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Co-prescription of Gastroprotective Agents and Their Efficacy in Elderly Patients Taking Nonsteroidal Anti-inflammatory Drugs: A Systematic Review of Observational Studies

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Background & Aims: Guidelines recommend prescribing gastroprotective agents (proton pump inhibitors, misoprostol) to older patients (primarily ≥65 years old) taking nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent gastrointestinal ulcers. Older individuals are underrepresented in clinical trials of these agents. We systematically reviewed evidence from observational studies on the use of gastroprotective agents in elderly patients and their ability to prevent NSAID-related ulcers in this population.

Methods: We performed a systematic search of Embase and MEDLINE and identified 23 observational studies that focused on elderly patients and reported data on co-prescription of gastroprotective agents and NSAIDs and/or the effectiveness of the agents in preventing gastrointestinal events in NSAID users. We collected data on rates of co-prescription and NSAID-related gastrointestinal events in patients with and without gastroprotection.

Results: A median of 24% (range, 10%-69%) of elderly patients taking NSAIDs received a co-prescription for gastroprotective agents; this percentage was only slightly higher in the oldest age groups. All studies of efficacy showed a positive effect of gastroprotection. However, the adjusted results were not suitable for synthesis, and the 5 studies reporting unadjusted results were too heterogeneous for meta-analysis (I2 = 97%). The studies differed in outcomes, definitions of

co-prescription, and differences in baseline risk factors between patients with and without gastroprotection. None of the studies assessed adverse effects of gastroprotective agents. The 2 cost-effectiveness studies reached opposing conclusions.

Conclusions: In a systematic review, the observational evidence for the efficacy of gastroprotective agents in preventing NSAID-associated gastrointestinal events was in agreement with results of randomized controlled trials. However, because of heterogeneity of included studies, it is not clear what the effect would be if more patients were treated, or at what age gastroprotection should be recommended. We offer suggestions to facilitate comparison with other work and address the questions of risk and benefit in relation to age.

Abbreviations used in this paper

CI, confidence interval;
COX-2, cyclooxygenase-2;
GI, gastrointestinal;
H2RA, histamine-2 receptor antagonist;
NS, nonselective;
NSAID, nonsteroidal anti-inflammatory drug;
OR, odds ratio;
PPI, proton pump inhibitor;
RR, relative risk

As the population ages, care of older patients is becoming increasingly important. With age comes an increased incidence of chronic disease and disabilities, often accompanied by pain. Pain control is fundamental to maintaining quality of life, and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for control of pain and inflammation in elderly patients.[1] However, use of NSAIDs carries a risk of adverse events,[2] including gastrointestinal (GI) ulceration and bleeding, which can lead to hospitalization and mortality.[3] Metabolism of medications and pharmacokinetics change with age,[1] and older patients are also more likely to have conditions or medications that put them at increased risk for GI symptoms associated with NSAID use.[1 and 4]

Guidelines recommend gastroprotection for high-risk patients taking nonselective (NS)-NSAIDs, particularly proton pump inhibitors (PPIs) or misoprostol for older patients (defined as older than 65 or 70 years of age in most guidelines; Supplementary Table 1).[5, 6, 7, 8, 9 and 10] A Cochrane review of the evidence for the efficacy of gastroprotection to prevent endoscopic ulcers in high-risk patients showed that 800 μg/day misoprostol had an adjusted relative risk (RR) of 0.17, double-dose histamine-2 receptor antagonists (H2RAs) had an RR of 0.44, and PPIs had an RR of 0.40.[11]

Applicability of Evidence From Clinical Trials to Elderly Patients

There is reason to believe that the clinical trials may not be directly applicable to elderly patients.[12, 13 and 14] A 2006 study comparing trials of 5 gastroprotective

strategies suggested that elderly patients may benefit more from misoprostol or H2RAs but not cyclooxygenase-2 (COX-2) selective NSAIDs.[15] Older patients may also be more prone to adverse effects from the gastroprotective agents themselves, including more serious problems such as fractures,[16] pneumonia,[17]Clostridium difficile infection,[18] and others. [19 and 20]Finally, elderly patients are often excluded from clinical trials, [21 and 22] and there is evidence that elderly people are underrepresented in the trials in the Cochrane review. Because the average age of NSAID users is older than 65 years,[23] clinical trials of NSAID users should also have an average age of older than 65 years. Only 1 trial specifically studied older patients (>60 years of age), reporting 8 ulcers in 53 patients receiving ibuprofen and no ulcers in 60 patients receiving ibuprofen/misoprostol.[24] Only 5 of the other 38 studies in the Cochrane review had an average participant age of older than 65 years (Supplementary Table 2), [25, 26, 27,28 and 29] and none performed a subgroup analysis for patients older than 65 years. Although it is known that risk of a GI event increases with age and decreases with gastroprotection, evidence is lacking as to at what age co-prescription is indicated and for what patients the risks of therapy may outweigh the benefits.

Recent meta-analyses have shown that high-quality observational studies provide similar results to high-quality randomized controlled trials.[30, 31 and 32] Population-based observational studies can better represent elderly patients as encountered in daily practice, including those with multiple morbidities and complex medications. Gastroprotective agents are commonly used by elderly patients for gastroesophageal reflux disease and other indications. Patients with those indications are often at higher risk of GI events; thus the rate of co-prescription is important for determining what the effect might be if the entire population were treated.

Therefore, the objectives of this review were to assess the effectiveness of gastroprotective agents in clinical practice for prevention of GI ulceration related to NSAID use in elderly patients, quantitatively synthesize the evidence where possible, and assess the rate of co-prescription of gastroprotective agents with NSAIDs in elderly patients.

METHODS

Data Sources and Search

A researcher (S.E.) systematically searched Embase and MEDLINE for articles with the terms elderly,seniors, or 65 years; nonsteroidal anti-inflammatory drugs or NSAIDs; and gastroprotective agents,histamine 2 blockers, or proton pump inhibitors in the title, abstract, subject headings, or keywords (details of search in the Supplementary Appendix). The search was last performed on March 14, 2013.

Study Selection

Two authors (S.E. and Z.T.) independently selected articles for full-text screening on the basis of title and abstract, with disagreements resolved by discussion. Inter-rater agreement was assessed by using Cohen's κ (R 2.11.1; The R Foundation for Statistical Computing, package irr[33]). Two authors (S.M. and S.E.) evaluated the full text for inclusion in the study and extracted the data. References of the included articles were checked for additional studies.

The inclusion criteria were the following:
(1) The study is an observational study of clinical practice.
(2) The study population is elderly; the study explicitly includes only patients ≥65 years, has an average patient age ≥65, or presents any subgroup stratified by an age ≥65 years.
(3) The study must report the rate of concomitant prescription of NSAIDs and gastroprotective agents (co-prescription studies) and/or the effectiveness of gastroprotective agents at prevention of NSAID-related GI events (efficacy studies).
(4) The study is published in the English language.
Studies were included for full-text screening if the abstract indicated that the main subject of the study was the rate of co-prescription or efficacy of gastroprotective agents in NSAID users, and older age was mentioned as a factor that was assessed in the study. All studies published before January 1, 2013 were eligible for inclusion.

Data Extraction and Quality Assessment

Included studies were classified as co-prescription, efficacy, or both. We recorded the size, setting, objective, study design, and inclusion criteria. Drug exposure was assessed in terms of NSAID and gastroprotective agent exposure (which medications were assessed, dose, duration, incident or prevalent use, and consideration of over-the-counter exposure) and the criteria defining a co-prescription. We recorded the outcomes assessed, including adverse effects from the gastroprotective agents. From the co-prescription studies, we recorded the rate of co-prescription for patients over 65, the rate of co-prescription for any subgroups with age over 65, and factors influencing co-prescription. For meta-analysis of efficacy studies, we recorded the follow-up time, clinical outcome, the unadjusted number of patients with and without the clinical outcome, the adjusted result, and variables used in adjustment. Risk of bias was assessed by using the criteria proposed in the risk of bias section of the Grading of Recommendations Assessment, Development, and Evaluation system by Guyatt et al[34] (assessing eligibility criteria, measurement of exposure and outcome, control for confounding, and completeness of follow-up).

Data Synthesis and Analysis

We assessed heterogeneity (I^2) and the cumulative odds ratio (OR) by using a random effects model and assessed the risk of publication bias by using a funnel plot (RevMan 5.1.4; The Cochrane Collaboration). If the results of the meta-analysis were not reliable, then the cumulative OR would not be reported. We also recorded predictors of NSAID-associated GI events as reported in each study.

RESULTS

The search results are illustrated in Figure 1. The search yielded 223 articles, of which 30 were provisionally included on the basis of title and abstract. Inter-rater agreement was high ($\kappa = 0.98$). Review of the full text retained 23 articles.
Characteristics of the included studies are summarized in Table 1, with further details inSupplementary Table 3. Five studies reported both the rate of co-prescription and the efficacy of PPIs for prevention of GI events,[35, 36, 37, 38 and 39] fourteen reported

only on co-prescription,[40, 41, 42, 43, 44, 45, 46, 47,48, 49, 50, 51, 52 and 53] and 3 reported only on efficacy.[54, 55 and 56] A study reporting on the therapeutic intent of PPIs co-prescribed with NSAIDs was also included.[57]

[TABLE 1] [FIGURE 2]

Co-prescription

Table 1 shows the rate of co-prescription of NS-NSAIDs with gastroprotective agents. The rate of co-prescription for patients aged 65 and older was reported in 19 studies,[35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47,48, 49, 50, 51, 52 and 53] with rates ranging from 10.2%[41] to 69.4%[53] (median, 23.6%). The rate of co-prescription in these patients is shown in relation to the study period in Figure 2.

