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Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review

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ABSTRACT

Background

Proton pump inhibitors (PPIs) are among the most widely used medications worldwide. Dementia is an increasingly common cause of disability in older populations. Recent studies have suggested an increased risk of cognitive impairment and dementia diagnosis among people who consume PPIs. This systematic review explores dementia, cognitive impairment and the use of PPIs.

Methods

Systematic searches were conducted in the databases of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PSYCinfo, Scopus, Web of Science and ClinicalTrials.gov for articles published from inception to June 30, 2016. Primary outcomes of interest were the use of PPIs and diagnosis of dementia or acute cognitive impairment. Studies conducted on people aged less than 18 years old were excluded. All study designs were eligible for inclusion. Two reviewers independently assessed study quality and extracted data from included studies.

Results

The systematic search strategy and screening process yielded 11 studies for inclusion in the systematic review. Four studies explored PPI use and dementia and seven studies explored PPI use and acute cognitive impairment. Three of the four studies exploring dementia identified a positive association with PPI use. A positive association was also observed in the majority of studies exploring acute cognitive impairment.

Conclusions

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Based on the current published literature, this systematic review has identified that the reported association between PPI use and dementia is limited by methodological issues and conflicting results. Further longitudinal studies with robust bias limitation are required to explore the use of PPIs and dementia or acute cognitive impairment, and to ascertain the existence of any causal relationships.

Keywords: Gastroenterology, Gastric secretion, Gastroesophagus reflux disease (GERD)

INTRODUCTION

Dementia is a syndrome characterised by progressive cognitive decline and reduction in memory, thinking, behaviour and the ability to perform activities of daily living.¹ It is one of the major causes of disability among older populations around the world. The estimated worldwide cost associated with dementia in 2010 was USD\$604 billion,¹ which rose to an estimated USD\$818 billion in 2015.² Today, 46.8 million people worldwide have dementia, with this figure projected to triple to 131.5 million by 2050.²

Proton pump inhibitors (PPIs), already among the world's most widely prescribed medications, are being prescribed and used at an increasing rate.³⁻⁵ Although evidence supports the use of PPIs to treat gastroesophageal reflux disease,⁶ there is considerable PPI use, often in excess, in both the inpatient and outpatient settings.⁷ Observational studies have suggested that 40% to 60% of PPI prescriptions for older people may be inappropriate.^{8,9} PPIs are generally safe and well tolerated, with adverse events occurring at a rate of 1-3%, and serious adverse events are uncommon.¹⁰⁻¹⁴ However, potential adverse events include community acquired pneumonia,¹⁵ *Clostridium difficile*-associated disease,¹⁶ hip fracture,¹⁷ and vitamin and mineral deficiencies.¹⁸ A potential association between PPI use and electrolyte imbalance, particularly that of magnesium, has been described in the literature.^{19,20}

Recent observational studies have suggested that PPI use may also be associated with dementia.^{21,22} It has been demonstrated that PPIs increase deposition of amyloid protein in the mouse brains,²³ a known contributor to Alzheimer's disease in humans.²⁴ PPIs have also been identified as a potential factor in the development of vitamin B12 deficiency,²⁵ a factor which may also contribute towards the development of dementia.²⁶ The findings of case studies and small observational studies have suggested a link between PPI use and acute cognitive impairment.²⁷⁻³²

This systematic review sought to explore the association between PPIs and dementia and acute cognitive impairment.

METHODS

This systematic review was conducted according to the checklist outlined by Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Supplement 1).³³ The written protocol for this systematic review has been registered on PROSPERO: International prospective register of systematic reviews (unique ID number CRD42016042186).³⁴

Systematic searches of the following electronic databases were conducted on 30 June 2016 for articles published since database inception: MEDLINE (via Ovid), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PSYCinfo, Scopus, Web of Science and ClinicalTrials.gov. Electronic search strings included search key words and medical subject headings (MeSH) relating to or describing the outcome of dementia (of all subtypes), or cognitive impairment, in combination with the intervention proton pump inhibitors (PPIs). These search terms were adapted for use with other bibliographic databases in combination with database-specific filters (where these were available). A sample search strategy for MEDLINE (via Ovid) is

included (Supplement 2). A limit for the inclusion of human participants was established. Further limits in relation to study design, publication year, or sample population were not implemented.

