetic resonance imaging, lumbar puncture, EEG, and other blood tests. The protein

marker 14-3-3 β-isoform was, surprisingly, not detected in cerebrospinal fluid. A frontal lobe craniotomy and brain biopsy were done, and the diagnosis of Creutzfeldt-Jakob disease was confirmed by neuropathologic examination. Slides of blood samples were sent to The National Prion Disease Pathology Surveillance Center for registration and exploratory immunostaining, which identified a PrP gene mutation, E200K. The patient died 3½ months after the emergence of Creutzfeldt-Jakob disease symptoms.

Psychiatric disturbances constitute the prodromal manifestations in 18% to 39% of Creutzfeldt-Jakob disease patients.[1] The early psychiatric symptoms of Creutzfeldt-Jakob disease previously described in the literature include depression, depressive pseudodementia, mania, personality change, memory impairment, and psychosis.[2–7] Mood change and emotional lability are more common than psychosis in reported cases in the United States. Depression has been found in more than 30% of patients with Creutzfeldt-Jakob disease.[1] Psychotic symptoms such as delusion and hallucination, although less frequent, often coexist with confusion from the beginning.[6,7] When psychotic symptoms are treated with neuroleptics, the common side effects of neuroleptics, such as the extrapyramidal syndrome, are easily confused with the clinical picture of Creutzfeldt-Jakob disease because the clinical presentation of extrapyramidal syndrome and the early neurologic symptoms of Creutzfeldt-Jakob disease are almost identical. Our case is one of the typical examples. The same situation occurred in the case reported by Dunn et al.[7] Because of the lack of molecular genetic testing and family history in Dunn and colleagues' report, we do not know whether the case they reported was familial Creutzfeldt-Jakob disease or the more prevalent sporadic Creutzfeldt-Jakob disease.

The proportion of familial Creutzfeldt-Jakob disease is about 10%.[8] Familial Creutzfeldt-Jakob disease occurs as the result of specific point mutations or insertions in the prion protein gene and inherits as autosomal dominant type. Familial Creutzfeldt-Jakob disease can be further classified based on the locations of gene mutation or insertion. The most consistent clinical differences between familial Creutzfeldt-Jakob disease and sporadic Creutzfeldt-Jakob disease are that familial Creutzfeldt-Jakob disease patients have earlier age at onset and longer survival period. Brown et al.[9] found that, among the familial subgroup, patients with E200K had a mean ± SD age at onset of 55 ± 8 years, with progression to death in an average of 8 months. In our case, the patient presented with relatively early age at onset, short duration of disease course, and, unusually, initial psychotic symptoms. The meaning of this clinical presentation to the E200K group is not quite clear. In a study[10] of 11 cases of familial Creutzfeldt-Jakob disease E200K, no case presented with psychosis. Our case is the first one and only one with coexistent psychosis and confusion among these reported familial Creutzfeldt-Jakob disease E200K cases. More cases are needed to give an explanation of this phenomenon.

The authors thank David Wolfe, M.D., a neuropathologist at Mount Sinai Medical Center, for making the neuropathologic and molecular diagnosis of Creutzfeldt-Jakob disease in this case.

References

1. Will RG, Matthews WB. A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970–79, 1: clinical features. J Neurol Neurosurg Psychiatry 1984;47:134–140
2. Jiang TT, Moses H, Gordon H, et al. Sporadic Creutzfeldt-Jakob disease presenting as major depression. South Med J 1999;92: 807–808
3. Azorin JM, Donnet A, Dassa D, et al. Creutzfeldt-Jakob disease misdiagnosed as depressive pseudodementia. Compr Psychiatry 1993;34:42–44
4. Lendvai I, Saraway SM, Steinberg MD. Creutzfeldt-Jakob disease presenting as secondary mania. Psychosomatics 1999;40:524–525
5. Keshavan MS, Lishman WA, Hughes JT. Psychiatric presentation of Creutzfeldt-Jakob disease: a case report. Br J Psychiatry 1987;151:260–263
6. Stevens EM, Lament R. Psychiatric presentation of Jakob-Creutzfeldt disease. J Clin Psychiatry 1979;40:445–446
7. Dunn NR, Alfonso CA, Young RA, et al. Creutzfeldt-Jakob disease appearing as paranoid psychosis. Am J Psychiatry 1999;156: 2016–2017
8. Brown P, Gibbs CJ Jr, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. Ann Neurol 1994;35:513–529
9. Brown P, Goldfarb LG, Gibbs CJ Jr, et al. The phenotypic expression of different mutations in transmissible familial Creutzfeldt-Jakob disease. Eur J Epidemiol 1991;7:469–476
10. Hsiao K, Meiner Z, Kahaha E, et al. Mutation of the prion protein in Libyan Jews with Creutzfeldt-Jakob disease. N Engl J Med 1991; 324:1091–1097

