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Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis

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This study was presented at the American College of Chest Physicians meeting in Pittsburgh (PA, USA) in October 2011. The study objective was to evaluate the association of proton pump inhibitors (PPIs) and community-acquired pneumonia (CAP). The design was a meta-analysis of nine case–controlled and cohort studies. 120,863 pneumonia cases from 1987 to 2006 were included in the meta-analysis. PubMed and Ovid Medline were searched from inception through May 2011 by two investigators independently using keywords: PPI, pneumonia, CAP, anti-ulcer, antacid, omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. This meta-analysis only included case–controlled and cohort studies that were published in full in English and evaluated PPI use and CAP incidence. Studies were excluded if they included the following patients: pediatric, *Helicobacter pylori* treatment and critically ill. Bibliographies of recent review articles and systematic reviews were hand-searched. Quality of studies was assessed using the Newcastle–Ottawa Quality Assessment Scale. Two investigators independently extracted data into standardized data collection forms that were confirmed by a third investigator. Data were analyzed based on current use of PPIs, duration of PPI use (<30 days or >180 days) and PPI dose (high vs low). Overall association of PPI and CAP was analyzed using the random effects model (Comprehensive Meta analysis® Version 2.0). Nine studies met all criteria for the primary outcome. Newcastle–Ottawa Quality Assessment Scale scores ranged from 4 to 8 out of 9. Current use of PPIs (odds ratio [OR]: 1.39; 95% CI: 1.09–1.76), PPI use <30 days (OR: 1.65; 95% CI: 1.25–2.19), PPI high dose (OR: 1.50; 95% CI: 1.33–1.68) and PPI low dose (OR: 1.17; 95% CI: 1.11–1.24) were significantly associated with CAP. There was no association between CAP and PPI use >180 days (OR: 1.10; 95% CI: 1.00–1.21). In conclusion, patients currently receiving PPIs, particularly <30 days or high dose, showed an association with CAP. Practitioners need to be vigilant about adverse effects of PPIs and consider alternative therapies.

KEYWORDS: esomeprazole • lansoprazole • omeprazole • pantoprazole • pneumonia • PPI • rabeprazole

Proton pump inhibitors (PPIs) are routinely utilized in both inpatient and outpatient settings. PPIs are indicated in the prevention and treatment of acid-related disorders. The efficacy of PPIs for these indications and their safety profile has led to overuse in both inpatient and outpatient settings, with some studies citing more than 50% inappropriate or overusage [1–4]. The most common adverse effects include headache, nausea, abdominal pain, flatulence and diarrhea, which are usually mild and self-limiting [5,6].

Despite the overall tolerability of PPIs, their use has been associated with several rare but serious adverse effects including increased *Clostridium difficile* infections, osteoporosis, acute interstitial nephritis and pneumonia (both community and hospital acquired) [7–11].

Community-acquired pneumonia (CAP) is a substantial burden on our health system. In 2005, CAP led to 1667 hospitalizations per 100,000 persons [12]. The length of stay of these hospitalizations averaged 5 or more days and 10–20% of

these resulted in intensive care unit admissions [13,14]. Thirty-day mortality rates based on the CURB-65 score can range from 0.6 to 57% and 30-day readmission rates and have been reported to be as high as 20% [15,16]. CAP has also resulted in 4.2 million ambulatory care visits in 2006 [17]. This accounts for more than US\$17 billion spent on CAP in the USA annually in the inpatient and outpatient care settings combined [18]. Thus, the economic implications of treating pneumonia in a healthcare environment are substantial.

With the prevalent use of PPIs and their over-the-counter availability, serious adverse effects such as pneumonia are concerning. The pathophysiology of pneumonia secondary to PPIs has been hypothesized to be associated with increased gastric pH. The normal pH of stomach contents promotes a sterile environment [19]. PPIs increase intragastric pH, which allows for several species of bacteria to grow in the stomach. One study evaluating omeprazole found an increase in bacterial organisms such as streptococci, coagulase-negative *Staphylococcus*, *Micrococcus* and enteric bacteria, among others [20]. The increase in gastric bacteria may lead to microaspiration and lung colonization with a potential for causing pneumonia [21].