Study Selection

All accessible articles were reviewed, irrespective of study design, in which primary data indicated or confirmed exposure to PPIs, accompanied by the diagnosis of dementia of any subtype or the development or worsening of acute cognitive impairment. Studies for inclusion were also identified by screening references of included articles. Authors of potentially relevant abstracts or conference proceedings were contacted via email for additional information. All studies that explored the use of PPIs in humans over the age of 18 years, and dementia outcomes of any subtype or acute cognitive impairment outcomes, were included. Studies were excluded if they included PPI concomitant therapy without the assessment of PPI as an independent risk factor (e.g. as part of *Helicobacter pylori* therapy or as gastric ulcer prophylaxis in dual antiplatelet therapy). Non-English language articles were excluded during title and abstract screening.

Data Extraction

One review author (RB) independently screened titles and abstracts of studies identified via the systematic search strategy. Studies that potentially met the inclusion criteria were identified, and full texts were retrieved and independently assessed for eligibility by two review authors (RB and JG). A third author (DL) adjudicated any discordance in assessments via discussion with the two review authors. Two review authors (RB and JG) independently extracted data from the included studies using a standardised pre-piloted data

extraction form, which was based on the minimum requirements recommended in the Cochrane Handbook for Systematic Reviews.³⁵

Risk of Bias Analysis and Results Analysis

Risk of bias was assessed by two authors (RB and DL) and discrepancies were resolved by consensus with a third review author (IH). The Cochrane Tool for Assessing Risk of Bias³⁶ was used to assess the methodological quality of randomised controlled trials. The Newcastle-Ottawa Scale³⁷ was used to assess the quality of observational studies. A modified version of the Newcastle-Ottawa Scale, piloted by Mata *et al*, was used to assess prevalence data (Supplement 3).^{37, 38} Case reports were evaluated by the causal criteria for adverse events caused by medications outlined by the World Health Organization.³⁹

Descriptive statistics, including mean values and ratios, were summarised and used to describe the quantitative characteristics of included studies. A meta-analysis was not performed due to considerable clinical and methodological diversity among included studies (e.g. large variability of study populations and study designs).

RESULTS

Search Results

The systematic search strategy identified 1,928 unique articles, 1,895 of which were excluded during title and abstract screening. Thirty-three remaining full text articles were assessed for eligibility, and of these, 11

met the inclusion criteria for this systematic review.^{21, 22, 27-32, 40-42} Reasons for study exclusion are documented using the PRISMA flow diagram (Figure 1).³³

FIGURE 1

Of the 11 studies included in this systematic review, four (two cohort studies, one case-control study and one cross-sectional study) returned data on dementia outcomes with PPI use, and seven (one randomised controlled trial, two cohort studies, one case series and three case reports) returned data on acute cognitive impairment. These studies are summarised in Tables 1 and 2. A risk of bias assessment was conducted for each included study (Supplement 4).

Dementia

An association between PPI use and dementia was observed in three of the four non-randomised (observational) studies.^{21, 22, 40} Omeprazole, esomeprazole, lansoprazole and pantoprazole were examined in all three studies demonstrating a positive association.^{21, 22, 40} Rabeprazole was examined by two studies,^{21, 22} and dexlansoprazole examined by one study.²²

Herghelegiu *et al* performed a single centre cross-sectional study of 148 outpatients and compared use of PPIs with a control group of non-users.⁴⁰ The authors concluded that PPI use was statistically significantly associated with dementia (OR=3.67, 95%CI 2.23-19.15, p=0.002).⁴⁰ Although bias in this study was determined to be low, a small sample with limited representativeness was involved, and potentially

important confounders such as age, sex, history of stroke and smoking status were not considered.^{40, 43}

Furthermore, due to the nature of cross-sectional prevalence data, results should be considered cautiously.