Shoudu Zeng, M.D.
Chong Hwan Kim, M.D.
Habibur Rahman, M.D.
Mount Sinai School of Medicine
Elmhurst Hospital
Elmhurst, New York

High Prevalence of Bipolar Spectrum Disorders

Sir: I read with interest the *Journal* article by Ghaemi et al.[1] (October 2000) reporting that bipolar spectrum disorders were very common (found in 60% of their sample) and that many subjects diagnosed with "unipolar" depression (56%) were found to have bipolar disorder in a primary care psychiatric setting when patient assessment was made by trained clinicians who systematically and carefully interviewed about past hypomania. These findings support recent studies showing that, in samples of depressed outpatients, the prevalence of bipolar II disorder was 30% to 50%.[2–8] A community prevalence of bipolar spectrum disorders of 3% to 8.3% has been reported,[9] whereas a 0.5% community prevalence was reported in DSM-IV. The apparent increased prevalence of bipolar II disorder in these recent studies may be related to systematic questioning about past hypomania of depressed patients[4–8] and the use of a criterion of a minimum duration of hypomania shorter than the 4 days specified by DSM-IV (a cutoff not based on data[10]). Hypomania lasting 1 to 3 days (the modal range of duration of hypomania[11]) has been validated.[9,12,13]

Persons rarely present with hypomania and rarely report it spontaneously, because hypomania is often a brief and pleasant period of improved functioning.[2] Skillful systematic questioning about past hypomania and collateral information from family members are required to make the diagnosis.[1,2] The diagnosis can be unreliable because it is left to the patient's memory and to the skill of the interviewer. Reliability may also be reduced by the lack of clear boundaries between mania and hypomania and by different definitions of bipolar II disorder.[2,14]

Interrater reliability of diagnosis of bipolar II disorder has been found to be high with clinical interview ($\kappa = 0.85$) and low with structured interviews.[14,15] In another study,[16] trained clinicians using a semistructured interview made a bipolar II diagnosis more often than nonclinicians using a structured interview

and had high diagnostic agreement (κ = 0.94). Dunner and Tay[16] found that the screening section was a major limitation of the DSM-III structured interview for hypomania (a limitation also present in the DSM-IV structured interview): if the screening criteria in a given section were not met, the rest of the questions in the section were not asked, and further probing of the diagnostic subarea was not pursued. On the other hand, clinicians using the semistructured interview were able to pursue a clinical area repeatedly, since that interview did not restrict probing. In an important study reporting high long-term stability of bipolar II diagnosis,[13] diagnosis was made by trained clinicians. Poor reliability between diagnoses made by nonclinicians using structured interviews and those made by clinicians using nonstructured or semistructured interviews has been reported.[17] Structured interviews may reduce validity, since they include no clinical evaluation.[17]

These studies suggest that careful assessment (better if semistructured interviews are used) by trained clinicians can find many bipolar spectrum disorders misdiagnosed as unipolar disorders. These findings have important treatment implications in that antidepressants may worsen the course of bipolar disorders by inducing hypomania, rapid cycling, and mixed states.[2,18]