The majority of the data relating PPIs and CAP are derived from observational studies, which yield varying results. Given the over-use of PPIs and the considerable burden of CAP on the healthcare system, this meta-analysis was designed to evaluate the association of PPIs with the development of CAP.

Methods

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines [22].

Data sources & searches

Our aim was to identify all relevant clinical studies that reported an association of CAP with the use of PPIs. To identify all applicable publications, a systematic literature search of PubMed and Ovid Medline was conducted by two investigators independently using the following medical subject headings and keywords: PPI, pneumonia, CAP, anti-ulcer agent, antacids, omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. Databases were searched from 1988 to present (November 2011), as the first PPI was approved in 1990. Bibliographies of recent review articles and systematic reviews were hand-searched to identify any additional studies.

Study selection

Abstracts of full-text articles were independently screened for quality and inclusion by two reviewers. This meta-analysis only included case-controlled and cohort studies, which were published in full in English and evaluated PPI use and CAP incidence in human subjects. Studies of pediatric patients, critically ill patients or *Helicobacter pylori* treatment were excluded. In addition, studies were excluded if the reported data were not evaluable.

Data extraction & quality assessment

Two of the investigators independently extracted data from all eligible studies by using a standardized form. Accuracy of data

was confirmed by a third investigator. For included studies, study design, sample size, study duration and patient demographics were collected. Data were also gathered on study setting, patient population, acid-suppressive therapy (AST) used and occurrence of CAP. The assessment of the quality of observational studies including case-control and cohort studies was done using the Newcastle-Ottawa Quality Assessment Scale (NOQAS) [101]. Any discrepancy that developed regarding the inclusion, quality of a publication or interpretation of data was resolved through consensus.

Data synthesis

The primary outcome of this meta-analysis was the association of CAP with current PPI use. We used the published adjusted odds ratio (ORs) and corresponding 95% CIs from each included study, which were log transformed and analyzed using Comprehensive Meta analysis® (Ver 2.0). We report binary outcomes as ORs. Summary effects estimates are presented with 95% CIs. For all analyses, a p-value of 0.05 or less (two-sided) was considered as significant. We assumed a class effect and pooled data for all PPIs. Data was analyzed based on our primary outcome of current use of PPIs as well as prespecified subgroup analyses including duration of PPI use (<30 or >180 days) and PPI dose (high vs low, defined as >1 defined daily dose vs ≤1 defined daily dose) [23]. Tests for interactions between PPI dosage and duration subgroups were preformed. Measures were also taken to assess the individual quality of studies included in this review, as well as adjusting for heterogeneity among studies. The I² statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). The Cochrane handbook suggests that an I² value greater than 50% indicates significant heterogeneity [102]. As statistical heterogeneity was expected, we used a random-effects model. In addition, a sensitivity analysis was performed based on parameters defined *a priori*. These parameters included a NOQAS score <6 or studies that had included non-population-based sample. A funnel plot was used to evaluate whether there was publication bias.

Results

We identified 817 studies initially, of which 724 studies were not relevant to the current analysis. A total of 93 abstracts were reviewed and 47 articles were excluded. Of the 46 remaining articles, 12 were included for full review. Three articles were excluded in the primary analysis owing to the inability to separate PPI and H-2 Receptor Antagonists (H2RA) data [24], reporting of hospital-acquired pneumonia [25] and inappropriate methodology [26]. Two retrospective cohort analyses [27,28] and seven case-control studies [29-35] were included for the final analyses for the primary outcome. One study did not have sufficient information to be included in the primary outcome analysis but was included in a subgroup analysis [24]. The authors agreed on all included studies. FIGURE 1 illustrates the search strategy related to primary outcome.