Booker *et al* conducted a case-control study of 11,956 outpatient cases and 11,956 matched controls from a database of general practice medical records in Germany, reporting a statistically significant reduction in the risk of dementia with PPI use (OR=0.94, 95%CI 0.90-0.97, p=0.0008).⁴¹ Controls were matched based on age, sex, type of health insurance and physician.⁴¹ Unlike the studies reporting a positive association, Booker *et al* did not identify individual PPI subgroups.⁴¹ This study was judged to have a moderate risk of bias, with the main limitations being that case definition was based on codes entered by general practitioners (that is, cases of dementia were not verified) and non-rigorous ascertainment of PPI exposure.⁴¹ Additionally, the control matching was not sufficiently robust to account for large dementia confounders, such as family history of dementia, smoking status, and hypertension.^{43, 44} The comparatively large sample size of participants was an advantage of this study.⁴¹

Gomm *et al* conducted a pharmacoepidemiological claims analysis, using data drawn from the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe), and estimated the hazard ratio (HR) for dementia with frequent PPI use to be 1.44 (95%CI 1.36-1.52, p<0.001).²¹ Haenisch *et al* conducted a cohort study from data derived from the same longitudinal multicentre study (AgeCoDe), estimating a HR for dementia with PPI use to be 1.38 (95%CI 1.04-1.83, p=0.02).²² Both cohort studies accounted for key confounders, such as age, sex, diabetes status and history of cardiovascular disease via multivariable Cox regression modelling.^{21, 22} Neither study accounted for hypertension, family history of dementia or physical exercise.^{21, 22} The study by Gomm *et al*²¹ of inpatients and outpatients further demonstrated that occasional PPI use, defined by one to five PPI prescriptions in an interval of 18 months (as opposed to frequent PPI use,

which was at least six prescriptions over the same interval), was also associated with a lower (but still increased) HR for dementia (HR=1.16, 95%CI 1.13-1.19, p<0.001). While the study by Gomm *et al*²¹ did not include the use of neuropsychological tests for dementia diagnosis and cognitive status, the study by Haenisch *et al*²² used detailed test results for diagnosis, including the Mini Mental State Examination (MMSE),⁴⁵ Score from Structured Interview for Diagnosis of Dementia (SISCO),⁴⁶ and the Global Deterioration Scale (GDS).⁴⁷ The results of these tests were not published with the study.²² Subgroup analysis was performed by Gomm *et al* for omeprazole, pantoprazole, and esomeprazole, which resulted in statistically significant HRs of 1.51 (p<0.001), 1.58 (p<0.001), and 2.12 (p<0.001), respectively.²¹ A potential limitation was that the analyses did not differentiate between dementia subtypes, due a large number of 'unspecified' and poorly defined dementia diagnoses.²¹ Furthermore, there was potential for selection bias because 66% of database patients were excluded on the basis of inconsistent data.²¹ In contrast, the study by Haenisch *et al* differentiated HRs for all dementia subtypes (HR=1.38, 95%CI 1.04-1.83, p=0.02) and Alzheimer's disease specifically (HR=1.44, 95%CI 1.01-2.0, p=0.04).²² This study also had a low percentage of total participant exclusion.²² However, Haenisch *et al* did not include subgroup analyses on PPI type and studied a smaller cohort.²² The study conducted by Gomm *et al*²¹ was assessed as being of high risk of bias, primarily owing to significant potential for confounding and a high likelihood of selection bias in the setting of a high participant exclusion rate due to incomplete data. The study conducted by Haenisch *et al*²² was assessed as being of moderate risk of bias, owing to potential for confounding and detection bias in the absence of an accurate means of assessing PPI dosage.