References

1. 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
2. Akiskal HS. Mood disorders: clinical features. In: Sadock BJ, Sadock VA, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000: 1338–1377
3. Angst J. Comorbidity of mood disorders: a longitudinal prospective study. Br J Psychiatry 1996;168(suppl 30):31–37
4. Benazzi F. Prevalence of bipolar II disorder in outpatient depression: a 203-case study in private practice. J Affect Disord 1997;43:163–166
5. Benazzi F. Prevalence and clinical features of atypical depression in depressed outpatients: a 467-case study. Psychiatry Res 1999;86: 259–265
6. Benazzi F, Rihmer Z. Sensitivity and specificity of DSM-IV atypical features for bipolar II disorder diagnosis. Psychiatry Res 2000;93: 257–262
7. Benazzi F. Bipolar II depression in late life: prevalence and clinical features in 525 depressed outpatients. J Affect Disord. In press
8. Hantouche EG, Akiskal HS, Lancrenon S, et al. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study. J Affect Disord 1998;50: 163–173
9. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
10. Dunner DL. Diagnostic revisions for DSM-IV. In: Goodnick PL, ed. Mania: Clinical and Research Perspectives. Washington, DC: American Psychiatric Press; 1998:3–10
11. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996;16(suppl 1):4S–14S
12. Akiskal HS, Djenderedjian AM, Rosenthal RH, et al. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 1977;134:1227–1233
13. 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
14. Coryell W. Bipolar II disorder: the importance of hypomania. In: Goldberg JF, Harrow M, eds. Bipolar Disorders: Course and Outcome. Washington, DC: American Psychiatric Press; 1999:219–236
15. Dunner DL. Bipolar depression with hypomania (bipolar II). In: Widiger TA, Frances AJ, Pincus HA, et al, eds. DSM-IV Sourcebook, vol 2. Washington, DC: American Psychiatric Association; 1996: 53–63
16. Dunner DL, Tay LK. Diagnostic reliability of the history of hypomania in bipolar II patients and patients with major depression. Compr Psychiatry 1993;34:303–307
17. Brugha TS, Bebbington PE, Jenkins R. A difference that matters: comparisons of structured and semi-structured psychiatric diagnostic interviews in the general population. Psychol Med 1999;29: 1013–1020
18. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990

Franco Benazzi, M.D.
National Health Service
Forlì, Italy

Dr. Ghaemi Replies

Sir: Dr. Benazzi raises some exceedingly important points regarding the diagnosis of bipolar spectrum illness. Currently, the DSM-IV nosology recognizes mania (type I) and hypomania (type II), but there is a large group of patients who are neither classically bipolar (type I) nor classically unipolar (no symptoms at all suggestive of hypomania). In my experience, many practitioners, especially those in private practice, treat a large group of patients in this category. If one were to use a DSM term, one would have to label these patients as having bipolar disorder, not otherwise specified (NOS). However, clinicians are sometimes hesitant to make NOS diagnoses because some insurance plans do not reimburse for NOS diagnoses. Thus, on rather unscientific grounds, many patients are getting labeled as having unipolar depression who do not classically fit those criteria.

In my opinion, many of these patients match the descriptions—suggested by Akiskal and Pinto,[1] Goodwin et al.,[2,3] and others—of bipolar spectrum illness. However, since we do not have generally accepted operationalized criteria for a specific bipolar spectrum disorder, these patients live in a purgatory in which sometimes they are diagnosed and treated as if they have unipolar depression and sometimes as if they have bipolar disorder. It is sometimes assumed that this bipolar spectrum group must be too heterogeneous to characterize and study diagnostically or genetically.[4] Yet, this assumption itself needs to be tested. There is some evidence, in fact, that patients with bipolar II illness may actually have more genetic loading than patients with bipolar I illness.[5] Although this finding may or may not be replicated, it raises the need for serious attention, including in genetics, to bipolar spectrum illness, in addition to the classic bipolar I and unipolar diagnoses. Clearly, more genetic, diagnostic, and treatment work needs to be done in the bipolar spectrum population.

References

1. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:vii, 517–534
2. Goodwin FK, Jamison KR. Manic Depressive Illness. New York, NY: Oxford University Press; 1990
3. Goodwin FK, Ghaemi SN. An introduction to and history of affective disorders. In: Gelder M, Lopez-lbor J, Andreasen N, eds. New Oxford Textbook of Psychiatry, vol 1. New York, NY: Oxford University Press; 2000:677–682
4. Baldessarini RJ. A plea for the integrity of the bipolar concept. Bipolar Disord 2000;2:3–7
5. DePaulo JR, McMahon FJ. Recent developments in the genetics of bipolar disorder. Cold Spring Harbour Symposia on Quantitative Biology 1996;61:783–789

S. Nassir Ghaemi, M.D.
Cambridge Hospital
Cambridge, Massachusetts