

Analysis of Antipsychotic Dose Reduction

TO THE EDITOR: In the June 2010 issue of the *Journal*, Chuan-Yue Wang, M.D., Ph.D., et al. (1) conducted an open-label randomized controlled trial to examine the effects of reducing the risperidone dose in schizophrenia patients who had completed an acute phase treatment. The authors concluded that maintenance treatment at the initial dose for at least 1 year was safer and more effective in relapse prevention than the reduced dose strategy.

First, Drs. Wang et al. separately examined dropout rates as a result of "relapse" or "any reason other than relapse." However, overall treatment failure as a result of any reason is a more clinically pragmatic outcome. Had this outcome measure been adopted, the significant superiority in the no dose reduction group would have disappeared ($\chi^2=1.57$, $df=2$, $p=0.455$). Second, positive effects of reducing risperidone exposure on cognition (2) and subjective experience (3) were not considered. Third, the mean doses in the 4-week and 26-week groups were 2.2 mg/day (SD=0.4) and 2.1 mg/day (SD=0.3), respectively, after the dose reduction. This indicates that a number of subjects were maintained on less than 2.0 mg/day. Given that the lowest limit of dose range of risperidone approved for younger adults with schizophrenia is 2.0 mg/day, reducing the dose below this limit is not standard practice and may raise some ethical considerations. In a recent meta-analysis of published double-blind randomized controlled trials, we demonstrated that moderately low dose treatment may be as effective as the standard dose therapy for relapse prevention, while adopting a very low dose strategy (less than one-half the standard dose) is inferior to both standard and moderately low dose strategies (4). Fourth, a lack of dose retitration phase following symptom worsening limits translation of these results to clinical practice, since transient increase in clinical symptoms would be expected to be reversible with a small dose increase (5). Finally, inspection of Figure 2 and Figure 3 suggests that the 26-week group experienced worsening well before the dose reduction, limiting the interpretation of the observed differences compared with the maintenance group.

Taken all together, the safety and potential benefits of appropriate antipsychotic dose reduction in the maintenance phase should not be rejected.

References

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Reply to Uchida et al. Letter

TO THE EDITOR: We thank Dr. Uchida et al. for their interest in our recent article. Our response to their concerns are as follows. First, as we stated in the article, the primary outcome measure was relapse, namely, the estimated time from entry to relapse and the risk of relapse by the end of the study. In order to compare the primary outcome measure between the three groups, survival analysis, rather than chi-square test, is needed. Chi-square test is not appropriate here because relapses at different follow-up evaluations have different clinical implications. In addition, in the statistical analysis section, we clearly stated that the survival analyses included patients who relapsed and those who were lost to follow-up evaluation without documented relapse and were not considered relapsed at their last assessment, meaning that we examined dropout rates as a result of "relapse" and "any reason other than relapse" concurrently rather than separately. Second, because of logistical reasons, some secondary outcome measures, such as cognition, quality of life, etc., were not included in this study. Third, it is true that some patients were maintained on <2.0 mg/day in our sample. The Guidelines for the Prevention and Treatment of Schizophrenia in China recommend 2–6 mg/day as the therapeutic dose of risperidone for Chinese patients, a lower figure than the recommendation for their Caucasian counterparts (1). Since the recommended therapeutic dose range of risperidone for Chinese patients is lower than that for their Caucasian counterparts, the maintenance dose should be lower also; that is, the lowest dose of risperidone approved for Chinese adults with schizophrenia is not 2.0 mg/day but less than that. Because the flooring dose of maintenance treatment with risperidone for Chinese patients has not been determined, a rather cautious and closely monitored dose reduction strategy could hardly raise serious ethical considerations. This is particularly true in light of the placebo-controlled antipsychotic trials in the long-term treatment of schizophrenia. Furthermore, in our study, we did