TABLE 1

Acute cognitive impairment

Of six total cases included in this systematic review, three were case reports²⁷⁻²⁹ and three were presented as case series.³⁰ Four were cases of hypomagnesemia-associated delirium or confusion,^{28, 30} one was a case of hyponatremic delirium,²⁷ and one was a case of delirium of unknown cause.²⁹ One case demonstrated that withdrawal of trial esomeprazole therapy resulted in the resolution of symptoms and restoration of magnesium levels.²⁸ The significance of PPI therapy in causing low levels of magnesium or sodium was judged as probable in the majority of cases, and was most frequently observed in patients using omeprazole.²⁷⁻²⁹

Across the seven studies exploring PPI use and acute cognitive impairment, two cohort studies included data on PPI use and risk of delirium.^{31, 32} Diagnosis of delirium was established via the use of high quality diagnostic scales in both cohort studies, with Otremba *et al* using the widely accepted Confusion Assessment Method (CAM)⁴⁸ and Mini Mental State Examination (MMSE),⁴⁵ and Fujii *et al* using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)⁴⁹ for delirium diagnosis. Fujii *et al* compared PPI use with histamine-2 receptor antagonist (H2RA) use in a small group of 60 outpatients undergoing post-operative management of oesophageal cancer surgery.³¹ This study did not involve a non-acid suppressant control group, reporting an increase in delirium risk with H2RA therapy when compared to PPI therapy (OR=3.824, 95%CI 1.15-12.71, p=0.047).³¹ The study was judged to have a high risk of bias due to a lack of comparability and use of a 'niche' oncology inpatients population, exposing it to a number of confounding factors.³¹ A cohort study conducted by Otremba *et al* reported an increased risk of delirium associated with PPI use (OR=1.67, 95%CI 1.11-2.53, p=0.014) in 675 older people admitted to an acute geriatric ward.³² This study adjusted for some key risk factors for delirium: age, dementia, congestive heart disease and previous episodes of delirium, but not all, most notably type of acute illness and concurrent medications.³² Indeed,

the study did not even describe medication use, including of PPIs, among participants. Thus while PPI use was noted to be associated with incident delirium, it was not known how common this 'risk factor' was.³²

A randomised controlled trial conducted by Akter *et al* recruited a small population of 60 young (mean age 21-23 years old), healthy, non-PPI users, to explore the short-term effect of multiple PPI types on performance while undertaking a series of computerised neuropsychological tests (nine total Cambridge Neuropsychological Test Automated Battery subtypes).^{42, 50} It was demonstrated that a statistically significant reduction occurred in sensorimotor ability, visual memory and learning, reaction time, rapid visual information processing and spatial working memory in intervention groups.⁴² Some variance in results per PPI medication subtype was observed, with omeprazole demonstrating the most significant reduction in cognitive function (seven significant sub-test reductions) and esomeprazole demonstrating the least (three significant subtest reductions).⁴² However, all intervention groups demonstrated a general reduction in assessment performance when compared to the placebo group. Although this study was assessed as being of low risk of bias, it was limited by the short time frame of exposure (one week) and the small study sample.

TABLE 2

CONCLUSIONS

This systematic review of 11 studies demonstrated an increased risk of dementia and acute cognitive impairment with PPI use. The most robust observational studies included in this systematic review reported an approximate 1.4-fold increased risk of any dementia in cohorts using PPIs. However, a large case-control study demonstrated no increase in dementia risk. A series of case reports and small observational studies demonstrated a weak association between PPI use and acute cognitive impairment, primarily focused on delirium.

Dementia

Studies included in this systematic review were subject to variable levels of bias, and limited primarily by their observational designs. Although the positive effect of PPIs on dementia was evident in three observational studies,^{21, 22, 40} conflicting results were found in a fourth.⁴¹ Residual confounding is a major limitation that must be taken into account when interpreting findings from observational studies reporting a positive association, especially when insurance claims data are used (Gomm *et al*), as these datasets often lack complete information on significant potential confounders.²¹ Although both cohort studies^{21, 22} reporting a positive association between PPI use and dementia identified, and adjusted for, a broad range of known confounders, neither accounted for family history of dementia or hypertension (known risk factors for dementia).^{43, 44} In addition, recently recognised risk factors for dementia, such as sugar intake, physical exercise, air pollution and intestinal microbiota, were not included in any of the analyses included in this review and may therefore represent unaccounted additional confounders.⁵¹⁻⁵³ The use of aluminium containing medications, such as antacids, was also not adjusted for.^{21, 22} This is potentially a relevant omission, as aluminium may be linked with an increased risk of Alzheimer's disease,⁵⁴ and the use of

