Antipsychotics with a high binding affinity for alpha-2-adrenergic and M1-muscarinic receptors are associated with a greater risk for stroke than other types of antipsychotics, new research suggests.

"The association appears to be dose-related and noted only in the first 28 days of antipsychotic use," Susan Shur-Fen Gau, MD, PhD, from the National Taiwan University Hospital and College of Medicine in Taipei, told *Medscape Medical News*.

"The antipsychotic-related stroke risk was higher in the patients who were older and/or who suffered from dementia," she added.

The study was published March 1 in *Biological Psychiatry*.

In a statement, John Krystal, MD, editor of *Biological Psychiatry*, who was not involved in the research, said antipsychotics have "a wide range of receptor profiles. The stroke risk profiles from this study suggest that it may be possible to use antipsychotics more safely in the elderly."

**Receptor Profile Matters**

Prior studies have suggested a link between antipsychotic use and stroke, but until now the relationships between receptor-binding profiles of antipsychotics and the risk for cerebrovascular events were unclear.

Using the National Health Insurance Research Database in Taiwan, Dr. Gau and colleagues analyzed 14,584 stroke patients who had at least 1 antipsychotic prescription during the year before the first-time hospitalization for stroke.

Their mean age at stroke onset was 68.5 years. Roughly half were women (50.8%), 17.5% had dementia, and 72.7% had ischemic stroke. The mean cumulative days of antipsychotic use in the previous year was 66.9.

The researchers report that antipsychotic use during the 2 weeks before the stroke was associated with a 1.6-fold increased risk for stroke after adjusting for health system utilization and proposed confounding medications.

The risk for stroke with antipsychotic use increased in individuals of older age and in those with dementia ($P < .001$ for both).

"However, the stroke risk of antipsychotic use in the 2 weeks before stroke was inversely associated with the cumulative days of antipsychotic use during the previous year ($P < .001$)....Patients who used antipsychotics over longer periods (more than 28 days) had no excess risk of stroke.

"This is consistent with previous findings that the risk of stroke is highest in the initial weeks of antipsychotic treatment," the researchers write.

**Clinical Implications**

The investigators also observed that higher dose of antipsychotics (150 mg chlorpromazine-equivalent dose) was associated with a greater stroke risk than the use of a lower average daily dose (odds ratio, 1.24; 95% confidence interval [CI], 1.11 - 1.38).
They also found that antipsychotics with high binding affinity for serotonin (serotonin 1A, 5-HT2A, serotonin 6, and serotonin 7), dopamine (D2 and D4), histamine (H1), muscarinic (M1), and adrenergic receptors (alpha-1 and alpha-2) were associated with a greater risk for stroke than those with low binding affinity.

After stepwise model reduction, high affinity of the M1-muscarinic and alpha-2-adrenergic receptors was significantly associated with increased stroke risk. The adjusted odds ratio with M1-muscarinic high-binding affinity (vs low) was 1.47 (95% CI, 1.28 - 1.69). For alpha-2-adrenergic receptors (high vs low), it was 1.84 (95% CI, 1.64 - 2.07).

The researchers note that more research into the possible biological mechanisms underlying the relationship between stroke and antipsychotic type is warranted.

The clinical implications, Dr. Gau said, are straightforward.

"For those patients who need to be treated with antipsychotics, we suggested choosing antipsychotics with lower binding affinity of M1-muscarinic and alpha-2-adrenergic receptors, starting antipsychotics at low dosages, and closely monitoring the side effects in the initial treatment, particularly for individuals with older age and the presence of dementia," she said.

This study was supported by grants from Far Eastern Memorial Hospital and National Health Research Institute, Taiwan. Dr. Gau has received speaking honoraria and travel funds from Eli Lilly, has been an investigator in 2 clinical trials from Eli Lilly, and has received speaking honoraria from Janssen and AstraZeneca. A complete list of author disclosures is given in the original article.


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Cite this article: Specific Antipsychotics Linked to Stroke Risk Identified. Medscape. Mar 21, 2013.