Potential Association Between Risperidone and Cerebrovascular Events

Sir: We read with interest the recently published discussion concerning the use of atypical antipsychotic medications in the primary care setting.[1] The role of risperidone and olanzapine in managing adverse behavioral manifestations of dementia, including aggression and other behavioral dyscontrol problems, was of particular interest. We were appreciative of the emphasis placed upon judicious use of low doses of these medications and the emergence of significant side effects such as falls and somnolence at very low doses of risperidone in particular.

Our own approach to challenging behavioral manifestations in dementing disorders involving the use of atypical antipsychotic medications such as risperidone echoes these concerns. We would only add that in light of recent concerns about a possible association between risperidone exposure and increased rates of cerebrovascular adverse events such as stroke and transient ischemic attacks relative to placebo observed in dementia trials,[2] further caution may be warranted in elderly patients with histories of dementia with concomitant cardiovascular disease. We recognize, however, that the nature of this apparent association has not received further systematic study and that a cause-effect relationship has not been proved.

Although a 4% versus 2% (risperidone vs. placebo) incidence of cerebrovascular adverse events was reported,[2] it was unclear to what degree—if at all—these results achieved statistical significance. Since the incidence data were calculated by totaling results from 4 separate placebo-controlled trials, it is unclear whether or not there was true randomization between study "arms." The importance of this point rests in the possibility that significant differences in rates of medical comorbidity alone may have explained the differences in the observed frequency of cerebrovascular illness onset between exposure groups. Furthermore, the mechanism by which risperidone may increase vulnerability to cerebrovascular events in the susceptible elderly is unknown; however, one potential target may include exaggerated hypotensive effects due to risperidone-induced peripheral adrenergic receptor blockade. Such an effect may be more pronounced in patients who are severely dehydrated or taking antihypertensive medications. Other potential mechanisms may include drug-induced arrhythmias, dyslipidemia, and diabetes mellitus. Although these effects have been observed with several antipsychotic medications, they seem to be observed less consistently in patients taking risperidone,[3,4] especially at lower geriatric doses. Despite these unknown factors, we are in agreement with Drs. Mintzer[1] and Wooltorton[2] that specific target symptoms should be managed with low medication doses and that the risks of risperidone exposure, which may include susceptibility to cerebrovascular events, should be discussed with patients or decision makers, whichever is appropriate.

The views expressed herein are those of the authors and do not necessarily reflect the views of the U.S. Navy.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Editor's Note: On April 16, 2003, Janssen distributed a Health Care Professional letter alerting clinicians to the following addition to the Risperdal package insert. This addition was based on the analyses[2] alluded to in the letter by Drs. Bobo and More.

Warnings: Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia. Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73–97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. Risperdal has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.