[TABLE 2]

Effect of age on prescribing behavior

Eleven studies investigated the effect of age on the rate of co-prescription.[37, 39, 40, 41, 42, 44, 47, 48, 49,50 and 53] Increasing age was positively associated with increasing rates of co-prescription in 8 of 11 studies.[37, 39, 40, 41, 42, 48, 49 and 50] Four studies compared older patients with younger patients with 1 or more risk factors and found an adjusted OR of 4.1, confidence interval (CI), 2.3-7.4 (reference category, 18-45 years)[40]; an adjusted OR of 1.71, CI, 1.30-2.23 (reference category, 50-65 years)[48]; no difference in rate of co-prescription for young low-risk patients (57.5%), young high-risk patients (69.4%), and older patients (69.4%)[53]; and that other factors predicted co-prescription better than age (adjusted OR, 3; CI, 2.3-4.1).[50]The other 7 studies included only patients aged 65 and older. One reported an adjusted OR of 1.11 (CI, 1.03-1.91) for patients ≥75 years compared with those <75 years,[42] and another reported a hazard ratio of 1.02 (CI, 1.02-1.02) per year.[37] Five reported differences per age category: significant differences per 10-year category,[39] adjusted OR (significant for age ≥85, OR, 1.12; CI, 1.02-1.22),[41] a nonsignificant increase per 5 years,[44] a nonsignificant decrease per 5 years,[47] and significantly higher rates of prevalent but not incident use of gastroprotective agents starting at 80 years of age (per 5-year category) (OR, 1.28; CI, 1.12-1.43 and OR, 1.10; CI, 0.83-1.46, respectively).[49] Two studies reported the rates of co-prescription per 5-year age category but did not analyze them.[38 and 51] In all studies reporting the rate of co-prescription with respect to age, the largest absolute difference was 9.6% (22.3% in ages 65-70 and 31.9% in ages >85).[51]

Other factors influencing prescribing behavior

Eleven of the included studies reported on statistically significant predictors of co-prescription. Apart from age, only a few factors were investigated in more than 2 studies. These factors included a history of upper GI problems (significant in 7 of 7 studies)[37, 40, 41, 42, 46, 48 and 50]; more concurrent medications (3 of 3 studies),[37, 41 and 47] particularly corticosteroids (7 of 7 studies),[37, 41, 42, 44, 46, 47 and 48] anticoagulants (4 of 6 studies),[37, 42, 44, 46, 47 and 48] and aspirin (2 of 3 studies)[37, 47 and 50]; high NSAID dose (2 of 4 studies)[40, 46,48 and 50];

duration of prescription (positively associated in one study,[49] negatively associated in one study,[46]and nonsignificant in the third[50]); and female gender (4 of 7 studies).[37, 40, 42, 44, 47, 48 and 50] Three studies investigated the influence of the type of NSAID. Indomethacin and ketoprofen were significantly associated with higher rates of co-prescription in all 3 studies,[44, 47 and 48] but other NSAIDs were also significant in each study. An additional 41 factors were investigated in 1 or 2 studies, including economic status, race, previous NSAID tolerance, and year of prescription.

Study quality and risk of bias

Most of the studies in this category had a low risk of bias in inclusion criteria, because they included all patients in a region or hospital or all patients with exposure to study medications, although 3 studies asked doctors to voluntarily include patients.[40, 50 and 53] Risk of bias in measurement of exposure and outcome was also low in most studies, although the same 3 studies relied on exposure and outcome reporting by participating doctors and also reported the highest rates of co-prescription. The definition of exposure and outcome (co-prescription) varied widely. Definition of NSAID exposure varied in the types of NSAIDs (COX-2s, NS-NSAIDs, aspirin, and/or acetaminophen), dose, duration, and whether incident (new) users or prevalent users were included (Supplementary Table 3). The definition of exposure to gastroprotective agents also varied by class (PPIs, misoprostol, H2RAs, and/or sucralfate), dose, duration, and incident or prevalent use. The definition of co-prescription varied from prescription by the same doctor on the same day,[44] to any overlap in use,[38, 39 and 54] to prescription within the same year.[51] A sensitivity analysis of this definition was performed or referenced in 7 studies (Supplementary Table 3).[37, 38, 39, 44, 48, 49 and 54]

Efficacy

Eight studies reported on efficacy.[35, 36, 37, 38, 39, 54, 55 and 56] Five reported the incidence of GI events in patients taking NS-NSAIDs[36, 37, 38 and 39] or low-dose aspirin[35] with or without a concomitant PPI (Table 2). All 5 investigated PPI use in patients older than 65 years of age, with 2 in the same population.[37 and 38] Three of the 5 were population-based, representing 1 national cohort[39] and 1 regional cohort.[37 and 38] The other 2 consisted of a referral center population[35] and a national sample from participating general practices.[36] The forest plot in Figure 3 shows little overlap in the CIs, indicating high heterogeneity (I^2 = 97%). The study investigating low-dose aspirin[35] was included in the analysis because aspirin has also been shown to be associated with GI bleeding (mitigated by use of PPIs),[58] and excluding this study did not reduce the heterogeneity (I^2 = 98%). Meta-analysis will not provide reliable results with high heterogeneity,[59] and assessment and adjustment for heterogeneity cannot be performed with a small number of studies.[60]Likewise, the funnel plot (Supplementary Figure 1) is not considered reliable with fewer than 10 studies.[61]Potential sources of heterogeneity include differences in the choice of outcome measure (self-reported GI complaints,[36] GI hospitalization rate,[37 and 38] hospitalization with upper GI event,[39 and 54] ulcers found on endoscopy,[35] or serious ulcer complications[55 and 56]), the definitions of drug exposure and co-prescription, and differences in prescribing behavior leading to greater or lesser differences in baseline risk between treated and untreated patients. Three of these 5[37, 38 and 39] plus an additional 2 studies[54 and 55] reported efficacy of PPIs after

adjustment for various risk factors (Table 2) but did not report outcome measures that could be combined. In addition, these 5 studies took place in only 3 distinct populations.

[TABLE 2] [FIGURE 3]

All studies reported a significant benefit for patients co-prescribed PPIs while taking NSAIDs. One of the 2 cost-effectiveness studies reported that co-prescription was not cost-effective (net cost of €4907, approximately $6900 US, per ulcer complication prevented, which is based on the average cost of treating a complicated ulcer),[56] and the other concluded that it was cost-effective (50% overall cost reduction, which is based on individual medical, radiologic, and surgical costs).[54]

Risk factors for gastrointestinal events in elderly nonsteroidal anti-inflammatory drug users

Four studies reported on statistically significant independent predictors of GI ulceration or hospitalization for a GI problem.[37, 38, 39 and 55] Use of PPIs was significantly protective,[37, 38, 39 and 55] and age was a significant risk factor in all studies that assessed it.[37, 38 and 39] No other risk factor was consistently significant, although female gender tended to be protective,[37, 38 and 39] and use of anticoagulants, corticosteroids, or aspirin tended to increase risk.[37, 38, 39 and 55] An additional 23 factors were investigated by 1 or 2 studies, including use of other medications and use of coxibs.

Study quality and risk of bias

These 8 studies carry a low risk of bias in their eligibility criteria (Table 2). Five were population-based[37, 38,39 and 54] or included all patients in the hospital database,[57] and 2 included successive patients undergoing endoscopy[35] or visiting participating general practices.[36] One was a case-control study including all admissions to the regional hospital with NSAID-related ulcers,[56] which acknowledged the limitation that no age-matched controls could be found for the oldest patients diagnosed with NSAID-related ulcers.[55] Four studies used sensitivity analysis or comparison of different measures of exposure.[37, 38, 39 and 54] The outcome measures pose little risk of bias, with the exception of 1 study that used patient surveys.[36] Five studies reported an outcome adjusted for various confounders,[37, 38, 39, 54 and 55] and 2 reported unadjusted results.[35 and 36] Follow-up time was adequate in all studies.

Use of Nonsteroidal Anti-inflammatory Drugs and Proton Pump Inhibitors/Gastroprotective Agents in the Elderly Population

Seven studies reported on the use of NSAIDs among elderly patients or on the use of gastroprotective agents in patients who do not use NSAIDs (Table 3).[44, 45, 47, 48, 49, 51 and 52] The single study investigating the indication given for co-prescribing gastroprotective agents with NSAIDs found that 949 of 1069 prescriptions described an "appropriate therapeutic intent," but only 119 of these suggested NSAID-related gastroprotection as a reason for the prescription.[57]

[TABLE 3]

Side Effects of Gastroprotective Agents

Only 1 study investigated possible side effects of gastroprotective agents.[36] This study did not report on which medication (NSAID or the gastroprotective agent) may have caused the side effects.

