tion of anxious or panic disorder patients who often are fearful that their anxiety symptoms signal impending death. These patients hardly appear to embrace their own demise as a solution to their problems. However, anxiety disorders cover a wide spectrum of clinical presentations, and we have also reported that posttraumatic stress disorder (PTSD) increases the risk of suicidal behavior (6). Indeed, in a recent work describing a mostly independent sample (7), we replicated this finding but found that the association between PTSD and suicidal acts was related to the frequent comorbidity of cluster B personality disorders in depressed patients with PTSD. Thus, not all anxiety disorders are the same in terms of their relationship with suicidal acts.

For the current article, we examined our data in detail to determine whether anxiety and suicidal ideation were inversely related within or across episodes of depression in patients with major depressive disorder. We could find no evidence for this or for the opposite relationship, although, clearly, our measures of both anxiety and suicidal ideation were limited. We compared only the ratings on the Hamilton Depression Rating Scale, as was the goal of our article. Thus, an examination of anxiety and suicidal behavior, such as the ones we previously reported, may have yielded different results. Moreover, the relationship between suicidal behavior and anxiety may differ in unipolar and bipolar depression. This would not be totally surprising, given the fact that suicidal behavior is almost twice as common in bipolar disorder as in major depressive disorder (8–11), further underscoring the fact that these two disorders are different entities that share some commonalities.

References

1. Phillips ML, Drevets WC, Rauch SL, Lane R: Neurobiology of emotion perception, II: implications for major psychiatric disorders. Biol Psychiatry 2003; 54:515–528
2. DePaulo JR Jr: Genetics of bipolar disorder: where do we stand? (editorial). Am J Psychiatry 2004; 161:595–597
3. Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ: Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am J Psychiatry 2004; 161:1433–1441
4. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R: Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990; 147:1189–1194
5. Placidi GPA, Oquendo MA, Malone KM, Brodsky B, Ellis SP, Mann JJ: Anxiety in major depression: relationship to suicide attempts. Am J Psychiatry 2000; 157:1614–1618
6. Oquendo MA, Friend JM, Halberstam B, Brodsky BS, Burke AK, Grunebaum MF, Malone KM, Mann JJ: Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. Am J Psychiatry 2003; 160: 580–582
7. Oquendo MA, Brent DA, Birmaher B, Greenhill L, Kolko D, Stanley B, Zelazny J, Burke AK, Firinciogullari S, Ellis SP, Mann JJ: Posttraumatic stress disorder comorbid with major depression: factors mediating the association with suicidal behavior. Am J Psychiatry (in press)
8. Bostwick JM, Pankratz VS: Affective disorders and suicide risk: a reexamination. Am J Psychiatry 2000; 157:1925–1932
9. Chen Y-W, Dilsaver SC: Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. Biol Psychiatry 1996; 39: 896–899
10. Goodwin FK, Jamison KR: Suicide in Manic-Depressive Illness. New York, Oxford University Press, 1990
11. Sharma R, Markar HR: Mortality in affective disorder. J Affect Disord 1994; 31:91–96

MARIA A. OQUENDO, M.D.
ANDRES BARRERA, M.D.
STEVEN P. ELLIS, PH.D.
SHUHUA LI, M.D.
AINSLEY K. BURKE, PH.D.
MICHAEL GRUNEBAUM, M.D.
JEAN ENDICOTT, PH.D.
J. JOHN MANN, M.D.
New York, N.Y.

Tardive Dyskinesia and Second-Generation Antipsychotics

TO THE EDITOR: We read the systematic review of tardive dyskinesia associated with second-generation antipsychotics by Christoph U. Correll, M.D. and colleagues (1) with interest in view of its importance in clinical management. We evaluated this article based on the guidelines prescribed in the Cochrane Collaboration Handbook (2) and the Jadad et al. score (3).

There are certain methodological shortcomings in this systematic review. First, only the MEDLINE database was searched for studies in this area. A thorough search of other databases, including studies published in nonindexed journals, could have yielded more studies. Second, the studies were not assessed for their methodological qualities, and no definitive criteria were used that are usually recommended as an integral part of a systematic review (2, 3). Only three of the 11 studies included were randomized, double-blind, controlled trials; the rest were open-label studies. Even among these three, one was a study involving demented patients. Third, the studies included had used different modes of drug administration (injectable/oral), comprised patients of different age extremes, and included patients who had illnesses such as dementia and Parkinson's disease—all of which have a bearing on the development of tardive dyskinesia.

The authors have acknowledged the limitations of the database with regard to the lack of studies with rigorous methodology on tardive dyskinesia. Hence, we feel that given the heterogeneity of the sample, it was inappropriate for the authors to have calculated the rates of tardive dyskinesia by combining results from the studies. Such calculation might result in a faulty assessment of the risk of tardive dyskinesia with second-generation antipsychotics.

These limitations make it difficult to interpret the results of the review. It is worth considering whether the authors could have written a narrative review instead of a systematic review of the available database.