Nine studies with 120,863 pneumonia cases from 1987 to 2006 were included in the meta-analysis. PPI usage in pneumonia cases ranged from 4.3 to 47%. NOQAS scores ranged

from 4 to 8 out of a maximum of 9. Six of the studies were population-based studies in various countries including the UK, The Netherlands, Canada and Denmark [28,30,31,33–35]. Two studies used the same UK patient database but evaluated different populations [33,34]. Other studies included a single-center hospital-based study, a stroke rehabilitation center database study, and an Australian Veteran Affairs study [27,29,32]. All studies made statistical adjustments for confounding variables for the development of pneumonia, although studies did not all evaluate the same confounding variables. Many of the studies did not evaluate gastroesophageal reflux disease, alcohol use and smoking as potential confounders. One study only controlled for dysphagia, tracheostomy and feeding tube [32]. Acid-suppressive agents used varied among the studies. Three studies evaluated only PPI use [27,30,35], whereas other included studies evaluated both H2RA and PPI use [28,29,31–34]. TABLE 1 summarizes the study and patient characteristics of each study.

Statistical heterogeneity was present in this analysis ($I^2 = 97.8\%$); therefore, a random-effects model was used. Our primary analysis showed an increased risk of developing pneumonia with current use of a PPI (odds ratio [OR]: 1.39; 95% CI: 1.09–1.76). A preplanned sensitivity analysis showed no change in the association of PPI with the development of CAP. When excluding the study that had a NOQAS score <6, the risk remained significant (OR: 1.37; 95% CI: 1.05–1.78; $I^2 = 98.1\%$) [33]. Also, after excluding studies that evaluated a specific patient population (elective surgery or stroke), risk remained significant (OR: 1.45; 95% CI: 1.13–1.89; $I^2 = 97.2\%$) [28,32]. These results are displayed in FIGURE 2. Prespecified subgroup analysis included PPI dose and PPI duration. PPI use less than 30 days (OR: 1.65; 95% CI: 1.25–2.19), high PPI dose (OR: 1.50; 95% CI: 1.33–1.68) and low PPI dose (OR: 1.17; 95% CI: 1.11–1.24) were significantly associated with CAP. There was no association between CAP and PPI use for more than 180 days (OR: 1.10; 95% CI: 1.00–1.21). Heterogeneity decreased in the PPI dose subgroups, although the test for interaction was not significant ($p = 0.15$). Heterogeneity remained high in the short duration subgroup but decreased in the longer duration subgroup. Test for interaction was significant between the treatment duration subgroups ($p < 0.005$). These results are displayed in FIGURE 2.

Expert commentary

Our meta-analysis shows that the use of PPIs is associated with an increased risk of developing CAP. CAP is hypothesized to develop during PPI therapy due to an increased gastric pH, leading to

subsequent bacterial colonization and aspiration of bacteria [19–21]. This meta-analysis also showed an association with higher dose (defined as higher dose than the usual dose) and shorter duration of PPI use with the development of CAP. No increased risk was seen with long-term therapy. The higher dose of PPI leading to an increased risk of CAP could be hypothesized to be related to a further increase in pH over standard dosing leading to an increased risk of bacterial colonization. Long-term PPI use showing no increased risk for CAP has been hypothesized to be related to the following reasons: decreased immune response regulation from PPIs; patients more likely to develop pneumonia developing it within the first 30 days of PPI use; and decreased compliance with long-term PPI use leading to lower suppression of gastric acid [7,8].

Two other meta-analyses have evaluated the risk of CAP with PPI use [7,8]. Our findings are in agreement with these meta-analyses; however, there are some differences between our meta-analysis and the others. We have included a greater number of studies than previous meta-analyses, and we conducted a prespecified sensitivity analysis based on the quality of studies determined by the NOQAS and the patient population. This allowed us to determine possible reasons for heterogeneity, although heterogeneity still remained high except in some of the subgroup analyses. We