DISCUSSION

The risk-adjusted outcomes of the studies in this review are in concordance with data from clinical trials[11] in high-risk patients, pointing toward the effectiveness of PPIs at preventing GI ulcers in NSAID users. However, the evidence is insufficient to quantify this effect, to advise on which age groups benefit most from gastroprotection, or to estimate what the effect would be if more elderly patients received gastroprotection. A median of 24% of elderly patients received gastroprotection in the included studies and only increased slightly in the oldest age groups. The studies investigated different clinical outcomes, different NSAIDs and gastroprotective agents, different definitions of a concomitant prescription, and adjusted for different risk factors. Many seniors take gastroprotective agents for GI complaints rather than for gastroprotection, and higher-risk patients are more likely to be taking gastroprotective medication. These factors must be taken into account when assessing the effectiveness and cost-effectiveness of PPIs and other gastroprotective agents in elderly patients.

The rate of co-prescription found in the included studies is similar to the rate reported in a 2006 review[62] and is only slightly higher than the usage of gastroprotective agents in the population of elderly people who do not use NSAIDs.[44, 45, 47, 48, 49, 51 and 52] This implies that most co-prescriptions are attributable to patients taking gastroprotective agents for other indications, in concordance with the study investigating prescriber's intent.[57] Prevalent use of PPIs is associated with a higher risk of a GI event[39]; thus, distinguishing incident from prevalent use is important in determining efficacy and predicting efficacy if the rate of co-prescription were higher.

Although older age was generally associated with higher rates of co-prescription, results were inconsistent when compared with younger high-risk patients, with 1 study reporting a higher co-prescription rate in younger patients (79.7% vs 55.4%)[50] and 2 reporting similar rates in both groups.[46 and 53] Variation in local guideline recommendations (Supplementary Table 1) may impact the rate of co-prescription, but if this were the main cause of variation, then we would expect a much higher rate in older seniors (eg, >75 years) for whom gastroprotection is consistently recommended. Instead, we see that the rate of co-prescription was only slightly higher in the oldest age groups.

The 2 included studies assessing cost-effectiveness reached opposing conclusions. This may be due to differences between countries but may also be attributable to calculating cost that is based on the average cost of treating a complicated ulcer[56] versus the cost of services used by patients with and without co-prescription.[54]

We chose to analyze observational data because elderly people appear to be underrepresented in clinical trials, but also because observational data can provide a

valuable adjunct to trial data. Clinical trials control for comorbidities, interacting medications, and compliance.[12] By contrast, elderly patients often have comorbidities[63] and multiple medications,[64] and patient preference, variation in guidelines, and reimbursement policy[65] may affect compliance. Observational studies, particularly population-based studies, can represent the complexity of the elderly population to reach conclusions about both efficacy and adverse effects.

There are some limitations to our study. It is possible that some relevant studies were missed in the search process. Two researchers independently evaluated the articles for inclusion, but it is possible that examination of the full text of articles excluded on the basis of title and abstract could yield additional studies, particularly those with subgroup analyses of patients older than 65 years. The main limitation is that the small number of studies and heterogeneity prevented quantitative assessment of the effectiveness of gastroprotective agents in preventing NSAID-related GI events. Our review found 7 studies reporting results with the potential to be combined in a meta-analysis (3 reporting both adjusted and unadjusted results,[37,38 and 39] 2 reporting only adjusted results,[54 and 55] and 2 reporting only unadjusted results[35 and 36]), which took place in only 5 distinct populations. We chose to approach this review by identifying as many relevant studies as possible and then eliminating studies if necessary on the basis of heterogeneity.[14] To this end, we chose fairly broad inclusion criteria. We chose to include all studies with a population averaging older than 65 years of age. Although an average age of 65 and older does not ensure that the results are applicable to all elderly patients, an average age younger than 65 years virtually ensures that the elderly patients were underrepresented. Therefore, we chose to use this broad criterion, although it could have contributed to heterogeneity by including small studies with a few very old patients skewing the average age. However, no such studies were identified, and 3 relevant studies were included that would have otherwise been missed.[52,55 and 56] We also chose not to restrict definitions of outcome, definition of exposure (co-prescription), or the baseline risk of the population, because there are not yet any standard definitions, and any chosen set of definitions would be very likely to exclude relevant studies.

Although meta-regression can be used to test and adjust for heterogeneity, a limitation of this approach is that only factors reported by all studies can be used, and the number of variables in the adjustment should not exceed 1 per 5-10 studies.[60] The studies could also be stratified on the basis of study population (national or regional cohorts, referral center, or general practice populations), type of GI event measured, and type of gastroprotective agent used. All of the included studies focused on the efficacy of PPIs; the use of misoprostol and H2RAs in the elderly also warrant investigation. To address the clinical question of how effective gastroprotection is for elderly patients and at what age patients should receive it, future reporting of observational data should be directed at facilitating comparison with other studies.

Recommendations for Reporting to Facilitate Comparison Between Studies

To compare results between studies, future studies should attempt to standardize reporting in the areas of heterogeneity identified in the included studies: the choice of outcome measure, the definitions of drug exposure and co-prescription, and assessing differences in baseline risk in treated and untreated patients.

Outcome measure

If possible, multiple outcomes should be assessed. Potentially relevant outcomes include GI events treated on an outpatient basis, hospitalization for GI events, serious/complicated ulcers, and deaths that are due to GI events. Efficacy and cost-effectiveness studies should account for a possible difference in the severity of ulcer complications in patients taking gastroprotective agents, which could result in lower treatment costs. Adverse effects from the gastroprotective agents themselves should also be measured: both common side effects such as GI disturbance and the potential for more serious side effects such as increased risk of pneumonia or osteoporosis.

Definition of co-prescription/exposure

Abraham et al[39] demonstrated the importance of the definition of co-prescription in establishing efficacy, showing a 3-fold difference in hazard ratio between patients who had received a gastroprotective agent for <20% of the duration of NSAID prescription vs >80% of NSAID prescription. A recent study showed similar results, with patients who had discontinued prescriptions for PPIs having a significantly higher chance of a GI event than patients who were still taking a PPI (OR = 1.45).[66] An estimate of the actual percentage of overlapping duration can be used in analysis of heterogeneity. Incident and prevalent users of gastroprotective agents should be reported separately. Patients already taking gastroprotective agents have a higher baseline risk,[38] and data from incident users can be used to extrapolate to nonusers. Results should also be reported separately for different classes of gastroprotective agents, and subtherapeutic doses should be excluded.

Difference in baseline risk between treated and untreated patients

Development and validation of a prediction model for GI events resulting from NSAID use remain a subject for future research. Until such a model is available, researchers can adjust for well-known risk factors and report the difference in risk between the treated and untreated groups. This difference could then be assessed as a source of heterogeneity in future meta-analyses. To establish the influence of age on the effectiveness and need for therapy, results should be reported at least per 5-year age group.

CONCLUSIONS

The observational evidence for the effectiveness of co-prescription of gastroprotective agents with NSAIDs to prevent GI events in elderly patients is in concordance with the evidence from randomized controlled trials in high-risk patients. All included studies show a substantial benefit to gastroprotection in preventing GI events associated with NSAID therapy in elderly patients. However, the evidence is insufficient to quantify this effect in a meta-analysis, and we cannot extrapolate to determine at what age NSAID treatment should be accompanied by gastroprotective agents and what the effect would be if a higher percentage of elderly patients received gastroprotection. The median rate of co-prescription for patients older than 65 years of age is 24% in the included studies, and the rate of co-prescription for very old patients is only slightly higher. We suggest that future observational studies report results to facilitate future meta-analysis, including a measure of the difference in baseline risk between the treated and untreated patients, and assess the adverse effects as well as the benefits of gastroprotection.

SUPPLEMENTARY APPENDIX. DETAILS OF SEARCH

Database: Embase 1980 to present, Ovid MEDLINE <1946 to week 1, March 2013>

1 antiarthritic.mp [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1109)
2 non steroidal anti inflam*.mp (24,343)
3 NSAID*.mp (41881)
4 (elder* or senior*).mp (441,880)
5 gastrointestinal.mp (601,703)
6 anti-inflammatory agents, non steroidal.mp (49,907)
7 1 or 2 or 3 or 6 (92,390)
8 renal.mp (1,016,005)
9 peptic ulcer.mp. or exp Peptic Ulcer/ (180,392)
10 gastric ulcer.mp. or exp Stomach Ulcer/ (60,339)
11 exp Duodenal Ulcer/ or Duodenal Ulcer.mp. (58,780)
12 5 or 9 or 10 or 11 (751,925)
13 4 and 7 and 12 (1308)
14 remove duplicates from 13 (875)
15 limit 14 to abstracts (830)
16 limit 15 to English language (687)
17 from 16 keep 1-567 (567)
18 from 17 keep 1-567 (567)
19 gastrointestinal protective.mp (48)
20 gastrointestinal preventive.mp (2)
21 gastroprotective.mp (3220)
22 Histamine 2 blocker.mp (26)
23 proton pump inhibitor*.mp (32,373)
24 h2 blocker*.mp (2905)
25 19 or 20 or 21 or 22 or 23 or 24 (37,616)
26 18 and 25 (141)
27 remove duplicates from 26 (141)
28 4 and 7 and 25 (312)
29 remove duplicates from 28 (222)
30 limit 29 to abstracts (218)
31 limit 30 to English language (172)
32 ("65 year" or "65 years").mp (100,057)
33 32 or 4 (517,027)
34 33 and 7 and 25 (411)
35 remove duplicates from 34 (284)
36 35 (284)
37 limit 35 to abstracts (280)
38 limit 37 to English language (222)

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FIGURES AND TABLES

Figure 1. Search flow diagram. GPA, gastroprotective agent.