antacids in patients with an indication for PPI use is likely to be high.⁵⁵ It is difficult to say with certainty that cases of dementia in the German cohort identified by Gomm *et al* were accurate diagnoses, with objective cognitive test results not available for the analysis.²¹ The study instead used ICD-10 codes provided by the insurance database to classify dementia. Thus there was no staging by severity, and information may have been inaccurate, given that only 3% of the cohort were coded for Alzheimer's disease, a disease which accounts for 60-80% of dementia in the elderly.⁵⁶ In contrast, the study by Haenisch *et al* used detailed neuropsychological tests to establish the diagnosis of dementia. Nevertheless, both cohort studies reported a positive association between PPI use and dementia^{21, 22} and both used data derived from the same German database (AgeCoDe), increasing the chance of data overlap. The Haenisch *et al* study performed subgroup analyses for Alzheimer's disease,²² with other observational studies failing to consider dementia subtype:^{21, 40, 41} thus the impact of PPI use on major neurocognitive disorders is difficult to evaluate. Although the study conducted by Gomm *et al* compared occasional and frequent PPI use, referencing defined prescription intervals,²¹ sufficiently accurate means to establishing a dose response were not outlined. In addition, PPI dosing and duration of therapy was not adequately addressed by the other studies included in this review.^{21,}

40, 41

The proposed pathogenic mechanism by which PPIs may affect risk of dementia is uncertain. In animal models, there is weak evidence to suggest that lansoprazole use may increase the production of amyloid-beta peptide by acting as an inverse γ -secretase modulator, though this evidence stems from a single 2013 study.²³ Amyloid-beta peptide deposition is a major component contributing to the pathogenesis of Alzheimer's disease in humans.²⁴ It has been hypothesised that PPIs cross the blood-brain barrier and may inhibit the action of vacuolar proton pumps found in microglia and macrophages, thereby inhibiting clearance of fibrillar amyloid beta peptide in the brain.⁵⁷ It has also been suggested that a link exists

between PPI use and suboptimal vitamin B12 absorption,²⁵ resulting in a deficiency that is harmful to cognition and a likely contributing factor towards dementia risk.²⁶ Additionally, esomeprazole has been demonstrated to inhibit lysosomal acidification and thus impair proteostasis.⁵⁸ The resultant accumulation of protein aggregates can accelerate endothelial senescence and vascular dysfunction, potentially a starting point for cognitive decline and vascular dementia in PPI users.⁵⁸

Acute cognitive impairment

A major limitation in evaluating PPI use and acute cognitive impairment was that the majority of included studies were case reports that were not representative of reliable non-randomised data sets. Of the two cohort studies identified for their relevance to acute cognitive impairment, data sets were subject to significant bias and difficult to compare due to control group differences. The study by Otremba *et al* engaged a non-acid suppressant control group³² and the study by Fujii *et al* compared PPI use to H2 antagonists.³¹ In addition to excluding a number of important confounders from multivariate analysis, the study by Otremba *et al*³² omitted data on drug use, including PPIs. The study by Fujii *et al*³¹ enrolled a Japanese cohort of oncology patients in whom delirium may have been multifactorial, potentially arising from chemo- or radiotherapy, medications (such as opioids), or neurological or systemic tumour involvement. It is therefore difficult to excuse this study from selection bias.

