A new study has confirmed an association between proton pump inhibitors (PPIs) — drugs that treat heartburn, peptic ulcers, and other acid-related disorders of the upper gastrointestinal tract — and increased risk for dementia in older patients.

An earlier study by the same researchers found the same connection between PPI use and dementia risk, although the current study is larger and based on information from a pharmaceutical database rather than on medical records, as the previous one was.

The new study, by Willy Gomm, PhD, from the German Center for Neurodegenerative Diseases, Bonn, Germany, and colleagues and published online February 15 in JAMA Neurology, is important, as PPIs are among the most frequently prescribed drugs and their use has been increasing sharply, especially among the elderly.

"Unfortunately, overprescribing of PPIs is reported frequently," said study coauthor Britta Haenisch, PhD, also from the German Center for Neurodegenerative Diseases.

According to some research, up to 70% of all PPI prescriptions could be inappropriate, she told Medscape Medical News.

"In general, clinicians should follow guidelines for PPI prescription to avoid overprescribing PPIs and inappropriate use."

The study used the largest mandatory public health insurer in Germany, which includes one third of the overall population and as much as 50% of the elderly population. Its database includes information on diagnoses and drug prescriptions.

The analysis included 73,679 subjects aged 75 years or older who initially did not have dementia at baseline. Over the course of the study (2004 - 2011), 29,510 subjects were diagnosed with dementia. More than half (59.0%) had a diagnosis of at least two different types of dementia.

Researchers focused on regular PPI prescription for at least 18 months. They looked at intervals starting with a 1-year baseline in 2004 followed by 18-month intervals, with the last interval lasting 12 months.

Regular PPI use was defined as at least one prescription per quarter in these intervals of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.

The results showed that 2950 patients were regularly using a PPI. These users had a significantly higher risk for dementia compared with those not taking this drug (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.36 - 1.52; \( P < .001 \)).

**Depression and Stroke**

Several confounding factors were significantly associated with increased dementia risk; for example, depression (HR, 1.28; 95% CI, 1.24 - 1.32; \( P < .001 \)) and stroke (HR, 1.37; 95% CI, 1.29 - 1.46; \( P < .001 \)).

Having diabetes and being prescribed five or more drugs other than the PPI (defined as polypharmacy) were also associated with significantly elevated dementia risk.

"In our analysis, polypharmacy elevated the risk for occurrence of dementia by about 16%," commented Dr Haenisch.
For the three most prescribed PPIs (omeprazole, pantoprazole, and esomeprazole), researchers performed subgroup analyses and found similar results.

To examine the effect of duration of PPI use, the researchers analyzed occasional use, defined as a prescription in less than six quarters within an interval. They found a lower HR for occasional use (HR, 1.16; 95% CI, 1.13 - 1.19).

The risk for dementia with PPI use gradually decreased with age, with the highest HR among those aged 75 to 79 years. Depression and stroke also had lower effect sizes with increasing age.

"This might reflect the decreasing influence of external and internal factors on dementia progression with age, possibly owing to an already initiated disease process," the authors write.

Researchers are not clear on how PPI use might raise dementia risk. Evidence suggests some PPIs may cross the blood–brain barrier and interact with brain enzymes and, in mice, may increase beta amyloid levels in the brain.

Although the current study did not include vitamin B_{12} levels, other research has linked PPI use to vitamin B_{12} deficiency, which has been shown to be associated with cognitive decline, Dr Haenisch noted.

The new results coincide with those of the research group's earlier study: the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe). That study, which included 3327 community-dwelling patients aged 75 years and older, also found a link between PPI use and dementia, with an HR of 1.38 (95% CI, 1.04 - 1.84).

Because the claims data used in the current study lack detailed sociodemographic parameters, the researchers could not integrate education levels into the analysis.

"This is a limitation of the study that has to be taken into account when interpreting the results," commented Dr Haenisch. "In the previous AgeCoDe study, we were able to include education into the analysis, and it did not mainly affect the result."

Also unlike the earlier study, the current one did not assess the effect of APOE 4 status.

There are several alternatives to PPIs to treat gastrointestinal disorders in the elderly. According to Dr Haenisch, these include histamine H2 receptor antagonists, prostaglandins, and antacids.

Dr Haenisch stressed that the study can only provide a statistical association between PPI prescription and occurrence of dementia and does not prove that PPIs cause dementia. To evaluate the cause-and-effect relationships in the elderly, randomized, prospective clinical trials are needed, she said.

More People With Dementia

In his accompanying editorial, Lewis H. Kuller, MD, DrPH, from the Graduate School of Public Health, Department of Epidemiology, University of Pittsburgh, Pennsylvania, notes that even a relatively small increased risk for dementia could translate into many more people in the population having dementia.

For example, he writes, a 1.4-fold increased risk, as suggested by the study, would increase the estimated incidence rate of dementia from 6.0% to about 8.4% per year.

In the United States, 13.5 million people are in the 75- to 84-year-old age bracket. If 3% of them were receiving PPIs, this could result in an increase of about 10,000 new cases of incident dementia per year in this age group alone, said Dr Kuller.

Dr Kuller also pointed to evidence of PPIs possibly increasing both production and degradation of amyloid, at least in animals, and of reduced B_{12} and other nutrients among PPI users, which could be tied to dementia risk. However, he
said, it is possible that the association between PPI use and dementia is not causal.

Older people, said Dr Kuller, often take many drugs, which may reflect the extent of disease and comorbidities. Specific drugs may be associated with both PPI use and dementia.

The authors, said Dr Kuller, "have provided an important and interesting challenge" to evaluate the possible association between PPI use and dementia risk. Their study raises the issue of "whether a careful evaluation of cognitive changes and/or neuropathology should be a component of the evaluation of drugs that are widely used among the elderly," he concludes.

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