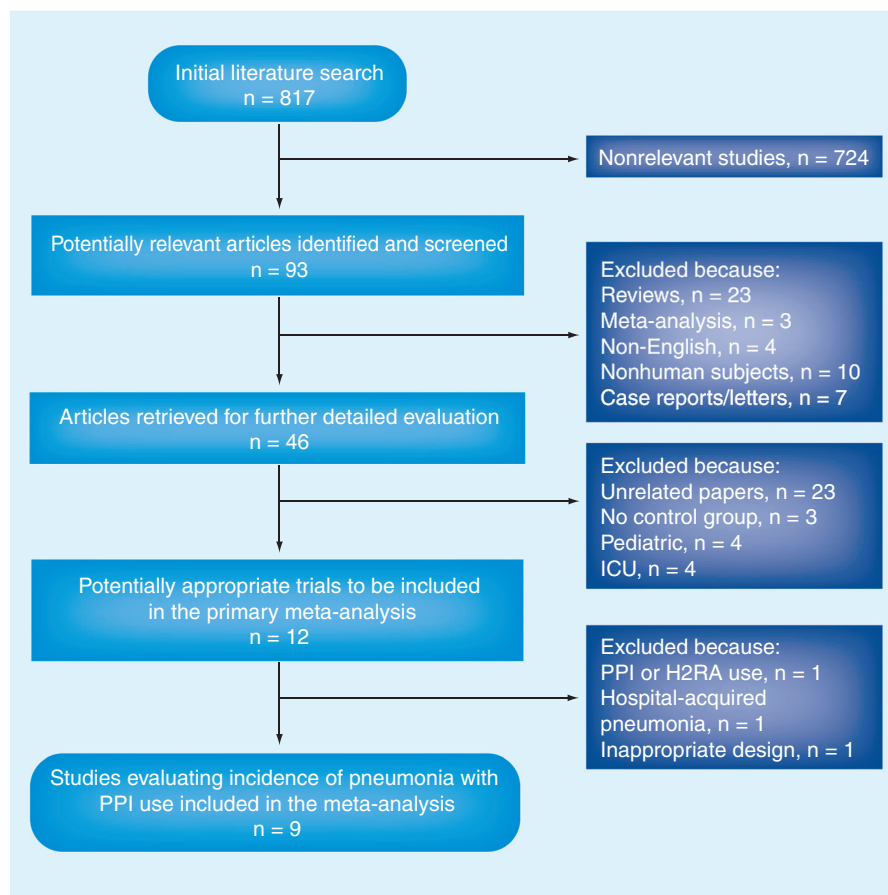


Figure 1. Systematic literature search for studies evaluating proton pump inhibitor use and association of community-acquired pneumonia.

H2RA: Histamine 2 receptor antagonist; ICU: Intensive care unit; PPI: Proton pump inhibitor.

Study (year)	Statistics for each study					Ref.
	Odds ratio	Lower limit	Upper limit	Z-value	p-value	
Dublin <i>et al.</i> (2010)	1.130	0.883	1.446	0.973	0.331	[29]
Gulmez <i>et al.</i> (2007)	1.500	1.309	1.719	5.837	0.000	[30]
Laheij <i>et al.</i> (2004)	1.890	1.362	2.623	3.806	0.000	[31]
Marciniak <i>et al.</i> (2009)	1.800	0.488	6.638	0.883	0.377	[32]
Myles <i>et al.</i> (2009)	1.550	1.359	1.768	6.520	0.000	[33]
Redelmeier <i>et al.</i> (2010)	0.970	0.884	1.065	-0.642	0.521	[28]
Rodriguez <i>et al.</i> (2009)	1.160	1.029	1.308	2.419	0.016	[34]
Roughead <i>et al.</i> (2009)	1.160	1.101	1.222	5.619	0.000	[27]
Sarkar <i>et al.</i> (2008)	2.050	1.957	2.147	30.413	0.000	[35]
Pooled odds ratio	1.386	1.091	1.760	2.673	0.008	

Heterogeneity: $\tau^2 = 0.115$; $I^2 = 97.8\%$

Association of high PPI dose and development of CAP

Gulmez <i>et al.</i> (2007)	1.400	1.177	1.666	3.798	0.000	[30]
Laheij <i>et al.</i> (2004)	2.280	1.264	4.113	1.738	0.006	[31]
Rodriguez <i>et al.</i> (2009)	1.310	0.839	2.046	1.186	0.235	[34]
Sarkar <i>et al.</i> (2008)	1.560	1.330	1.830	5.462	0.000	[35]
Pooled odds ratio	1.496	1.332	1.681	6.786	0.000	

