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.