Many pathological links may be drawn between PPI use and the development of delirium and other forms of acute cognitive impairment. PPIs have been identified as a cause of hypomagnesemia^{19,20} as well as a likely risk factor for other electrolyte imbalances⁵⁹ known to be causative in cognitive disturbances. This relationship may be observed in the case reports²⁷⁻²⁹ and case series³⁰ presented in this systematic review. Furthermore, PPIs have been shown to increase patients' risk of community acquired pneumonia¹⁵ and

Clostridium difficile enterocolitis,¹⁶ among other conditions that increase risk of delirium or confusion. Akter *et al*'s⁴² finding that PPI use reduced cognitive performance in healthy subjects is notable and may suggest a more substantial effect of PPIs more generally. However, it would be premature to conclude that the findings of the Akter *et al*'s⁴² supports any link between PPI use and Alzheimer's disease or delirium, as the study population was young, healthy, and were not being assessed for dementia. Furthermore, the authors did not assess for potential mechanisms to explain the observed cognitive decline in neuropsychological test performance, as cortex amyloid, vitamin B12 and serum electrolytes were not measured.

Study strengths and limitations

This study adopted a comprehensive and systematic approach to reviewing current published literature on PPI use and risk of dementia and acute cognitive impairment. The use of a broad search strategy across a large number of databases, accompanied by manual review of a larger number of studies, reduced the likelihood that data were excluded by search string omission. This systematic review engaged multiple authors in the development and implementation of the search strategy and in the identification and analysis of included studies.

In terms of study limitations, a meta-analysis was not undertaken due to the nature of included studies. Relevant data were largely heterogeneous, study designs were variable and there was variability in clinical diversity and risk of bias. As a result, it is unclear whether positive studies were favoured and whether a performance bias existed. In addition, publication bias was difficult to be assessed accurately. Secondly, despite being potentially useful in examining an association, primary prevalence data on PPI use and dementia (available in studies investigating alternative disease outcomes) was not evaluated. This is because

it is unlikely that all studies containing baseline demographic data were encapsulated by the search strategy. The third limitation pertained to selection bias. Potentially relevant non-English language articles may have been excluded, and three of four studies outlining data on PPI use and risk of dementia were conducted in Germany (with the remaining study conducted in Romania). Furthermore, Haenisch B is involved as first author (Haenisch *et al*) and senior author (Gomm *et al*) in the two most robust studies reporting a positive association between PPI use and dementia. Both cohort studies utilised the same database (AgeCoDe) to derive their results. Given the similarity in authorship and study ethnicities, it may be difficult to generalise findings of this systematic review until these results are validated in alternate settings.

Implications for practice

PPIs have been demonstrated to be effective in the treatment of gastroesophageal reflux disease⁶ and are useful therapy in the treatment of peptic ulcer disease.⁶⁰ In a setting of widespread PPI use,⁷ often without adequate indication,^{8,9} this systematic review offers another opportunity to re-evaluate prescription of PPIs in patients who may no longer require PPI therapy. Where an indication for PPI use exists, findings of this systematic review should not change current practice. However, this systematic review may be useful in discussing potential risks of PPI therapy with patients who require a more robust risk-benefit analysis, such as those at high risk of, or in the early stages of, dementia or acute cognitive impairment.

Conclusion

This rigorous systematic review indicated that overall, the majority of studies suggest an increased risk of dementia with the use of PPIs, with the exception of one large case-control study. All studies investigating

PPI use and dementia or acute cognitive impairment were observational, with the exception of one randomised controlled trial. Quantification of the risk of dementia and cognitive impairment was not possible, as the heterogeneous nature of included studies prevented a meta-analysis. Under these circumstances, the proposed association between PPI use and dementia or acute cognitive impairment is limited by methodological issues accompanying relevant studies. Assessment of causality and the exposition of underlying mechanisms of action requires the engagement of large prospective longitudinal studies with robust methods for limiting bias, with these findings validated away from Germany. The findings of this systematic review should be interpreted with caution, but nonetheless taken into account, given the widespread use of unwarranted^{8,9} PPI use and increasing burden of dementia on the healthcare system.^{1,2} Meticulous risk-benefit analysis when prescribing PPIs should be considered in all cases, especially among older patient populations.

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Table 1: Qualitative analysis of four studies of PPI use and dementia.

