



Short Report

Proton pump inhibitors and the risk of severe cognitive impairment: The role of posttraumatic stress disorder

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Abstract

Introduction: Proton pump inhibitors (PPIs), a common treatment for gastroesophageal reflux disease (GERD), were recently associated with increased risk of dementia. However, severe or chronic stress including, for example, posttraumatic stress disorder (PTSD) was not accounted for. This study examined whether PPI use was associated with severe cognitive impairment (SCI) and whether PTSD explained this association in a cohort of World Trade Center (WTC) responders.

Method: A prospective cohort study of 3779 WTC responders attending a university-based monitoring and treatment program. Prescriptions for PPIs and SCI determined using the Montreal Cognitive Assessment were the focus of the analysis.

Results: Overall, 1451 (38.4%) responders were dispensed PPIs, and 83 (2.2%) had SCI. Bivariable analyses revealed significant associations between being-dispensed PPIs in relation to SCI. After adjusting for PTSD, major depressive disorder, WTC exposures, age, and sex, being-dispensed PPIs were significantly associated with odds of SCI (adjusted odds ratio = 1.67 95% confidence interval = 1.054–2.643).

Conclusions: Being-dispensed PPIs were associated with SCI in this analysis of WTC responders. Results suggest that clinicians treating GERD seek to both understand patients' mental health history and monitor cognitive functioning when designing treatment routines. Overall, results confirmed that this is an important area of investigation with potential direct clinical implications.

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Keywords:

Cognitive impairment; Proton pump inhibitors; Posttraumatic stress disorder

1. Introduction

Proton pump inhibitors (PPIs) are widely prescribed, potent gastric acid suppressants used to treat acid-related disorders, including gastroesophageal reflux disease (GERD) [1]. Recent research has found an association between PPI use and diagnoses of Alzheimer's disease (AD), the most common form of dementia [2,3]. AD is indicated by evidence of development of severe cognitive impairment (SCI) that is uncharacteristic

of past capabilities and might be accompanied by functional limitations. Prior studies did not recognize, however, the potential for clinic biases that may emerge if those who are getting routine care for chronic conditions are more likely to be diagnosed with AD in a timely fashion. Studies also did not examine whether increases in chronic stress including chronic posttraumatic stress disorder (PTSD), which is known to correlate with the risk of GERD [4,5], confounded associations between PPI use and AD. Insofar, as PPI-use is linked with risk of AD, it is most concerning if this is due to an increased risk of SCI and not to other factors influencing risk of diagnosis. This study of a sample of health workers who responded to the World Trade Center (WTC) attacks on

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9/11/2001 examined whether PPIs were associated with SCI [6–8] and also whether PTSD explained the association.

2. Method

When the WTC towers collapsed, the men and women who helped in rescue and recovery operations experienced an array of psychological exposures and ingested a huge amount of toxic dust [9]. Starting in 2002, the health of responders has been monitored by a network of Centers for Disease Control and Prevention-funded WTC-Health Programs. Extensive outreach efforts and cohort recruitment protocols have been described elsewhere [10]. Once enrolled, responders receive comprehensive annual medical and psychiatric examinations and are entitled to free treatment for WTC-related conditions. Cognitive impairment screens were added to the monitoring examination at the Stony Brook University clinics starting in 2014.

The source population for this study included 5658 responders who had ever had a monitoring visit and had valid exposure information. In total, 34.7% of the source population ($n = 2121$) were dispensed PPIs between the years 2011–2016. Of these, 3855 responders were successfully screened for cognitive assessments between 2014–July 2016 (response rate = 93.8% of those approached for testing). Among responders who completed the screen, $n = 3779$ had complete data on the key study variables (GERD, PTSD, major depressive disorder [MDD], and WTC exposure severity). The analytic sample did not differ from those who were cognitively assessed in terms of PTSD, MDD, and WTC exposure but were more likely to have GERD and to have been dispensed PPIs (Supplementary Table 1). The sample included police and nontraditional responders (e.g., construction workers, utility workers). The average age on 9/11/2001 was 39 years. Most were male and employed in 2001.

The Stony Brook University Review Board approved this study, and all responders provided informed written consent for their clinical data to be used for research purposes.

3. Measures

Proton pump inhibitor dispensing was recorded in medical records starting 07/2011. Thus, data were available for a 5-year period ending in July 2016. A dichotomous measure of PPI prescription was used to indicate whether individuals had been dispensed PPIs before the cognitive assessment.

Severe Cognitive Impairment was assessed by performance on the Montreal Cognitive Assessment [11], a multitest screening tool that was administered by trained clinicians. The assessment contains multiple short-forms of common neuropsychological tests scored in a standard way. Responders' first assessments were used in this analysis to avoid potential retest effects. SCI was operationalized using a cutoff of <20 [12].

