Ziprasidone and QTc Prolongation

Sir: We read with great interest Dr. Sharif's report about the safety of antipsychotics in primary care.[1] He states that ziprasidone and thioridazine caused a clinically significant increase of QTc. An open-label, parallel-group phase 1 study (054 study)[2] found that mean QTc increases were comparable for ziprasidone and 4 other antipsychotics—haloperidol, quetiapine, risperidone, and olanzapine—at maximum steady-state plasma concentrations. In this study,[2] no cardiovascular symptoms or QTc ≥ 500 ms were observed. The U.S. Food and Drug Administration has used QTc intervals ≥ 500 ms as a clinically significant cutoff. Therefore, although ziprasidone, as well as other antipsychotics (haloperidol, quetiapine, risperidone, and olanzapine), increases the QTc, this increase is not clinically significant. Apart from this, ziprasidone has not been associated with torsades de pointes, sudden death, or increased cardiac mortality.[3]

Drs. Ortega, Cano, and Díez are employees of Pfizer.

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Dr. Sharif Replies

Sir: The exact statement in my article is as follows: "One study showed that risperidone, olanzapine, quetiapine, and haloperidol had a negligible effect on QTc, but ziprasidone and thioridazine caused a clinically significant increase" (p. 4).[1] This statement does not imply that the QTc prolongation associated with ziprasidone and thioridazine was the "same" but rather that both drugs were associated with this change to a greater extent than other antipsychotics tested. Secondly, Drs. Ortega et al. state that the QTc prolongation for ziprasidone and other antipsychotics (olanzapine, risperidone, quetiapine, haloperidol) were "comparable" based on the 054 study. The statement in the U.S. label for ziprasidone based on the results of the 054 study is "The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for 4 of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine."[2] The U.S. label for ziprasidone includes a bolded warning regarding QT prolongation. It is true that there were no clinical events associated with this increase noted in the clinical trials. I refer Drs. Ortega et al. to my article[3] (from which this report was extracted as a summary) for a more complete discussion of this issue.

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