Author (year), study design	Country (time period)	Setting	Population, age (years), % female	Intervention	Control	Confounders included in analysis	Outcome
Herghelegiu <i>et al</i> ⁴⁰ (2016), cross-sectional study	Romania (2014-2015)	Geriatric outpatients clinic	N=148 (PPI users=74, non-users=74), users 76.3±8.7 non-users 74.2±10.3, users 66.21% non-users 77.02%	Omeprazole, esomeprazole, lansoprazole, pantoprazole	Non-use of PPI	Diabetes and hypertension in midlife	Odds ratio (OR) dementia with prolonged PPI use = 3.67 (95%CI 2.23-19.15) p=0.002. Relative risk (RR) of dementia with PPI use = 2.85.
Booker <i>et al</i> ⁴¹ (2016), case-control study	Germany (January 2010-December 2014)	General practice (Records database)	N=23,912 (11,956 cases, 11,956 matched controls), 80.4±5.3, 61%	Unspecified PPI(s)	Non-use of PPI	Age, sex, health insurance, physician	OR dementia with PPI use = 0.94 (95%CI 0.90-0.97) p=0.0008.
Gomm <i>et al</i> ²¹ (2016), cohort study	Germany (2004-2011)	Older inpatients and outpatients (Insurance records)	N=73,679 (PPI users=2,950, non-users=70,729), users 83.0±5.6 non-users 83.8±5.4, users 77.9% non-users 73.6%	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole	Non-use of PPI	Age, sex, stroke, depression, ischemic heart disease, diabetes, polypharmacy, anticholinergic use	Hazard ratio (HR) dementia with PPI use = 1.44 (95%CI 1.36-1.52) p<0.001 with potential confounders. HR (males) = 1.52, HR (females) = 1.42 with confounders. Without potential confounders, risk of incident dementia HR 1.66 (95%CI 1.57-1.76) p<0.001. HR (males) = 1.78, HR (females) = 1.61. Dementia with occasional PPI use HR = 1.16 (95%CI 1.13-1.19) p<0.001.
Haenisch <i>et al</i> ²² (2015), cohort study	Germany (6 years)	General practice (Database)	N=3,076 (PPI users=713, non-users=2,363), users 79.6±3.4 non-users 79.7±3.6, users 68.7% non-users 64.0%	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole	Non-use of PPI	Age, sex, education, ApoE4 allele status, polypharmacy, depression, ischemic heart disease, stroke	HR dementia with PPI use = 1.38 (95%CI 1.04-1.83) p=0.02. HR dementia with PPI use = HR 1.44 (95%CI 1.10-1.90) p=0.008 when confounders not included in analysis.

							HR Alzheimer's disease with PPI use = 1.44 (95%CI 1.01-2.06) p=0.04. Exclusion of confounders did not clearly impact the effect of PPI use on Alzheimer's Disease HR 1.45 (95%CI 1.03-2.05) p=0.03.
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Author (year), study design	Country, (time period)	Setting	Population, age (years), % female	Intervention	Control	Confounders included in analysis	Outcome
Bebarta <i>et al</i> ²⁷ (2008), case report	United States (2008)	Emergency department	N=1, 46, 0%	Omeprazole	N/A	N/A	Acute onset of delirium due to hyponatremia possibly induced by omeprazole.
Delgado <i>et al</i> ²⁸ (2013), case report	Spain (2011-2012)	Emergency department	N=1, 76, 0%	Omeprazole, esomeprazole	N/A	N/A	Three episodes of confusion due to omeprazole induced hypomagnesemia. Esomeprazole used to test induction of hypomagnesemia and then withdrawn to demonstrate resolution.
Heckmann <i>et al</i> ²⁹ (2000), case report	Germany (Not stated)	Neurology inpatients	N=1, 77, 100%	Omeprazole	N/A	N/A	Delirium, suspected to be induced by use of omeprazole.
Pasina <i>et al</i> ³⁰ (2016), case series	Italy (February 2014- November 2014)	Internal medicine inpatients	N=3 (of 9 cases presented relevant), 77, 86, 83. 100%	Unspecified PPI(s)	N/A	N/A	One episode of confusion due to hypomagnesemia, probably induced by PPI. One episode of delirium due to hypomagnesemia, probably induced by PPI. One episode of mild cognitive impairment due to hypomagnesemia with possible link to PPI in the absence of alternative cause for symptomology.
Fujii <i>et al</i> ³¹ (2012), cohort study	Japan (January 2006- July 2007)	Oncology outpatients	N=60 (PPI users 30, controls 30), PPI users 65.2±6.5 controls	Unspecified PPI(s)	Histamine-2 receptor antagonists	None	OR delirium with histamine-2 receptor antagonist = 3.82 (95%CI 1.15-12.71), when compared to PPI group, p=0.047.