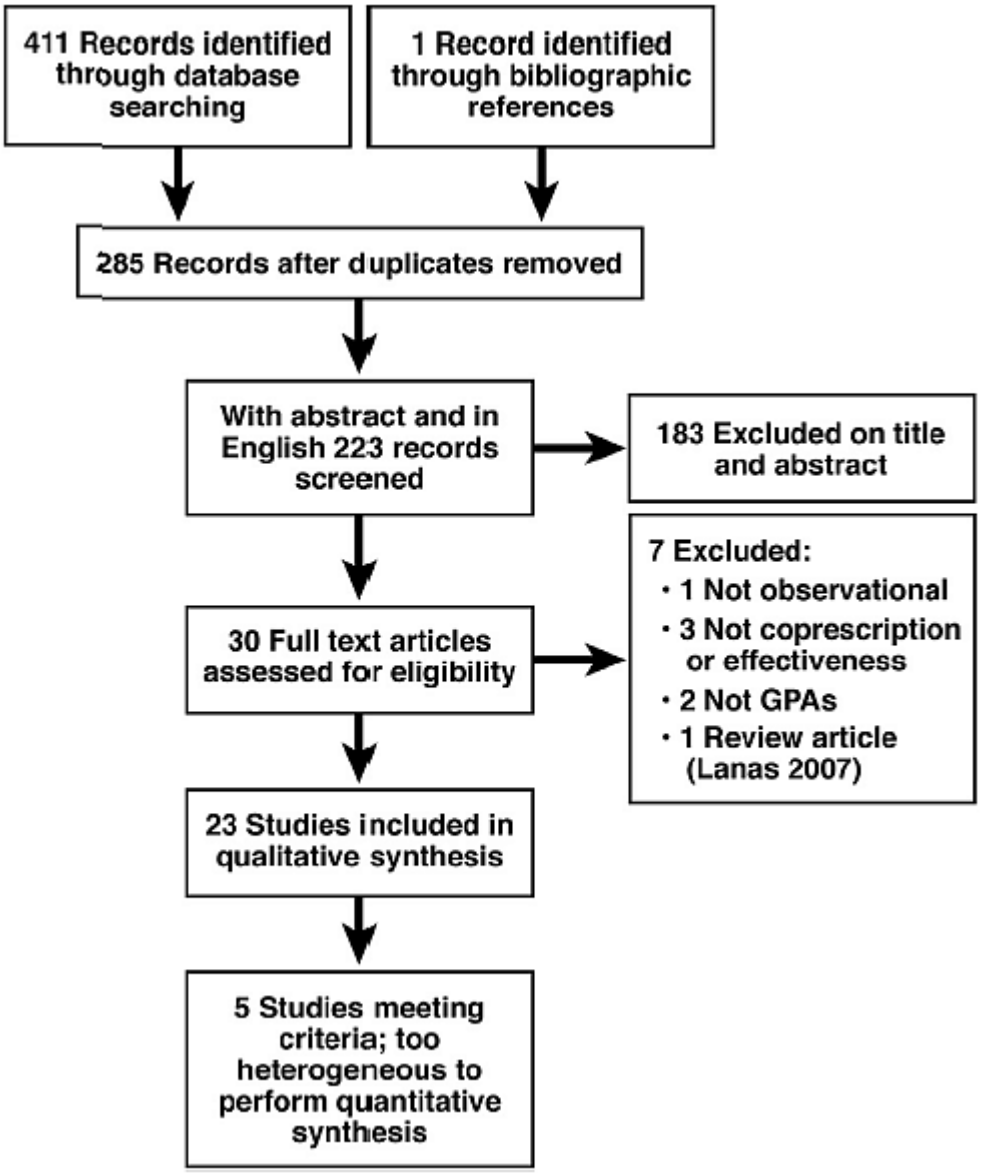

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Table 1. Summary of Included Studies

Study	Size (n)	Setting	Eligibility	Exposure (co-prescription)	Rate of co-prescription >65 y
Pilotto,[35] 2004	245	Italy (referral center); Jan 1998–Dec 2001	≥65 y; using low-dose aspirin; undergoing endoscopy	NSAID + gastroprotective agent at time of endoscopy	Low-dose aspirin + PPI: 20% (49/245)
van Leen,[36] 2007	432	Netherlands (national, participating GPs); Apr 2003–Mar 2005	≥65 y, general practice; consecutive patients prescribed NSAID	Taking NSAID and any gastroprotective agent; efficacy measured for pantoprazole	Any NSAID + any gastroprotective agent: 37.7% (163/432)
Rahme,[37] 2007	332,491	Quebec (regional); Apr 1999–Dec 2002	≥66 y, dispensed NSAID	Dispensed the same day or with duration that overlapped first day of NSAID (average overlap 98.5%)	NS-NSAID + PPI: 12.1% (19,975/164,934)
Rahme,[38] 2008	644,183	Quebec (regional); Jan 1998–Dec 2004	≥65 y, dispensed NSAID, excluding GI hospitalization in last year	Exposure overlapped by any number of days (exposure = days dispensed + 25%)	NS-NSAID + PPI: 10.2% (26,281/257,312)
Abraham,[39] 2008	481,980	Veterans' (VA) facilities, USA (national); Jan 2000–Dec 2002	65–99 y, dispensed new NSAID	Any overlap based on dispensed doses	NS-NSAID + PPI: 12.0% (53,031/440,547)
Clinard,[40] 2001	791	Cote d'Or France (regional, participating GPs); Apr–Jun 1999	≥18 y, general practice; prescribed new NSAID	As reported by the GP	Any NSAID + gastroprotective agent: 49.7% (79/159)
Rahme,[41] 2002	70,218	Quebec (regional); Apr–Nov 2000	≥65 y, dispensed NSAID; random sample of population	Filled on same date	NS-NSAID + gastroprotective agent: 10.2% (840/8235)
van Dijk,[44] 2002	17,060	Netherlands (regional); Jan 1998–Dec 1999	≥65 y, prescribed NSAID	Overlap of at least 1 day (average of 67% overlap); separate analysis using same physician, same day	Any NSAID + gastroprotective agent: 34.3% (2252/6557); any NSAID + PPI: 19.2% (1262/6557)
Pilotto,[45] 2003	3154	Italy (regional, participating GPs); Feb–Mar 1999	≥65 y, general practice; consecutive patients	Currently using NSAID and GI medication (not further specified)	Any NSAID + GI drug: 24.0% (187/779)
Hartnell,[42] 2004	14,587	Nova Scotia, Canada (regional); Jan 2001–Aug 2002	≥65 y, reimbursed NSAIDs	Filled on same date	NS-NSAID + gastroprotective agent: 14.0% (1528/10,940)
Abraham,[46] 2005	707,244, 303,787 high-risk, 264,679 ≥65 y	Veterans' (VA) facilities, USA (national); Jan 2002–Dec 2002	18–99 y; using NS-NSAID, aspirin, or COX-2	Overlap of gastroprotective agent with first NSAID prescription in study period (index prescription)	NS-NSAID + gastroprotective agent: 23.6% (45,540/192,743)
Johnell,[45] 2008	41,626	Sweden (national); Oct–Dec 2005	≥75 y	Implies overlap by dose	NS-NSAID + gastroprotective agent: 22.3% (9020/40,378)
Valkhoff,[46] 2010	50,126	Netherlands (national); Jan 1996–Dec 2006	≥50 y, general practice; prescribed new NSAID; no prior gastroprotective agents	Prescribed within 2 days	Any NSAID + gastroprotective agent + "high risk": 14.6% (3170/21,685)
Superceaneau,[47] 2010	105,690	Nova Scotia, Canada (regional); Apr 1998–Mar 2003	≥65 y; reimbursed new NSAID	Use of both meds in the same month; or gastroprotective agent prescribed in the same month as new NSAID prescription	NS-NSAID + gastroprotective agent: any month: 40.1% (16,240/40,511); first month: 21.2%
Thiéfin,[50] 2011	2576 (516 ≥65 y)	France (national, participating GPs); Jun–Aug 2006	≥18 y; general practice; consecutive patients prescribed NSAID	GP reported patient was taking both NSAID and gastroprotective agent	Any NSAID + gastroprotective agent: 55.4% (286/516)
Gulmez,[43] 2011	1851	France (national); Aug 2003–Jul 2004	≥65 y, reimbursed NSAID + osteoarthritis	NR	Any NSAID + PPI: 36.82% (679/1851)
Ljung,[51] 2011	1,529,267 (257,963 with NSAID)	Sweden (national); 2008	≥65 y; ≥1 NSAID reimbursement	Any time in same year	Any NSAID + gastroprotective agent: 30.0% (377,302/25,796); any NSAID + PPI: 18.5% (47,791/25,796)
Bell,[52] 2011	1004	Helsinki, Finland (regional, long-term care); September 2003	Residents of long-term care wards in Helsinki, Finland	Both medications regularly used	NS-NSAID + any gastroprotective agent: 19.9% (76/382); PPIs 18.3%; H2RAs: 1.6%
Morini,[53] 2011	869 (602 ≥65y)	Rome, Italy (58 participating primary care physicians); 1 week	Consecutive patients visiting primary care, taking NSAIDs >3 times/wk for >6 mo	NSAID + gastroprotective agent at time of the visit	Any NSAID + gastroprotective agent: 69.4% (418/602)
Abraham,[54] 2010	3566	VA facilities, USA (national); Jan 2000–Dec 2004	65–99 y, dispensed NSAIDs, had a GI event recorded in database	Any overlap based on dispensed doses	Any NSAID + GI event + PPI: 1491/3566
Vonkeman,[55] 2007	104 cases + 284 controls	Enschede, Netherlands (referral center); Nov 2001–Dec 2003	Hospitalized with serious ulcer + using NSAIDs	"Concomitant"	Any NSAID + gastroprotective agent, cases: 26/104; controls: 106/284
Vonkeman,[56] 2008	Same	Same	Same	Same	Same
Dries,[57] 2009	1491	VA hospitals, Houston, USA (referral center); Jan 2000–Dec 2002	≥65 y, dispensed NSAID + PPI	At least 5 days of overlap	10% of concomitant prescriptions had NSAID gastroprotection as indication

