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Antipsychotics Tied to Brain Volume Loss in Schizophrenia

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Authors and Disclosures

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February 11, 2011 — A new study shows patients with schizophrenia receiving antipsychotic medication may lose a small, but measurable, amount of brain tissue over time. Patients who take the largest doses over the longest duration of time are apt to see the greatest declines, new research suggests.

Illness duration and severity were also associated with brain volume loss, but the association between antipsychotic drug use and brain volume remained significant after accounting for these factors. The volume losses occurred in gray matter and white matter.

"The clinical significance of these findings is extremely difficult to fully assess," study investigator Beng-Choon Ho, MD, MRCPsych, told *Medscape Medical News*. "To achieve this will require randomized controlled studies involving schizophrenia patients and healthy controls, but such studies do not meet current ethical standards in research."

Dr. Ho, from the University of Iowa Carver College of Medicine in Iowa City, said it's "important for clinicians to work with schizophrenia patients so as to find the minimum effective antipsychotic dosage for each individual patient." However, the findings do not support monitoring of patients by using follow-up brain imaging, he added.

The findings are reported in the February issue of the *Archives of General Psychiatry*.

Hot Debate

More than a decade of research has shown that patients with schizophrenia experience progressive reductions in brain volume, particular gray matter volume. Whether this is largely an effect of the disease or whether antipsychotic drugs also have a role is the subject of debate.

The study involved 211 patients with schizophrenia who underwent repeated magnetic resonance imaging (MRI) of the brain beginning soon after diagnosis. Each patient had an average of 3 scans over a little more than 7 years,

yielding a total of 674 for analysis. The initial MRI took place between 1991 and 2006 and the last between 1995 and 2009.

The researchers assessed the independent effects of 4 potential contributors to progressive brain volume loss: illness duration, antipsychotic treatment, illness severity, and substance abuse.

The types of antipsychotic drugs patients received were consistent with national trends at the time of their initial MRI (1991 - 2006) and their last MRI (1995 - 2009). Typical antipsychotics were the mainstay before the initial MRI, and nonclozapine atypical antipsychotics became the main choice (in roughly two thirds of the sample) later on. About 25% of patients received clozapine.

According to the study, longer follow-up correlated with smaller brain tissue volumes. Greater intensity of antipsychotic treatment correlated with indicators of generalized and specific brain tissue reduction, after adjustment for the effects of illness duration and severity and substance abuse.

"More antipsychotic treatment was associated with smaller gray matter volumes," the authors report. "Progressive decrement in white matter volume was most evident among patients who received more antipsychotic treatment."

Changes in brain volume with time were similar for all antipsychotic drug classes.

Illness severity had "relatively modest" correlations with tissue volume reduction, and substance abuse had no significant associations, after adjustments were made for the other variables.

"It is possible that, although antipsychotics relieve psychosis and its attendant suffering, these drugs may not arrest the pathophysiologic processes underlying schizophrenia and may even aggravate progressive brain tissue volume reductions," the authors conclude.

"This study does not mean that schizophrenia patients should stop taking antipsychotics," said Dr. Ho.

Interpret Cautiously

David A. Lewis, MD, from the University of Pittsburgh and author of an accompanying editorial agrees.

"A classic maxim in clinical medicine is to treat the patient, not the laboratory test — or in this case, the MRI," Dr. Lewis writes. "Thus, the findings of Ho and colleagues should not be construed as an indication for discontinuing the use of antipsychotic medications as a treatment for schizophrenia."

The findings do, however, "highlight the need to closely monitor the benefits and adverse effects of these medications in individual patients, to prescribe the minimal amount needed to achieve the therapeutic goal, to consider the addition of non-pharmacological approaches that may improve outcomes and to continue the pursuit of new antipsychotic medications with different mechanisms of action and more favorable benefit to harm ratios," Dr. Lewis concludes.

Dr. Ho adds that for patients with other psychiatric conditions who may benefit from antipsychotic treatment, it is important to weigh the benefits against potential risks associated with antipsychotic treatment.

"When clinically indicated in non-schizophrenia patients, antipsychotics should be prescribed at the lowest effective dosages and for a limited time duration," he said.

The study was supported in part by grants from the National Institute of Mental Health. Dr. Ho has disclosed relationships with Ortho-McNeil Janssen Scientific Affairs. Dr. Lewis has disclosed relationships with Bristol-Myers Squibb, Curridium Ltd, Pfizer, AstraZeneca Plc, BioLineRx, Merck and Co Inc., Neurogen Corporation, and SK Life Science Inc.

Arch Gen Psych. 2011;165:126-137. Abstract

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