Heterogeneity: $\tau^2 = 0.001$; $I^2 = 4\%$

Association of low PPI dose and development of CAP

Gulmez <i>et al.</i> (2007)	1.400	1.094	1.791	2.678	0.007	[30]
Laheij <i>et al.</i> (2004)	1.230	0.782	1.935	0.896	0.370	[31]
Rodriguez <i>et al.</i> (2009)	1.090	0.917	1.296	0.977	0.329	[34]
Sarkar <i>et al.</i> (2008)	1.170	1.102	1.242	5.137	0.000	[35]
Pooled odds ratio	1.173	1.110	1.239	5.709	0.000	

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0\%$

Association of PPI use <30 days and development of CAP

Gulmez <i>et al.</i> (2007)	5.000	2.118	1.802	3.673	0.000	[30]
Laheij <i>et al.</i> (2004)	2.240	1.419	3.537	3.461	0.001	[31]
Myles <i>et al.</i> (2009)	1.550	1.359	1.768	6.520	0.000	[33]
Redelemeir <i>et al.</i> (2010)	1.080	0.971	1.201	1.418	0.156	[28]
Rodriguez <i>et al.</i> (2009)	1.210	0.899	1.628	1.258	0.208	[34]
Sarkar <i>et al.</i> (2008)	1.960	1.684	2.282	8.682	0.000	[35]
Pooled odds ratio	1.651	1.247	2.187	3.499	0.000	

Heterogeneity: $\tau^2 = 0.095$; $I^2 = 91.3\%$

Association of PPI use >180 days and development of CAP

Laheij <i>et al.</i> (2004)	1.520	1.009	2.289	2.005	0.045	[31]
Rodriguez <i>et al.</i> (2009)	1.050	0.902	1.222	0.629	0.530	[34]
Sarkar <i>et al.</i> (2008)	1.090	1.022	1.162	2.626	0.009	[35]
Pooled odds ratio	1.097	0.998	1.206	1.920	0.055	

Heterogeneity: $\tau^2 = 0.002$; $I^2 = 27.7\%$

Odds ratio and 95% CI

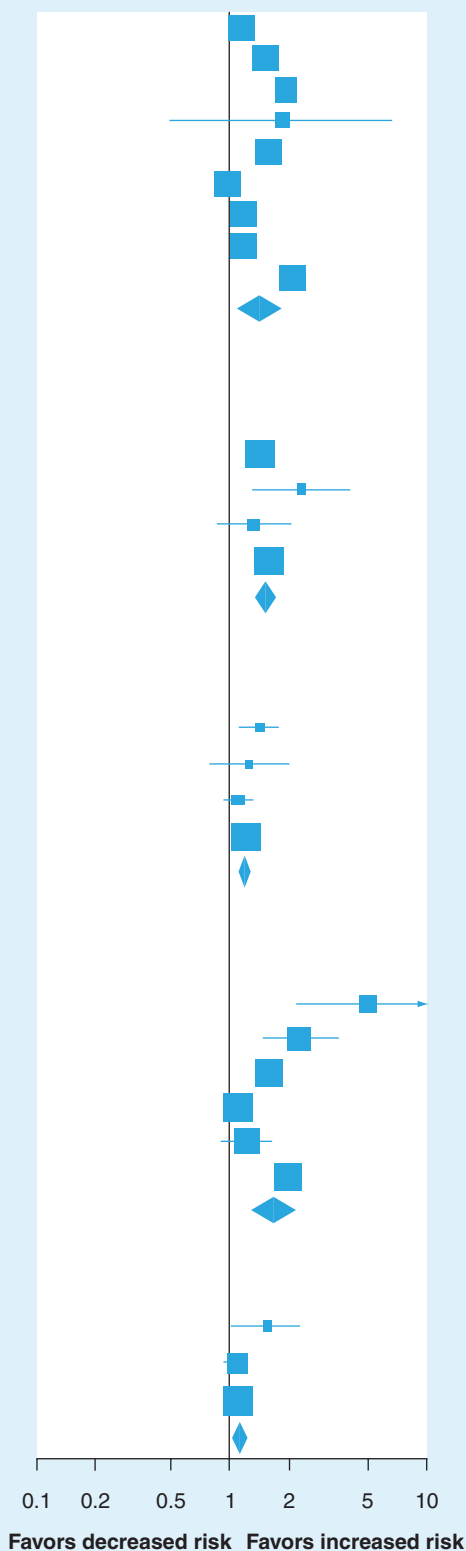


Figure 2. Proton pump inhibitor use and association of community-acquired pneumonia.