NOTE. Studies are referenced by the last name of the first author and the year of publication. Setting, size, eligibility criteria, reported definition, and rate of prescription of gastroprotective agents in patients taking NSAIDs (co-prescription) for patients ≥65 years. Additional study details can be found in Supplementary Table 3.
GP, general practitioner; NA, not applicable; NR, not reported.

Figure 2. Reported rates of co-prescription for patients 65 years and older. Each point represents the rate of coprescription reported for patients 65 and older in each study. The point is placed at the middle year of the study, with the line extending to show the years in which the study took place. Larger studies are represented with a larger point (smallest <1000 patients, largest >100,000 patients).

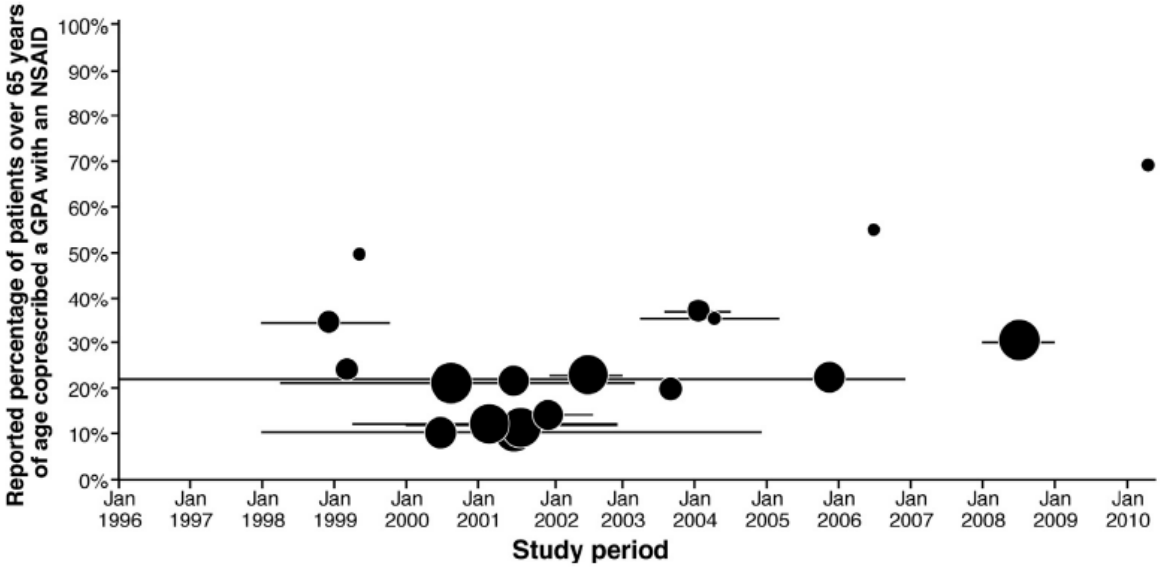

Table 2. Results From Efficacy Studies

Study	Outcome and follow-up	With PPI		Without PPI		Reported difference in risk	Covariates/confounders
		Events	Total	Events	Total		
van Leen,[36] 2007	GI complaints assessed by survey at 2 wk, 3 and 6 mo after visit Risk of bias: moderate (self-reported)	13[a]	163	107[a]	269	NR	Unadjusted
Rahme,[37] 2007	Unadjusted GI hospitalization rates, followed through last drug exposure day or end of study period Risk of bias: low	33	6430	301	46,192	Hazard ratio NS-NSAIDs vs NS-NSAIDs + PPI: 2.21 (1.56–3.24)	Celecoxib, sex, age, anticoagulants, corticosteroids, aspirin, anemia, GI hospitalization in previous 27 mo, outpatient diagnosis of ulcer, number of medications at index date; medication in prior year for diabetes, hypertension, and cardiovascular diseases; prescriptions in prior year for acetaminophen, NS-NSAIDs, and PPI (prior but not concurrent); diagnoses with cancer and cerebrovascular disease
Rahme,[38] 2008	Unadjusted GI hospitalization rates, followed through last drug exposure day or end of study period Risk of bias: low	39	19,839	403	91,379	Hazard ratio Referent NS-NSAID without PPI: All GI hospitalizations 0.65 (0.50–0.85) Upper GI hospitalizations 0.46 (0.33–0.65)	Sex, age, number of billings, alcohol, diagnosis of ulcers, visited a gastroenterologist, used PPIs in last year, used other gastroprotective agent, corticosteroids, osteoarthritis, use of aspirin, clopidogrel, or anticoagulants
Abraham,[39] 2008	UGIE by ICD code, median follow-up of 328 days for patients with event and 268 days for patients without event Risk of bias: low	406	53,031	1845	387,516	Hazard ratio No exposure as referent: NSAID alone: 1.8 (1.6–2.0) PPI alone: 3.1 (2.4–4.0) NSAID + PPI: 1.1 (0.7–4.6)	Demographics, UGIE risk factors, comorbidity, prescription channeling (ie, propensity score), geographic location, and multiple time-dependent pharmacologic covariates, including aspirin, steroids, anticoagulants, antiplatelets, statins, and selective serotonin reuptake inhibitors
Abraham,[4] 2010	UGIE by ICD code (cost-effectiveness) Risk of bias: low	NA	NA	NA	NA	OR PPI treatment: 0.7 (0.5–0.9)	Age, sex, race, Deyo comorbidity index, medications (coxib, anticoagulants, antiplatelets, statins, steroids), comorbidities (history of UGIE, gastroesophageal reflux disease)
Pilotto,[35] 2004 (low-dose aspirin)	Number of ulcers found in endoscopy patients Risk of bias: low	3	49	59	196	Absolute risk reduction with use of PPI: *Helicobacter pylori* positive −36.2 (−51.2 to −21.3), *H pylori* negative −12.6 (−23.9 to −1.2)	Unadjusted
Vonkeman,[55] 2007	Serious NSAID ulcer complications (case-control) Risk of bias: low	NA	NA	NA	NA	Adjusted OR With use of PPI: 0.33 (0.17–0.67)	Coumarin, heart failure, acetaminophen, low-molecular mass heparin ("final, parsimonious model")
Vonkeman,[56] 2008	Data from Vonkeman 2007 (cost-effectiveness)						

NOTE. Results from studies of efficacy of gastroprotection for NSAID-related GI events: outcome (type of GI event), follow-up period, and number of patients with and without GI events, with and without co-prescribed PPI. The difference in risk as reported by the authors is given, and if the risk was adjusted for covariates/confounding variables, those are also reported.
ICD, International Classification of Diseases; NA, not applicable; NR, not reported; UGIE, upper GI event.
[a]Numbers were estimated from information given in the study; precise numbers were not reported.

Figure 3. Unadjusted results from observational studies of efficacy of gastroprotective agents in elderly patients. A forest plot is shown for unadjusted results of the 5 studies reporting numbers of patients taking NSAIDs who had a GI event with and without PPIs (Mantel-Haenszel [M-H] OR, random effects model). The studies were highly heterogeneous (I2 = 97%), as indicated by minimal overlap of CIs in the graph; thus, the cumulative result is not considered reliable and is not shown. Number of events for van Leen et al36 were estimated from information given in the study.