			65.2±8.1, unspecified %				
Otremba <i>et al</i> ³² (2016), cohort study	Poland June 2013 – June 2014	Acute geriatric ward inpatients	N=675, 79.2±7.7, 66%	Unspecified PPI(s)	Non-use of PPI	Clinical, function and laboratory factors.	OR delirium with PPI use = 1.67 (95%CI 1.11-2.53) p=0.014
Akter <i>et al</i> ⁴² (2015), randomised controlled trial	Bangladesh (1 week in 2015)	Healthy non-patients	N=60, 21 (female) and 23 (male), % female not stated	Omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole	Placebo	N/A	<p>PPIs had a negative impact on cognitive performance. Statistically and clinically significant impairment in visual memory, attention, executive function and working and planning function in PPI groups.</p> <p>Omeprazole showed significant (p<0.05) results in seven subtests, lansoprazole and pantoprazole showed significant results in five tests, rabeprazole showed significant results in four tests and esomeprazole showed significant results in three tests.</p>

Table 2: Qualitative analysis of seven studies of PPI use and acute cognitive impairment.

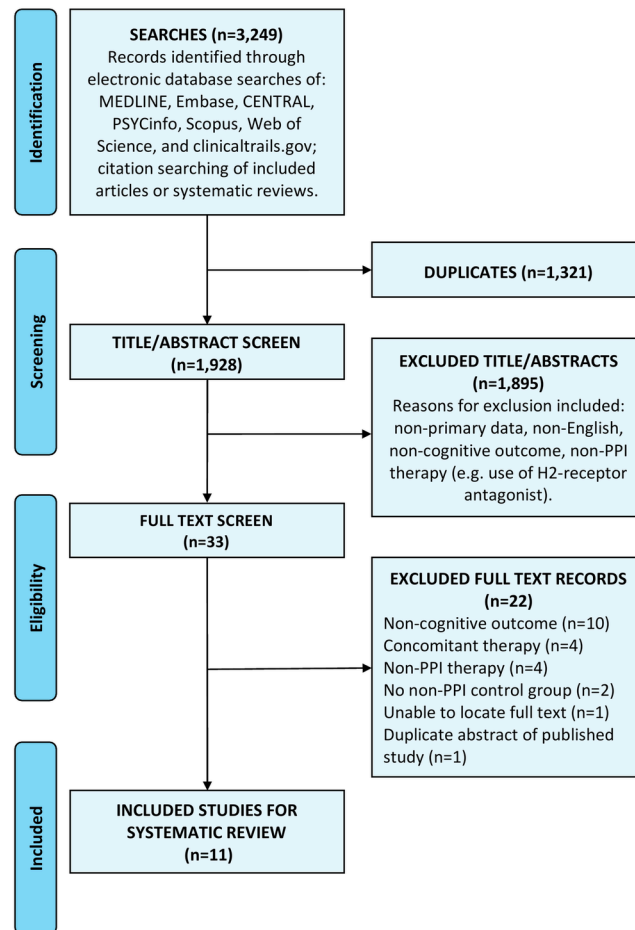


Figure 1.tif

**Dementia, cognitive impairment and proton pump inhibitor therapy – a
systematic review**

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RB conducted literature searches and compiled articles for review. RB & JG assessed full texts for eligibility and extracted data. IH & DL acted to resolve any disputes in study selection and data collection. RB & DL conducted risk of bias analysis. WK offered expert advice and manuscript edits. All authors reviewed and approved the final manuscript.

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