ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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The Possible Association Between Proton Pump Inhibitors and Dementia

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G&H What are the common indications for proton pump inhibitor therapy?

DJ The most common indication for proton pump inhibitor (PPI) therapy is gastroesophageal reflux disease, as this type of medication suppresses gastric acid secretion. Therefore, any gastrointestinal disease that has a pathogenesis related to acid reflux or acid secretion (eg, ulcerative diseases, gastric or duodenal ulcers) can effectively be treated with PPI therapy.

G&H What are the most commonly prescribed PPIs?

DJ The most commonly prescribed PPIs are dexlansoprazole (Dexilant, Takeda Pharmaceuticals) and esomeprazole. However, PPIs are also available as over-the-counter medications and include omeprazole, lansoprazole, and esomeprazole. These medications can be prescribed, but would typically be provided at higher doses.

G&H How prevalent is PPI use (prescription or over-the-counter) among the elderly, as well as in the general population?

DJ The exact prevalence of PPI use is unknown because purchases and use of over-the-counter medication are unreliable. However, given the prevalence of gastroesophageal reflux disease, the use of PPIs is very common. Hundreds of millions of patients have taken these medications since the release of the first omeprazole in 1989. Overall, PPI therapy is extremely effective and has been proven to be remarkably safe.

G&H Is there a relationship between PPI use and the risk of dementia?

DJ Results of a recent study by Gomm and colleagues have suggested a causal link between the diagnosis of dementia (based on diagnostic codes) and PPI therapy. This study has received a lot of attention because of the tremendous amount of focus being given to the prevalence of dementia among older patients. It is estimated that 35 million patients have a diagnosis of dementia, and this number is expected to increase nearly 2.5 times by the year 2040. Dementia has a major economic impact as well, with a worldwide cost of approximately $600 billion, according to a 2010 analysis. Therefore, this study generated some concern regarding whether PPIs could be causing dementia.

G&H How valid is this allegation of harm?

DJ I utilize a 4-step approach to evaluate medical assessments of harm: I consider the scientific hypothesis, the biologic plausibility, the scientific evidence, and what is seen in my practice. The scientific hypothesis of this study is that PPIs might cause or facilitate the development

of beta-amyloid plaques, the accumulation of which are a major component of Alzheimer disease. Biologic plausibility lies in the suggestion that exposure to PPIs might increase beta-amyloid plaques in animal models. The scientific evidence garnered acclaim when the retrospective study of a database, mentioned previously, was published in February 2016. The authors of this study suggested that men and women with dementia were 1.5 and 1.4 times more likely, respectively, to be taking PPIs. After evaluating those 3 aspects, I then consider whether the purported association of risk resonates with what I am seeing in my daily clinical practice.

The challenge in evaluating the evidence stems from the authors adjusting for some, but not all, of the confounding variables. In particular, they adjusted for age, sex, polypharmacy, stroke history, depression, ischemic cardiac disease, and diabetes. The analysis did not include alcohol use, family history of dementia, and hypertension, which are well-known, significant risk factors for dementia. Therefore, potential major risk adjustments that may confound the findings were not reported. Additionally, the study evaluated the use of prescribed PPIs but did not include over-the-counter medications, despite their use in Germany (where this study was conducted) since 2009. It is also important to recognize that dementia was chosen as a code base. Only 2% of the German cohort had Alzheimer disease (the disease suggested by the authors' concept of biologic plausibility); the rest were considered as having dementia. As there is no validated assessment tool to determine cognitive function, it is uncertain whether a patient had true dementia or if a patient presented with cognitive impairment without dementia. In many pharmacodiligence studies, focus on odds (or, in this case, hazard) ratios is associated with the medication and disease association (eg, PPIs and dementia). This study has a hazard ratio of less than 2, which is a very nominal ratio, and values less than 2 should raise concern for the validity of the allegation of harm unless there is a completed adjustment for all stratification bias risks, which was not done in this study.

G&H Did dose amount, length of use, or regular vs occasional use of PPIs affect the risk of dementia in the study?

DJ No; this particular study did not evaluate dose amount or length of use, and it only covered patients taking prescribed PPIs. It did, however, report the duration of exposure for occasional PPI use (defined as a PPI prescription in <6 quarters within an interval) as a hazard ratio of 1.16 (95% CI, 1.13-1.19), which is extremely low. Data are not currently strong enough to avoid or reduce the use of PPIs in patients with risk factors for dementia or in the general population.

G&H What are the alternatives to PPI therapy to treat gastrointestinal disorders?

DJ Alternative medications include histamine H2-receptor antagonists (eg, ranitidine, famotidine), antacids, and alginates (eg, Gaviscon, Sanofi Aventis). It is very important to emphasize targeting weight reduction, which has a significant effect on reflux percent. Results from the Nurses' Health Study showed that patients with primary or ongoing reflux symptoms, obese patients, and even patients with a normal body mass index benefited from weight loss.

G&H Are most clinicians aware of the possible relationship between PPIs and the risk of dementia?

DJ I do not believe that many clinicians are aware of the possible association unless they read the study or the press surrounding it. It is likely that more patients have heard about it than physicians.

G&H What should clinicians tell patients who are concerned about this possible connection?

DJ Clinicians should have an open dialogue with their patients. Discussion points should include the reason for taking the PPI, whether the medication is needed, and whether the patient has tried to stop the medication. After performing a risk analysis, clinicians should make a decision based upon what the patient actually needs. Many patients continue prolonged PPI usage beyond what is necessary. In patients who do not need to avoid interruption of PPIs (eg, patients with strictures, Barrett esophagus, or nonsteroidal anti-inflammatory drug prophylaxis use), clinicians should ask whether the patient has tried to stop taking the PPI and if any symptomatic relapse occurs, particularly in short-term disruption. The discussion should serve as a platform to remove any medication that might otherwise not be needed any longer. It is beneficial to remember that the association between PPI use and dementia does not have much scientific credibility based on the present evaluation of the allegation of harm.

G&H Is the possible risk of dementia addressed in any guidelines for gastroesophageal reflux disease or PPI use?

DJ The study associating PPI use and dementia was published in February 2016, and the most recent iteration of the national guidelines from the American College of Gastroenterology for the management of gastroesophageal reflux disease was published in 2013. However, there are some emerging consensus documents that will address the risk of dementia as well as several other allegations of PPI-related effects.

G&H What are the top priorities of research in this field?

DJ Because the class of PPI medications has been around since 1989 and is among the most utilized medications for physician-directed and over-the-counter use, the exposure index for this drug class is vast. Accordingly, it would be beneficial to evaluate any scientific hypothesis that generates a harm element against PPIs, given the population exposed. Such allegations of harm, however, should be pursued with appropriate scientific rigor, as opposed to retrospective database analyses without stratified adjustment of risks. There is more potential risk from poorly designed studies with related misdirected messages of harm.

Dr Johnson serves as a consultant to Pfizer, Procter & Gamble, and Medscape-WebMD.

Suggested Reading

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