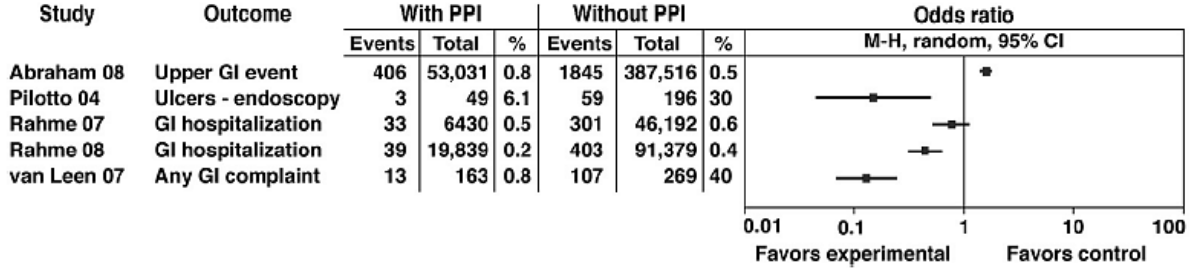

Table 3. NSAID and Gastroprotective Agent Use Separately and Concomitantly

Study	NSAID use (%)	Gastroprotective agent use (all elderly) (%)	Gastroprotective agent use in non-NSAID users (%)	Gastroprotective agent use in NSAID users (%)
van Dijk,[44] 2002	38.4	Gastroprotective agents 26.6 PPIs 14.8	Gastroprotective agents 21.8 PPIs 12.0	Gastroprotective agents 34.3 PPIs 19.2
Pilotto,[45] 2003	24.7	Gastroprotective agents 20.6 PPIs 3.1	NR	Gastroprotective agents 24.0
Johnell,[47] 2008	5.7	Gastroprotective agents 13.9	Gastroprotective agents 13.4	Gastroprotective agents 22.3
Valkhoff,[48] 2010	36.2	NR	Gastroprotective agents 10.4	Gastroprotective agents 14.6
Superceanu,[49] 2010	Average 9.9 (NS-NSAIDs average 6.3)	Gastroprotective agents average 18.1 (PPIs average 3.2)	NR	Gastroprotective agents 40.1
Ljung,[51] 2011	16.9	PPIs 19.3	NR	Gastroprotective agent 30.0 PPI 18.5
Bell,[52] 2011	25.1 (non-aspirin NS-NSAIDs 4)	24.0	Gastroprotective agents 21.6 (non-NSAID, non-SSRI users) PPIs 20.5	Gastroprotective agent 19.9 PPI 18.3

NOTE. In most studies, gastroprotective agent use in non-NSAID users is more than half that of NSAID users, implying that most NSAID users who do take gastroprotective agents do so for indications other than gastroprotection from NSAID-induced GI events. All rates are given as percentage of entire study population.
NR, not reported; SSRI, selective serotonin reuptake inhibitor.

Supplementary Table 1. Summary of Guideline Recommendations for Use of Gastroprotective Agents for Safer NSAID Prescribing in Older Adults

Guideline	Year	Recommendation
American College of Gastroenterology: Guidelines for prevention of NSAID-related ulcer complications	2009	Age >65 y = moderate risk Patients considered to be at moderate risk can be treated with COX-2 inhibitor alone or NSAID + misoprostol or PPI Two or more risk factors are in a high-risk category; these patients should also be treated with COX-2 inhibitor and either misoprostol or PPI therapy
RAND Corporation: Assessing Care of Vulnerable Elders – 3	2007	If age ≥75 and treated with NS-NSAID, then treat concomitantly with misoprostol or PPI If 2 or more risk factors and treated with daily aspirin, then treat concomitantly with misoprostol or PPI
National Institute for Health and Clinical Excellence (NICE): Osteoarthritis: The care and management of osteoarthritis in adults	2008	When offering treatment with oral NSAID/COX-2 inhibitor, the first choice should be either standard NSAID or COX-2 inhibitor co-prescribed with PPI
Institute for Clinical Systems Improvement: Assessment and Management of Chronic Pain	2011	All NSAIDs have GI risks of gastritis and possible bleeding. Risk benefits should be weighed, especially when treating elderly patients or those at higher risk for GI adverse effects. Consider using in combination with gastroprotective agent misoprostol or PPI
Kwaliteitsinstituut voor de Gezondheidszorg (CBO)	2003	If age ≥70 or age ≥60 with another risk factor, NS-NSAIDs should be prescribed with PPI or misoprostol or use COX-2 selective NSAID
American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons	2009	Demographers, insurers, and employers have defined older persons as age 65 and older. By age 75, many persons exhibit some frailty and chronic illness; focused its attention on this older frail population in preparing this update. NS-NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals. Older persons taking NS-NSAIDs should use PPI or misoprostol for GI protection. Patients taking COX-2 selective inhibitor with aspirin should use PPI or misoprostol for GI protection (high quality of evidence, strong recommendation)

NOTE. Most guidelines recommend use of a gastroprotective agent, most commonly misoprostol or PPI, for patients older than age of 75 who are using NS-NSAIDs. Some also recommend gastroprotection for younger patients (age 65 and older), especially those with at least 1 additional risk factor. Some also recommend gastroprotection for those taking COX-2 selective NSAIDs as well as NS-NSAIDs.

Supplementary Table 2. Details of Randomized Controlled Trials Included in Cochrane Review With a Population Aged 65 Years or Older

Study	Objective	Population	Eligibility criteria	Conclusion
Roth SH, Tindall EA, Jain AK, et al. A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. Arch Intern Med 1993;153:2565–2571	Compare nabumetone, ibuprofen, and ibuprofen + misoprostol on endoscopically diagnosed ulcers at 2, 6, and 12 weeks after start of study	148 patients aged 60 and older with osteoarthritis. Included patients of the following ages: nabumetone: 15 (60–64), 34 (65–74), 9 (≥75); ibuprofen: 17 (60–64), 32 (65–74), 4 (≥75); ibuprofen + misoprostol: 22 (60–64), 35 (65–74), 3 (≥75)	Osteoarthritis functional class 2 or 3, used NSAIDs for at least 3 mo before enrollment and expected to continue this medication for at least 3 mo. Excluded patients with history of allergy to study medications, intolerance of ibuprofen, heart disease, history of GI disease in last year, use of steroids, anticoagulants, immunosuppressives, or ulcer therapy; or patients prescribed multiple NSAIDs or joint replacement. Co-medication with acetaminophen was allowed	Nabumetone is equivalent to ibuprofen + misoprostol and significantly less ulcerogenic than ibuprofen alone
Chan FK, Sung JJ, Ching JY, et al. Randomized trial of low-dose misoprostol and naproxen vs nabumetone to prevent recurrent upper gastrointestinal haemorrhage in users of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2001;15:19–24	Compare nabumetone vs naproxen with low-dose misoprostol for secondary prevention of recurrent upper GI bleeding or major GI events in 24 weeks	90 patients presenting with upper GI bleeding and requiring NSAID therapy. Median age of misoprostol/naproxen group = 75 (range, 43–92); median age of nabumetone group = 74 (range, 42–89)	Presenting with bleeding peptic ulcers and had taken NSAIDs within 7 days; inadequate pain relief from simple analgesics; negative for *H pylori*; gave informed written consent. Excluded patients taking acid suppressive drugs, steroids, anticoagulants, aspirin; history of gastric surgery, concurrent upper GI diseases, history of treatment for *H pylori*; renal impairment, malignancy, or unable to return for follow-up	Misoprostol + naproxen is equivalent to nabumetone for secondary prevention of upper GI bleeding. Neither regimen is adequate in high-risk patients
Elliott SL, Yeomans ND, Buchanan RR, et al. Efficacy of 12 months' misoprostol as prophylaxis against NSAID-induced gastric ulcers: a placebo-controlled trial. Scand J Rheumatol 1994;23:171–176.	Determine long-term effect of misoprostol on development of gastric ulcers and erosions in NSAID users during a 12-month period	83 patients with chronic rheumatic disorders on NSAIDs for at least 3 mo. Mean age placebo group, 66 y (standard deviation ± 11.5); misoprostol group, 65 years (± 6.5)	Older than 18 years of age, on stable oral NSAID therapy, attending arthritis clinics for chronic rheumatic disorders. Excluded patients with overt upper GI hemorrhage within the last month, inflammatory bowel disease or chronic diarrhea, malignancy, or taking any other antiulcer drugs	Misoprostol decreases cumulative risk of NSAID-induced gastric ulcers