CAP: Community-acquired pneumonia; PPI: Proton pump inhibitor.

also excluded one study from our primary analysis as PPI and H2RA data were inseparable [24], although a previous analysis included this study [8]. Similar to other meta-analyses, we found a significant relationship between the development of CAP with high PPI dose and shorter duration of use.

There are several limitations to this meta-analysis. The studies included in our analysis had a high heterogeneity. This may be due to a number of factors. The quality of studies varied in our analysis based on NOQAS scores, although when lower quality studies were excluded heterogeneity remained high. Additionally, the NOQAS tool exhibits inter-rater variability [36]. Certain studies only evaluated specific patient groups, although when only population-based studies were included, heterogeneity still remained high. Among the studies, varying definitions of current PPI use and the differences in adjustment for confounding variables in each of the studies may have contributed to the high heterogeneity in our analysis. There are several patient factors that have been shown to increase the risk of CAP and are independent of acid suppression [37]. Several of these confounding variables were accounted for in the included studies. These variables included sex, age, tobacco use, alcohol use, total hospitalizations and/or physician office visits, past CAP, chronic obstructive pulmonary disease, asthma, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, cancer, myocardial infarction, dementia and specific medications. However, none of the included

studies controlled for gastroesophageal reflux disease, and many studies did not control for alcohol or tobacco use, which are also risk factors for development of CAP [37]. TABLE 1 lists CAP risk factors which were not accounted for in each of the studies. In addition to the primary outcome, subgroup analyses were carried out to analyze the PPI dose and duration. However, there were few studies that could be included. There were inconsistencies in the classification of the duration of PPI use in the included studies. Therefore, we could not evaluate the association of PPIs and CAP between 30 and 180 days of PPI use.

AST is commonly utilized in the institutional practice setting for prophylaxis of stress-related mucosal damage. Up to 71% of hospitalized patients receive AST and 73% of these patients lack appropriate indications [38,39]. In addition, up to 69% of patients who receive inappropriate AST while hospitalized continue therapy after discharge [38–41]. The widespread use of PPIs may have been proliferated due to the perception that PPIs have a favorable adverse effect profile. The current meta-analysis shows that short-term PPI use is associated with development of CAP, a serious adverse effect. Patients currently receiving PPIs, particularly for less than 30 days or high dose, showed an association with CAP. PPIs should be initiated in patients that have appropriate indications for use, and doses should be optimized for indications. Practitioners need to be vigilant about the adverse effects of PPIs and consider alternative therapies.

Table 1. Characteristics of included studies.

Study (year)	CAP cases (n)	Design	Population	Acid suppression	CAP risk factors unaccounted for	Newcastle–Ottawa Score	Ref.
Roughead <i>et al.</i> (2009)	13,876	RC	Australian VA study following patients exposed or not exposed to PPI from 2002 to 2006	PPI	GERD, ETOH use and smoking	6	[27]
Redelmeier <i>et al.</i> (2010)	6389	RC	Population-based study in post-surgical patients in Canada from 2001 to 2002	PPI or H2RA	GERD, ETOH use, smoking and functional status	8	[28]
Dublin <i>et al.</i> (2010)	1125	NCC	Prescription database of patients in Washington State, USA from 2000 to 2003	PPI or H2RA	GERD	7	[29]
Gulmez <i>et al.</i> (2007)	7642	CC	Population-based study in Denmark from 2000 to 2004	PPI	GERD and smoking	6	[30]
Laheij <i>et al.</i> (2004)	475	NCC	Population-based study in The Netherlands from 1995 to 2002	PPI or H2RA	GERD, ETOH use and smoking	6	[31]
Marciniak <i>et al.</i> (2009)	36	CC	Patients admitted to stroke rehabilitation unit from 1999 to 2003	PPI or H2RA	Only controlled for feeding tube, dysphagia and tracheostomy	6	[32]
Myles <i>et al.</i> (2009)	3709	NCC	Population-based study in the UK from 2001 to 2002	PPI or H2RA	GERD and ETOH use	4	[33]
Rodriguez <i>et al.</i> (2009)	7297	NCC	Population-based study in the UK from 2000 to 2005	PPI or H2RA	GERD and ETOH use	6	[34]
Sarkar <i>et al.</i> (2008)	80,066	NCC	Population-based study in the UK from 1987 to 2002	PPI	GERD	6	[35]

