



Published in final edited form as:

JAMA Neurol. 2016 August 01; 73(8): 1027–1028. doi:10.1001/jamaneurol.2016.1962.

Proton Pump Inhibitors and Dementia Incidence

Long Nguyen, MD, MS, Chin Hur, MD, MPH

Gastroenterology, Massachusetts General Hospital, Boston.

To the Editor We read the article by Gomm et al¹ with great interest as the long-term safety with prolonged proton pump inhibitor (PPI) use is of significant concern for both health care prescribers and patients. The investigators analyzed a prospective observational cohort of patients derived from the largest German statutory health insurer from 2004 to 2011 and reported that regular PPI use was associated with a significantly increased risk for incident dementia compared with those patients not receiving PPI therapy.¹

Proton pump inhibitors are among the top 10 prescribed medications globally, and we welcome the authors' contribution to the growing body of literature that suggests that PPIs may have previously underrecognized detrimental effects including increased risk for pneumonia, *Clostridium difficile* infection, hypomagnesemia, and hip fracture.^{2–5} These findings are even more concerning in light of some estimates that PPIs are frequently overprescribed in more than 40% of all dispensations.

However, several important shortcomings in study design raise concerns regarding the clinical applicability of the results. The study population of elderly patients from an administrative claims database relies on the fastidious and accurate coding of dementia-related *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes to assemble the cases among their cohort with the significant possibility of misclassification bias. This is in contrast to the more rigorous and validated cognitive testing and psychomotor assessments that characterized the group's prior work. Additionally, while the authors alluded to similar health care use between PPI users and nonusers, these data were not presented. Another concern relates to the underlying mechanism of action linking dementia and PPI use, which proposes that the modulation of enzymatic activity may result in increased β -amyloid levels; however, just 2.7% of the incident cases of dementia were identified strictly as Alzheimer type. Last, several important risk factors for dementia could not be controlled including apolipoprotein E4 allele carrier status, education level, alcohol use, hypertension, and family history of dementia.

We propose further investigations that may strengthen or refute the assertions of Gomm et al¹ of a valid link between PPI use and dementia; however, because of the aforementioned limitations of the study design, we believe that there is significant uncertainty regarding their conclusions. As with every clinical decision, the choice to prescribe PPIs should focus on

Corresponding Author: Chin Hur, MD, MPH, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (chur@mgh.harvard.edu).

Conflict of Interest Disclosures: None reported.

the potentially significant benefit a symptomatic patient may receive with regular PPI use vs the now emerging possible harms of this widely prescribed class of medicines.

References

1. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol.* 2016;73(4):410–416. [PubMed: 26882076]
2. Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. *Clin Endocrinol (Oxf).* 2008;69(2):338–341. [PubMed: 18221401]
3. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med.* 2007;167(9):950–955. [PubMed: 17502537]
4. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med.* 2010; 170(9):784–790. [PubMed: 20458086]
5. Khalili H, Huang ES, Jacobson BC, Camargo CA Jr, Feskanich D, Chan AT. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. *BMJ.* 2012;344:e372. [PubMed: 22294756]