Supplementary Table 2. Continued

Study	Objective	Population	Eligibility criteria	Conclusion
Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241–249	Determine whether misoprostol decreases the incidence of serious upper GI complications in older patients with chronic rheumatoid arthritis taking NSAIDs by using clinical/symptomatic diagnosis	8843 patients 52 y of age and older with chronic rheumatoid arthritis and taking NSAIDs for at least 6 mo. Misoprostol: 6 (<52), 349 (52–59), 1192 (60–64), 1231 (65–69), 929 (70–74), 695 (≥75); placebo: 6 (<52), 347 (52–59), 1222 (60–64), 1254 (65–69), 884 (70–74), 724 (≥75)	At least 52 years of age, with chronic rheumatoid arthritis, taking 1 of 10 NSAIDs at predefined minimum dose for at least 6 months. Excluded if they had had active peptic ulcer disease, not taking or needing antiulcer medication, enrolled in other medication studies, history of various GI diseases, malignancy, alcoholism, hepatitis, bleeding disorders, poor prognosis, or intolerance to misoprostol. Patients taking multiple NSAIDs were included	Misoprostol significantly reduces incidence of NSAID-induced, serious upper GI complications, including perforation, obstruction, and bleeding, in older patients with rheumatoid arthritis
Chan FK, Hung LC, Suen BY, et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. Gastroenterology 2004;127:1038–1043	Compare celecoxib with diclofenac + omeprazole in patients with arthritis and prior ulcers for incidence of recurrent clinical GI complications or endoscopically diagnosed gastric or duodenal ulcer	287 patients with arthritis presenting with bleeding ulcer while receiving NSAIDs. Mean age celecoxib group, 65.3 years (standard deviation ± 14.6); diclofenac + omeprazole group, 68 years (± 12.8)	Confirmed healed ulcer, no *H pylori* or successful treatment for *H pylori*, anticipated regular use of NSAIDs. Excluded patients taking anticoagulants, corticosteroids; history of gastric or duodenal surgery except a patch repair; erosive esophagitis or gastric outlet obstruction; renal failure, terminal illness, or cancer	Neither therapy was adequate to prevent reoccurrence. Treatment-induced dyspepsia is an indication for further investigation
Lai KC, Lam SK, Chu KM, et al. Lansoprazole reduces ulcer relapse after eradication of *Helicobacter pylori* in nonsteroidal anti-inflammatory drug users: a randomized trial. Aliment Pharmacol Ther 2003;18:829–836	Effect of lansoprazole on reoccurrence of ulcers in patients using NSAIDs with history of peptic ulcers and *Helicobacter pylori* eradication	45 patients with recent history of endoscopically diagnosed gastroduodenal ulcers with *H pylori* infection and taking NSAIDs for at least 3 mo. Mean age lansoprazole, 67.1 y (range, 41–78); no treatment (*H pylori* eradication only), 70.2 y (43–78). Older than 65 y: lansoprazole, 13 (59.1%); control, 12 (57.1%)	Age 18–80 years with recent endoscopically diagnosed gastroduodenal ulcers with *H pylori* infection and taking NSAID (excluding aspirin) for at least 3 mo. Excluded patients with esophageal ulcers, pyloric obstruction, erosive esophagitis, previous treatment for *H pylori*; taking antibiotics, bismuth compounds, sucralfate, PPIs, anticoagulants, or corticosteroids; previous gastric resective surgery, allergy to the study drugs, or major organ failure	Lansoprazole was significantly better than *H pylori* eradication alone in preventing relapse of ulcerative disease

NOTE. Six of 39 studies included in the Cochrane review of the efficacy of gastroprotective agents in preventing NSAID-related ulcers included a population with an average age of 65 years or older. Further details of these studies, as well as details of other 33 studies including mean/median age of participants, can be found in the Cochrane review.

Supplementary Table 3. Details of Included Studies

Study	Setting	Objective	Eligibility	NSAID exposure	Gastroprotective agent exposure	Concomitant/ co-prescription	Sensitivity analysis	Outcomes measured/ conclusion
Co-prescription + efficacy								
Pilotto 2004	Italy; Jan 1998–Dec 2001	Evaluate relationship between use of low-dose aspirin, *Helicobacter pylori*, and use of PPIs in gastroduodenal lesions	≥65 y; users of chronic low-dose aspirin undergoing endoscopy (excluded those taking other NSAIDs)	Self-reported aspirin 75–300 mg/day for at least 3 mo before endoscopy (including OTC); prevalent use	Omeprazole 20 mg/day, lansoprazole 30 mg/day, or pantoprazole 40 mg/day for at least 7 days before endoscopy	Taking both medications at time of endoscopy	NR	Number of ulcers found in endoscopy patients/*H pylori* infection may influence cost-effectiveness of PPI therapy
van Leen 2007	Netherlands; Apr 2003–Mar 2005	Assess risk factors for upper GI events; assess guideline compliance; assess influence and safety of pantoprazole	≥65 y; consecutive patients visiting a general practitioner and prescribed NSAID	Self-reported NSAID, probably includes OTC; incident and prevalent use reported separately	Any gastroprotective agent at time of interview (probably incident and prevalent)	Already taking NSAID and gastroprotective agent (not further specified)	NR	Self-reported GI complaints; asked about adverse effects/pantoprazole was effective in diminishing GI complaints
Rahme 2007	Quebec; Apr 1999–Dec 2002	Compare GI hospitalization rates in patients taking coxibs and NS-NSAIDs with and without PPI	≥66 y; dispensed NSAID; population-based	At least 1 dispensed prescription of NS-NSAIDs or celecoxib >3 days (incident and prevalent); estimate that 46.3% of acetaminophen, 17% of NS-NSAIDs, 2.2% of aspirin are OTC	PPI dispensed same day as NSAID or earlier (incident and prevalent); estimate that 1.1% of gastroprotective agents are OTC	Dispensed same day or with duration that overlapped first day of NSAID (average overlap 98.5%)	Yes	Unadjusted GI hospitalization rates/ addition of PPI to celecoxib conferred extra protection for patients ages >75 y. PPI did not seem necessary with celecoxib for patients ages 66–74 y
Rahme 2008	Quebec; Jan 1998–Dec 2004	Compare GI hospitalization rates in patients taking NS-NSAIDs/ acetaminophen with and without PPI	≥65 y; dispensed NSAID, excluding GI hospitalization in last year; population-based	At least 1 dispensed prescription of NS-NSAIDs or acetaminophen (incident and prevalent); estimate that 46.3% of acetaminophen, 17% of NS-NSAIDs, 2.2% of aspirin are OTC	At least 1 dispensed prescription of PPIs (incident and prevalent); estimate that 1.1% of gastroprotective agents are OTC	Exposure overlapped by any number of days (exposure = days dispensed + 25%)	Previously published	Unadjusted GI hospitalization rates/ use of combination of traditional NSAID and acetaminophen may increase risk of GI bleeding compared with either agent alone

Supplementary Table 3. Continued

Study	Setting	Objective	Eligibility	NSAID exposure	Gastroprotective agent exposure	Concomitant/ co-prescription	Sensitivity analysis	Outcomes measured/ conclusion
Abraham 2008	Veterans' (VA) facilities, USA; Jan 2000–Dec 2002	Quantify the effect of provider adherence on the risk of NSAID-related upper GI events	65–99 y; dispensed new NSAID; population-based	Dispensed aspirin >325 mg/day, salsalate, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, rofecoxib, valdecoxib, or celecoxib (full doses); >5 days, incident users (none in last 6 mo). Cannot assess OTC	Dispensed esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole at therapeutic doses (incident and prevalent). Cannot assess OTC, only low-dose H2RA available	Any overlap based on dispensed doses	Yes	UGIE by ICD code/ adherence to safer NSAID prescribing strategies is associated with fewer UGIEs among elderly patients. An adherent strategy lowers, but does not eliminate, risk of NSAID-related UGIE
Co-prescription								
Clinard 2001	Cote d'Or France; Apr–Jun 1999	Assess determinants of prescribing gastroprotective agents	≥18 y; visiting GP and prescribed new NSAID	GP-reported new prescription of any NSAID (incident)	GP reported co-prescription of any gastroprotective agent (incident)	As reported by the GP	NA	Inadequate NSAID prescription practices remain relatively frequent with regard to elderly patients
Rahme 2002	Quebec; Apr–Nov 2000	Compare use of COX-2, NS-NSAIDs, and gastroprotective co-prescriptions	≥65 y; dispensed NSAID; random sample of population	At least 1 dispensed prescription of NS-NSAIDs, coxib, or acetaminophen, analyzed incident patients separately; estimate that 46.3% of acetaminophen, 17% of NS-NSAIDs, 2.2% of aspirin are OTC	NR; estimate that 1.1% of gastroprotective agents are OTC	Filled on same date	NR	Adjusted ORs showed 47% decrease in gastroprotective agent co-prescriptions with COX-2 inhibitors compared with NSAIDs
van Dijk 2002	Netherlands; Jan 1998–Dec 1999	Investigate whether co-prescribing recommendations are being followed	≥65 y; prescribed NSAID; population-based	ATC code M01A, excluding drugs prescribed to <50 people (incident and prevalent)	Misoprostol, H2RAs, PPIs (incident and prevalent)	Overlap of at least 1 day (average of 67% overlap), separate analysis with both drugs prescribed by same physician on same day	Performed 2 analyses using different definitions of co-prescription	Rate of concomitant prescribing of gastroprotective agents in NSAID users aged 65 y and older is low