CAP: Community-acquired pneumonia; CC: Case–control; ETOH: Alcohol; GERD: Gastroesophageal reflux disease; H2RA: Histamine 2 receptor antagonist; NCC: Nested case–control; PPI: Proton pump inhibitor; RC: Retrospective cohort; VA: Veterans' Affairs.

Five-year view

Currently, the world population is approximately 7 billion. Over the next 5 years the percentage of patients classified as geriatric is expected to increase as the 'baby boomer generation' reaches their sixties. Due to increasing numbers of comorbid states in the geriatric population, acute diseases such as pneumonia are more likely to require hospitalizations and incur significant healthcare costs. In the era of decreasing healthcare funding, it is imperative to evaluate all drug therapies for appropriate use. When evaluating appropriateness the following should be considered: adverse reactions, drug interactions, duration of therapy, correct dose (supratherapeutic/subtherapeutic), appropriate indication and route of administration. Our meta-analysis evaluated one adverse effect from PPIs, and found an association with PPI use and the development of CAP, particularly with increased dosage and shorter duration of PPI use.

Postmarketing experience has evaluated many adverse effects of PPIs not initially recognized in clinical trials, such as *Clostridium difficile* infections, osteoporosis, acute interstitial nephritis and pneumonia (both community and hospital acquired). These adverse effects are typically studied individually and authors make conclusions based only on the specific adverse effect that is studied. In clinical practice, it is understood to some degree that these adverse effects may happen, but it is hard to quantify results between different trials. For example, what would the number needed to harm (NNH) be when adding all of the adverse effects of PPIs together? Should different adverse effects be weighed differently when calculating a number-needed to harm? If the indication is appropriate what is the number-needed to treat (NNT)? Should the NNT based on outcome be weighed differently against a NNH based on adverse effect? What is the NNT

and NNH difference when looking at H2RAs versus PPIs? All of these questions are important when trying to identify which patients will benefit the most from PPI therapy or when we should use alternate therapies such as H2RAs. Future studies should strive to answer these questions so a more systematic approach can be taken when deciding what the best choice is for a patient with an appropriate indication. It would also be important to look at all adverse effects in the same population, not compare incidences of adverse effects between different populations.

If PPIs continue to be overprescribed, the healthcare costs related to the adverse effects of PPIs will only increase with increasing geriatric populations. Several approaches can be taken to decrease these costs. First, PPI overuse needs to be curtailed. Educational programs, computerized reminders, emails, direct education, phone calls, pharmacist intervention and student intervention are all possible ways of discouraging overuse. Combining these methods would likely have the best results. Second, original studies that are conducted should evaluate all PPI adverse effects and efficacy so we can better quantify a benefit:risk ratio that is usable in clinical practice. By using these approaches, the unforeseen impact of PPIs on healthcare costs may be avoided at a time where decreasing healthcare funding is being carefully reviewed.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Proton pump inhibitors (PPIs) are overutilized owing to their perceived safety profile.
- Observational studies have shown varying degrees of association of community-acquired pneumonia (CAP) with the use of PPIs.
- CAP is a substantial economic burden on the healthcare industry.
- This meta-analysis showed an association between PPI use and the development of CAP.
- Subgroup analyses showed an association of higher dose and shorter duration of PPI use with the development of CAP.
- Practitioners need to be vigilant about adverse effects of PPIs and consider alternative therapies when appropriate.

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•• of considerable interest

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