Proton Pump Inhibitors and Dementia

By Sanaz MoharramZadeh, BSc, Nader Tavakoli, MD, and Amrit Parhar, MD

Hospitals can be dangerous places for older adults. One of these dangers is inappropriate medications — the most common of which is proton pump inhibitors (PPIs). Patients who are discharged taking a PPI often continue to receive it after their admission to a skilled nursing facility. But care needs to be taken: if the PPI is inappropriate, it must be discontinued. As this article highlights, PPIs have many risks to be considered when assessing their continued use with long-term care patients.

Proton pump inhibitors (PPIs) have become one of the most commonly prescribed medications worldwide. In 2017, over 100 million prescriptions were written in the United States alone for these medications (*Fed Pract* 2017;34:19–23). Some of the known side effects of PPIs are interference with calcium, magnesium, iron, and vitamin B12 absorption. They also increase the risk of *Clostridium difficile* infection, pneumonia, and interstitial nephritis. Therefore, prescribing these medications should be based on a valid clinical indication.

There have been conflicting studies on the association between long-term use of PPIs and increased risk of dementia in elderly patients (*Gastroenterology* 2017;153;35–48). Some studies that have explored long-term use of PPIs found that they may accelerate senescence in human endothelial cells and also may change amyloid metabolism, which can lead to Alzheimer's disease (AD). PPIs can also increase the risk of vitamin B_{12} deficiency by suppressing-gastric acid in the long term (*JAMA Neurol*. 2016;73(4):410–416).

Although some large studies have shown significant associations between PPI use and incident dementia, other studies have contradicted them. Multiple confounders — including age, depression, diabetes, stroke, ischemic heart disease, AD, genetics, and polypharmacy — can interfere with attributing dementia solely to long-term use of PPIs. Specific considerations also should be noted: in individual patients, the benefits of using PPIs may outweigh the potential adverse effects.

Britta Hänisch, PhD, of the German Center for Neurodegenerative Diseases and her fellow researchers in the German Study on Aging, Cognition and Dementia in Primary Care Patients conducted a multicenter cohort study to explore PPI use in long-term care and dementia (*Eur Arch Psychiatry Clin Neurosci* 2015;265:419–428). Of the 3,323 participants aged 75 and older who were observed for 18 months, 431 patients developed dementia, and AD was diagnosed in 260. Even allowing for potential confounders — including age, sex, education, polypharmacy, and comorbidities such as stroke, diabetes, and apolipoprotein E4 allele status — they concluded that patients receiving PPI medication had a significantly increased risk of any dementia.

When Paul Lochhead, MBChB, PhD, and colleagues of the Massachusetts General Hospital in Boston examined the prospective data on medication use collected in the Nurses' Health Study II from the 13,864 participating women, they found no convincing association between PPI use and cognitive function or dementia risk (*Gastroenterology* 2017;153:971–979.e4). Riley Batchelor, MBBS(Hons) MMed, and colleagues of Monash University in Melbourne, Australia, conducted a systematic review of 11 studies on the relationship of PPI use and dementia (four studies) or acute cognitive impairment (seven studies). Although the majority observed a positive association for acute cognitive impairment, the methodological issues and conflicting results with these studies limited the value of their

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"Serotonin Syndrome," Dec. 10, 2019; https://mayocl.in/2VSdkv0). We must review carefully (e.g., look up side effects on Google or Medscape) and address existing medications before getting psychiatric consultations and adding more medications.

It is true that simple nonpharmacological interventions can be very helpful or sufficient in addressing situations that might otherwise culminate in VPA. Over the years, we have often reduced aggression successfully by removing unnecessary and excessive restrictions and care that patients don't need or want (such as sliding-scale insulin and modified texture diets and liquids), which often lead to conflict and a substantial risk of VPA.

While nonpharmacological interventions and prudent medication reductions are sometimes sufficient, we all need to recognize the value of medications used appropriately (Lyketsos et al., Psychiatric Aspects of Neurological Diseases, Oxford UP, 2008; Desai and Grossberg, Psychiatric Consultation in Long-Term Care, Cambridge University Press, 2017). As have others, I have seen thousands of patients over the years who were helped greatly by getting the right psychopharmacological medications in the right doses based on effective diagnosis and clinical reasoning. In contrast, prescribing based on guessing rarely improves — and often exacerbates — aggression.

In summary, many things have been done over the years to try to reduce abuse, with some success. There is a lot we can all do to improve the situation further, but it requires going beyond the usual and customary approaches that can only get us so far. It is time to reopen a largely closed dialogue and get our facts and methods straight.

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conclusions (*J Gastroenterol Hepatol* 2017;32:1426–1435).

A study by Felicia Goldstein, PhD, and colleagues at the School of Medicine at Emory University in Atlanta, investigated the association between PPI use and mild cognitive decline, dementia, and AD in a longitudinal observational study (*J Am Geriatr Soc* 2017;65:1969–1974). Their 10,486 participants aged 50 and older, all with normal cognition level, were classified into three groups: regular PPI users (8.4%), intermittent PPI users (18.4%), and no PPI use (73.2%). After two to six annual visits, the continuous PPI users were found to be at lower risk of declining cognitive function (hazard ratio 0.78; 95% confidence interval, 0.66–0.93 $P = 0.005$). The intermittent users also had a lower risk of decline in their cognitive function (HR 0.84; 95% CI, 0.76–0.93; $P = 0.001$). So interestingly their study found PPI use to be associated with a *lower* risk of declining cognitive function and/or its conversion to AD.

In the most recent of the meta-analyses, Muhammad Ali Khan, MD, of the University of Alabama School of Medicine and his U.S. and Canadian coauthors examined 11 observational studies, comprising a total of 642,949 patients (64% women). They found no evidence for an association between PPIs and dementia, and they concluded that PPIs are appropriate among patients who have a valid indication for their use and should not be restricted because of concerns of dementia risk [*Am J Gastroenterol*, Jan. 2, 2020; doi:10.14309/ajg.0000000000000500].

To summarize these findings, recent studies have reached divergent conclusions about PPIs and their potential side effects for dementia in long-term care. Some studies have found that long-term PPI use may be associated with the development of dementia while others claim that PPIs may be protective against cognitive decline. In other words, there is no concrete evidence that PPI use is associated with the development of dementia; the claim that dementia may be related to PPI use is unsubstantiated.

The bottom line remains the same: when prescribing any medications to individual patients, the benefits must be weighed against the potential adverse effects. With PPIs, unfortunately the risks are many and are not entirely clear. But fortunately further research on long-term PPI use is currently underway.

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