Clinical diagnoses of WTC-related GERD, PTSD, and MDD were obtained from the monitoring database. GERD

diagnoses were required before responders can be dispensed medications including PPIs. To ensure that PTSD and MDD diagnoses preceded PPI dispensing, we defined diagnosis as a recorded diagnosis of PTSD and MDD that preceded July 2011 when PPI dispensing was observed or diagnoses of GERD among those who were diagnosed later. Prior work has noted that neurological components of PTSD are the largest component risk factor for SCI and are insensitive to reverse causation [6], thus we relied on the PTSD checklist [13] to detect neurological symptoms indicative of re-experiencing symptomatology and used a cutoff of 11 to detect re-experiencing symptomatology [14]. A four-level indicator of WTC-related exposure severity was included to identify potential exposures to toxins [15].

4. Analyses

Percentages and means with standard deviations were provided to describe the sample and were separated by SCI classification. Statistical analysis used χ^2 , Student's t , and multivariable logistic regression (Stata 14/IC; Stata-Corp). Power calculations suggested that 3656 responders (power = 80%, $\alpha = 0.05$) were needed to detect a 49% increase in the odds of SCI, consistent with published reports. Adjusted odds ratios were reported alongside 95% confidence intervals, and exact P values; $\alpha = 0.05$ was used to identify significant results.

To ensure results were robust, sensitivity analyses stratified by sex, age, and both GERD and PTSD diagnoses and examined dose-response relationships by examining whether an increase in the number of years that PPIs were dispensed was associated with an increase in risk of SCI.

5. Results

One-third of the sample ($n = 1458$) had been dispensed PPIs, and 2.2% ($n = 82$) had SCI (see Table 1). In total, 54.9% of those with SCI were dispensed PPIs, only 38.8% of those without SCI were prescribed PPIs, a significant difference in bivariable analyses. Among the other predictors, age, PTSD, and MDD were significant in the bivariable analyses. Not shown here, 67.8% of those with PTSD versus 40.9% of those without PTSD were diagnosed with GERD (odds ratio = 2.13, 95% confidence interval = 1.73–2.62, $P < .001$).

In multivariable analyses (Table 2), we first noted that the associations between PPIs and SCI were evident after accounting for demographic factors (model 1). Further adjusting for WTC exposures and related diagnoses improved model fit but did not explain associations linking PPI use with SCI (model 2).

5.1. Sensitivity analyses

Stratification by sex, age, or by both PTSD and GERD diagnoses did not identify significant associations between PPI use and SCI. Finally, years of PPI dispensed revealed a strong

Table 1
Sample characteristics stratified by severe cognitive impairment status,
[Institutional] World Trade Center Aging Study

Categorical variables	Total sample		No SCI (n = 3696)		SCI (n = 83)		<i>P</i> ^a
	N	%	N	%	N	%	
Female	324	8.57	313	8.47	11	13.25	.124
Diagnosed PTSD	418	11.06	393	10.63	25	30.12	.000
Diagnosed MDD	303	8.02	283	7.66	20	24.10	.000
Dispensed PPIs	1451	38.40	1405	38.01	46	55.42	.001
Continuous Variables							
	Mean	SD	Mean	SD	Mean	SD	<i>P</i> ^b
Age in Years at 9/11	38.401	8.183	38.327	8.156	41.675	8.739	.000
Weeks spent at the WTC	8.771	9.284	8.705	9.230	11.716	11.098	.003

Abbreviations: MDD, major depressive disorder; PPI, proton pump inhibitor; PTSD, posttraumatic stress disorder; WTC, World Trade Center; SD, standard deviation.

^a*P* values were derived from χ^2 tests for categorical variables.

^b*z* values were derived from *t*-tests for continuous variables.

association in the first year but did not identify an incremental increase among individuals taking PPIs for longer periods of time.

6. Discussion

Many WTC responders have GERD in part from swallowing toxic particles at the WTC site. Since 2011, one-third of responders treated at the Stony Brook University WTC-Health Program were provided with PPIs. Responding

Table 2
Associations between PPIs dispensing from 2011 to 2016, demographic characteristics, and World Trade Center exposure severity and related conditions with severe cognitive impairment (SCI) in the World Trade Center Aging Study

Variable	Model 1 ^a		Model 2 ^b	
	aOR	95% CI	aOR	95% CI
Dispensed PPIs	1.982	1.277–3.074	1.669	1.054–2.643
Age in years on 9/11/2001	1.039	1.011–1.067	1.041	1.013–1.07
Chronic WTC exposure			1.024	1.004–1.045
Diagnosed PTSD			2.538	0.977–6.59
Diagnosed MDD			0.980	0.326–2.945

Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted odds ratio; MDD, major depressive disorder; PPI, proton pump inhibitor; PTSD, posttraumatic stress disorder; WTC, World Trade Center.