References

1. Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004; 161:414–425
2. Clarke M, Oxman AD: Cochrane Collaboration Handbook Version 4.0. Oxford, UK, Cochrane Library, Update Software, July 2000
3. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of ran-

domized clinical trials: is blinding necessary? Control Clin Trials 1996; 17:1–12

SUDEEP SARAF, M.D.
PRABHA S. CHANDRA, M.D.
Bangalore, Karnataka, India

TO THE EDITOR: I read with interest the recent excellent review on the risk of tardive dyskinesia with second-generation antipsychotic medications by Dr. Correll et al. However, for several reasons, the risk of tardive dyskinesia with certain second-generation antipsychotics may be higher than that reported in the original articles on which the review was based.

The use of 1 year as a minimum time period for inclusion of a study in the review was reasonable. However, tardive dyskinesia can occur for many years after treatment. Furthermore, many of these studies did not adequately assess acute-onset movement disorders—including parkinsonism, acute dystonia, and akathisia—that can increase the long-term risk of tardive dyskinesia. Of these, parkinsonism is particularly important for predicting the risk of tardive dyskinesia because it is associated with the masking of dyskinesia. Finally, in some of these studies, patients were treated with concomitant medications that can suppress dyskinesia.

For example, one study of risperidone and tardive dyskinesia (1) reported that parkinsonism increased significantly with risperidone treatment. Therefore, the patients with parkinsonism may have been at an elevated risk for developing tardive dyskinesia in the future. Furthermore, the dropout rate for this study was relatively high—60%. When questioned (2), the authors reported that some of the patients were excluded because of rigidity, but they did not report a percentage. The rigidity was probably due to parkinsonism. Therefore, it seems likely that patients at high risk of developing tardive dyskinesia were excluded from the study.

In another example, Csernansky et al. (3) reported that patients in their study were permitted to take several sedative-hypnotic or anxiolytic agents that can suppress antipsychotic-induced movement disorders. Little information was provided regarding the extent of use of these agents. Furthermore, as in the study by Jeste et al. (1), the study by Csernansky et al. (3) also had a relatively high dropout rate for the risperidone group—60%. The authors described the reasons for premature discontinuation in general terms, such as "patient's choice" or "adverse events," but it would have been helpful to understand the specific reasons for withdrawal. For example, did the patients withdraw because of acute-onset movement disorders?

The methodological limitations discussed should be addressed in the design of future studies of tardive dyskinesia. Until then, caution should be taken in interpreting the results of the review.

References

1. Jeste DV, Okamoto A, Napolitano J, Kane JM, Martinez RA: Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. Am J Psychiatry 2000; 157:1150–1155
2. Chaplin RH: Risperidone, tardive dyskinesia, and the elderly (letter). Am J Psychiatry 2001; 158:1336–1337
3. Csernansky JG, Mahmoud R, Brenner R: A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002; 346:16–22

DAVID E. ROSS, M.D.
Midlothian, Va.

Dr. Correll and Colleagues Reply

TO THE EDITOR: We thank Drs. Saraf, Chandra, and Ross for their comments regarding our article. Drs. Saraf and Chandra raise concerns regarding methodological shortcomings in our review. Their criticism focuses on the lack of screening of databases that contain nonindexed journals and the lack of specific criteria for the inclusion of studies that they feel were not assessed for their methodological quality. The authors conclude that because of the heterogeneity of studies, it was inappropriate to calculate incidence rates by combining results from these trials.

We agree with the notion that, unfortunately, too few studies are available that provide data on the development of tardive dyskinesia in patients treated with a second-generation antipsychotic for 1 year or longer. This is particularly true for randomized controlled trials. Given the dearth of long-term studies and the clinical importance of tardive dyskinesia, it seems unlikely that we would have found additional studies in journals that are not indexed by MEDLINE, although we cannot be certain of this. In addition to our comprehensive MEDLINE search, we screened proceedings and abstracts of major psychiatric meetings and contacted the manufacturers of all second-generation antipsychotics for unpublished data. In our Methods section, we clearly delineated the criteria used for inclusion of the reviewed studies. These were open or controlled treatment with any second-generation antipsychotic (i.e., amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, or zotepine) that involved at least 20 subjects, lasted 1 year or longer, and included data on newly identified cases of tardive dyskinesia or dyskinesia. Furthermore, we discussed the limitations of the reviewed studies regarding the open nature of most of the trials, differences in patient populations (e.g., age, ethnicity, gender, diagnosis, severity/chronicity of illness, etc.), employed rating scales and rating intervals, definitions of "caseness," doses of second-generation antipsychotics, the use of high-dose first-generation antipsychotic agents in the trials with an active comparator, the lack of data in drug-naive and pediatric populations, and shortcomings in some of the statistical analyses.

Given the heterogeneity of the available studies, it is surprising, however, that the reported 1-year incidence rates of tardive dyskinesia are relatively homogenous when stratified by age, which is the most robust risk factor for the development of tardive dyskinesia. In adults, the rates varied from 0% to 1.5%; in the elderly, the rates varied from 0% to 13.4%. These figures are about one-fifth of the widely reported 1-year incidence rates of tardive dyskinesia associated with first-generation antipsychotics, which are approximately 5% in adults (1–3) and 25%–30% in the elderly (4–7). Although the relatively small number of available studies and differences in their design precluded a formal meta-analysis based only on randomized controlled trials, explicit inclusion and exclusion criteria were used to justify a systematic review.