Supplementary Table 3. Continued

Study	Setting	Objective	Eligibility	NSAID exposure	Gastroprotective agent exposure	Concomitant/ co-prescription	Sensitivity analysis	Outcomes measured/ conclusion
Pilotto 2003	Italy; Feb–Mar 1999	Identify prevalence of medication use and association between GI symptoms and therapies	≥65 y; visiting GP with medical problem	Self-reported use of ATC M01; differentiated occasional, acute (7–30 days), or chronic (>30 days) use; differentiated low-dose (<300 mg/day) and high-dose aspirin; (prevalent use); probably includes OTC	Self-reported use of antacids, H2 antagonists, PPIs, sucralfate, misoprostol, or prokinetics for preceding 7 days or more (prevalent use); probably includes OTC	NR	NR	Use of NSAIDs/aspirin was significantly associated with greater number of upper GI symptoms and prescriptions for GI drugs
Hartnell 2004	Nova Scotia, Canada; Jan 2001–Aug 2002	Assess use of gastroprotective agents	≥65 y; reimbursed NSAIDs; population-based	Dispensed NS-NSAID, COX-2, or aspirin >325 mg/day (incident and prevalent). Cannot assess OTC use	Misoprostol, PPIs (omeprazole, esomoprazole, pantoprazole, and lansoprazole), and H2RAs (ranitidine, famotidine, cimetidine, and nizatidine) (incident and prevalent). Cannot assess OTC use; ranitidine was available	Filled on same date	NR	Mention that side effects of misoprostol can lead to noncompliance
Abraham 2005	Veterans' (VA) facilities, USA; Jan 2002–Dec 2002	Ascertain adherence to evidence-based guidelines for the safe prescription of NSAIDs among patients at VA facilities	18–99 y; dispensed NSAID, salicylate >325 mg/day, or coxib; population-based	Dispensed NSAID, incident or prevalent (NSAIDs: choline magnesium trisalicylate, diclofenac, diclofenac potassium, diflusinal, etodolac, fenoprofen Ca, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, meclofenamate, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, salsalate, sulindac, tolmetin); coxibs (celecoxib, rofecoxib, valdecoxib); salicylates >325 mg	Dispensed gastroprotective agent (cimetidine, ranitidine, nizatidine, famotidine, omeprazole, rabeprazole, pantoprazole, esomeprazole, lansoprazole, or misoprostol) (probably incident and prevalent)	Gastroprotective agent dispensed during index NSAID prescription (first NSAID prescription recorded in study period)	NR	Adherence to guideline (co-prescription for patients >65 y, with history of upper GI events, use of anticoagulants or corticosteroids, or exceeding recommended NSAID dose). Adherence to evidence-based guidelines for safe prescription of NSAIDs among high-risk individuals is low, even in presence of multiple risk factors; and lower in long-term NSAIDs

Supplementary Table 3. Continued

Study	Setting	Objective	Eligibility	NSAID exposure	Gastroprotective agent exposure	Concomitant/ co-prescription	Sensitivity analysis	Outcomes measured/ conclusion
Johnell 2008	Sweden; Oct–Dec 2005	Assess rate of and factors affecting co-prescription	≥75 y; dispensed medications; population-based	Dispensed any M01A, excluding M01AX (incident and prevalent); cannot assess OTC use	Dispensed any PPI, misoprostol, or H2 antagonists (incident and prevalent); cannot assess OTC use, PPIs available	NR; implies overlap by dose	NR	Underutilization of gastroprotective agents was more common than overutilization
Valkhoff 2010	Netherlands; Jan 1996–Dec 2006	Examine time trends in preventative strategies	≥50 y; prescribed new NSAID in general practice; no prior gastroprotective agents	Newly prescribed NS-NSAIDs, coxibs, or high-dose aspirin (>325 mg/day) excluding topical, and no use within last 6 mo (incident use); cannot assess OTC use	Prescribed H2RA, PPI, or misoprostol (including misoprostol/ diclofenac combination) within 2 days of new NSAID prescription and no use within last 6 mo (incident use); cannot assess OTC use, H2 blockers available	Prescribed within 2 days	Shown to have positive predictive value of 85%–90%	Underutilization has decreased from 1996–2006, but 60% of at-risk NSAID users still do not receive gastroprotection
Superceneau 2010	Nova Scotia, Canada; Apr 1998–Mar 2003	Describe rate, timing, and duration of GI prophylaxis	≥65 y; reimbursed new NSAID; population-based	Reimbursed NSAIDs including celecoxib, rofecoxib, aspirin, diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid and tolmetin, no use in last year (incident use); cannot assess OTC use	Reimbursed H2RA, PPI, or misoprostol, no use in last 2 mo (incident use) and prevalent use analyzed separately; cannot assess OTC use	Use of both meds in the same month; or gastroprotective agent prescribed in same month as new NSAID prescription	2 analyses using different definitions of co-prescription	Rate of co-prescription was low; most seniors received regular-dose H2RAs despite evidence that this is not sufficient prophylaxis
Thiefin 2011	France; Jun–Aug 2006	Assess the prevalence of gastroprotective agent prescription in patients treated with NSAIDs in France and analyze the determinants of this prescription	≥18 y; prescribed NSAIDs	GP-reported prescription of NS-NSAIDs: propionic acid derivatives, phenylacetic acids, oxicams, other; COX-2: celecoxib	GP-reported prescription of PPI, H2RA, or misoprostol (probably incident and prevalent use)	Concomitant prescription of gastroprotective agent with NSAID	NR	Gastroprotection is still largely underprescribed. Only half of NSAID users >65 y are prescribed gastroprotective agents

Supplementary Table 3. Continued

Study	Setting	Objective	Eligibility	NSAID exposure	Gastroprotective agent exposure	Concomitant/ co-prescription	Sensitivity analysis	Outcomes measured/ conclusion
Gulmez 2011	France; Aug 2003–Jul 2004	Test adherence to Beer's criteria and French guidelines	≥65 y; reimbursed NSAID + osteoarthritis; population-based	Dispensed high-dose (anti-inflammatory) celecoxib, rofecoxib, or NSAIDs; divided into long-term (>6 mo supply dispensed) and short-term users, incident and prevalent	NR	NR	NR	Most common inappropriate use was 2 different NSAIDs in same month or NSAID + platelet aggregation inhibitor
Ljung 2011	Sweden; 2008	Estimate use of interacting drugs and gastroprotective agents	≥65 y; ≥1 NSAID reimbursement; population-based	Dispensed ATC class M01A, excluding glucosamine divided into <30 doses, 30–180 doses, and >180 doses (incident and prevalent use); cannot assess OTC use	Any dispensed H2RAs, misoprostol, or PPIs (incident and prevalent use); cannot assess OTC use, omeprazole available	Any time in same year	NR	Prescribers should be aware of interactions between NSAIDs and other medications. Increased use of gastroprotective medication may be justified
Bell 2011	Finland; September 2003	Estimate prevalence and predictors of SSRI/NSAID co-prescription and investigate use of gastroprotective agents	Residents of long-term care wards in Helsinki, Finland; complete medication data available	Regular use of oral diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, tolfenamic acid, and aspirin (including low-dose aspirin). Not coxibs. (prevalent use); OTC use NA	Regular use of PPIs and histamine H2RAs (prevalent use). There were no regular users of misoprostol; OTC use NA	Both medications regularly used	NR	Many subjects were exposed to medications that increase risk; only about one-fourth were prescribed a gastroprotective drug
Morini 2011	Rome, Italy; NR (2010)[a]	Assess the management of NSAID users in primary care, in relation to the appropriate use of gastroprotective therapies	Primary care patients already taking NSAIDs >3 times/wk for >6 mo	Practitioner-reported use of NSAIDs, COX-2s, or antiplatelet agents (aspirin, ticlopidine, or clopidogrel) (prevalent use)	Practitioner-reported use of PPI, H2RA, or misoprostol (probably incident and prevalent use)	Both medications reported by practitioner at time of assessment	NR	To ensure the correct prescription of gastroprotective therapy for NSAID users, tools to support practitioners further are required

Supplementary Table 3. Continued

Study	Setting	Objective	Eligibility	NSAID exposure	Gastroprotective agent exposure	Concomitant/ co-prescription	Sensitivity analysis	Outcomes measured/ conclusion
Efficacy								
Abraham 2010	VA facilities, USA; Jan 2000–Dec 2004	Effect of concomitant PPIs on hospitalization and resource use	65–99 years; dispensed NSAIDs; had GI event recorded in database	Dispensed aspirin, choline, or salicylate >325 mg/day; diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, rofecoxib, valdecoxib, or celecoxib (full dose); >5 days, incident users (none in last 6 mo). Cannot assess OTC use	Dispensed esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole (therapeutic doses, incident and prevalent). Cannot assess OTC use, only low-dose H2RAs available	Any overlap based on dispensed doses	Yes	UGIE by ICD code/if NSAID-UGIE occurs, the reduction in need for hospitalization results in a cost savings
Vonkeman 2007	Enschede, Netherlands; Nov 2001–Dec 2003	Determine risk factors for serious ulcers and compare effectiveness of different preventative strategies	Hospitalized with serious ulcer + using NSAIDs	Self-reported NSAIDs including COX-2s and aspirin >100 mg/day, at time of diagnosis; prevalent	Self-reported misoprostol, PPIs, or H2 blockers, at time of diagnosis; prevalent	"Concomitant"	NR	Hospitalized with serious ulcer/ concomitant PPIs (but not selective COX-2 inhibitors) were associated with reduced risk for NSAID ulcer complications
Vonkeman 2008	Same	Assess cost-effectiveness of concomitant PPIs with NSAIDs	Same	Same	Same	Same	Same	Concomitant use of PPIs for prevention of NSAID ulcer complications costs €4907 per NSAID ulcer complication prevented when using the least costly PPIs
Other								
Dries 2009	Houston, USA; Jan 2000–Dec 2002	Assess prescribing intent	≥65 y; dispensed NSAID + PPI	Prescribed NS-NSAID, COX-2 (incident and prevalent); does not address OTC use	Prescribed PPI (incident and prevalent); OTC PPIs not available during study period	At least 5 days of overlap	NR	Gastroprotection was poorly recognized as an indication for PPI prescription, except by rheumatologists and in highly comorbid patients

NOTE. Studies are referenced by their first author and year of publication.

ATC, Anatomical Therapeutic Chemical Classification System; GP, general practitioner; ICD, International Classification of Diseases; NA, not applicable; NR, not reported; OTC, over-the-counter; UGIE, upper GI event.

[a]Date was determined through communication with Dr Morini.