^aMultivariable logistic regression was used to account for age at 9/11/2001, sex, occupation, age at cognitive assessment, as well as whether responders had been dispensed PPIs. Models fit well (pseudo- $R^2 = 0.036$, $P < .001$).

^bMultivariable logistic regression accounted for all variables in model 1, and additionally adjusted for WTC exposure, and diagnoses of PTSD and MDD. Models improved model fit (pseudo- $R^2 = 0.064$, an increase of 0.028, $P < .001$). Model assumptions were tested and met including collinearity with condition index less than 30 and variance inflation factor less than 5. Goodness of fit on multivariable analyses was appropriate by both Pearson's χ^2 ($P = .541$) and Hosmer-Lemeshow ($P = .761$) methods.

to reports that PPI dispensing was associated with risk of AD in Germany, this study tested whether PPI dispensing was associated with an objective measure of SCI in a cohort of WTC responders. Results suggested that there was a 60% increase in the prevalence of SCI associated with PPI use after accounting for WTC-related exposures and PTSD.

6.1. Strengths and limitations

This is one of a small number of cohort studies that have measured PPI dispensing alongside diagnoses of PTSD and objective indicators of cognitive functioning and is sufficiently large to ensure power to study small risks, making it an excellent resource with which to examine these associations. Nevertheless, a number of limitations should be considered when interpreting these results. The etiology of SCI in this cohort is unknown. However, this sample had very high educational attainment, age was a strong determinant of SCI, and as a condition of employment most law enforcement officers passed detailed working memory and visuospatial functioning assessments, and prior work noted an association between possession of the apolipoprotein- $\epsilon 4$ allele, a strong genetic risk factor for AD [16], and cognitive impairment in this population [6]. This sample is not generalizable to the broader population. For example, the population was overwhelmingly employed on 9/11/2001, making responders a clinically monitored population of healthy workers, many of whom experienced chronic PTSD [17]. The prevalence of PTSD in WTC responders (13.6% of all responders) was higher than estimates in the general population (4% globally [18]). Yet, results did not differ in this study by stratification on sex, age, or PTSD status. This study lacked an external control population. Although we objectively identified responders who were dispensed PPIs, because data collection began after 2011, there is a chance that those who were dispensed PPIs more than three years before data collection were not captured in this study. Finally, this study utilized a single assessment of cognition using an objective screening method potentially resulting in detection of non-progressive SCI. Prior work has noted strong associations between this assessment and genetic risk factors for AD [6] in this population and strong associations with a computer-administered cognitive assessment. Since SCI is normally a precondition for dementia diagnosis, the present study extends previous reports on dementia using an objective examination unbiased by factors associated with increased risk of diagnosis for neurological diseases.

6.2. Implications

Results suggest that being-dispensed PPIs may have elevated the risk of SCI. Results also highlight the potential for confounding from related factors including PTSD. To date, biological mechanisms linking PPI use to cognitive functioning are unclear. Previously proposed mechanisms include modified production of amyloid β and

neuroinflammatory processes [3]. However, another pathway may link changes in gastric microflora found among individuals using PPIs [19] resulting in increased secretion of neurotoxic substances [20]. Because the overall risk is small, results may suggest that clinicians should determine whether patients are at increased risk of neurodegenerative disease before prescribing PPIs for chronic health conditions.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.trci.2017.08.007>.

RESEARCH IN CONTEXT

- 1 Systematic review: PubMed was searched for studies including the terms proton pump inhibitor or PPI and Alzheimer's disease or cognitive dysfunction. Proton pump inhibitors (PPIs), a common treatment for gastroesophageal reflux disease (GERD), were recently associated with increased risk of Alzheimer's disease. GERD is common among individuals with chronic stress disorders including posttraumatic stress disorder (PTSD). PTSD has also been found to be a risk factor for dementia.
- 2 Interpretation: The present observational study utilized data from a cohort of World Trade Center responders with very detailed psychiatric measures of PTSD and depression in order to extend prior findings by linking being-dispensed PPIs with the odds of severe cognitive impairment. Adjusting for PTSD reduced, but did not explain, this relationship in our data suggesting that PPIs may be associated with cognitive impairment via mechanisms external to behavioral or stress pathways.
- 3 Future directions: Results highlight the need to monitor cognitive functioning when utilizing PPIs and clarify the need for researchers to develop a better understanding of why PPI use might be associated with cognitive impairment, decline, and/or diagnosis.

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