

Revised PINCER Query Library 2015 Evidence-Based Summaries



Contents

Introduction	3
Aim of the PINCER Query Library/Reports	5
Additional information (<i>added July 2018</i>): Considering the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.....	6
Query A: In a patient aged ≥ 65 years prescription of an oral NSAID without co-prescription of an ulcer-healing drug.....	9
Query B: Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration.....	18
Query C: Prescription of an antiplatelet drug to a patient with previous peptic ulcer or GI bleed without co-prescription of an ulcer-healing drug.....	24
Query D: Prescription of warfarin or NOAC in combination with an oral NSAID	28
Query E: Prescription of warfarin or a New Oral Anti-Coagulant (NOAC) and an antiplatelet in combination without co-prescription of an ulcer-healing drug .	31
Query F: Prescription of aspirin in combination with another antiplatelet drug without co-prescription of an ulcer-healing drug.....	34
Query G: Prescription of a non-selective beta-blocker to a patient with asthma	38
Query H: Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid.....	42
Query I: Prescription of an oral NSAID to a patient with heart failure	45
Query J: Prescription of antipsychotics for >6 weeks in a patient aged ≥ 65 years with dementia but not psychosis	48
Query K: Prescription of an oral NSAID to a patient with chronic renal failure with an eGFR <45	51

Introduction

Medication errors, particularly those relating to prescribing or insufficient medication monitoring, are often associated with considerable risk of patient harm, including hospital admissions.¹ The highest rates of medication errors tend to be found in patients taking multiple medications and also in relation to certain drugs that are frequently associated with preventable morbidity e.g. anticoagulants, NSAIDs and diuretics.²⁻⁷

Researchers at the University of Nottingham conducted a large study of over 4000 patients admitted to a local hospital and found that 6.5% of these admissions were related to medication problems, and two-thirds of these were judged to be preventable.⁸ These findings echoed those of other national and international studies,¹ and so the research team set about finding ways of identifying patients at risk before they came to harm. They achieved this by developing a set of computerised queries which could be run on GP clinical systems to identify at-risk patients who were being prescribed drugs that are commonly and consistently associated with medication errors. These included the prescription of nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and β blockers, and the monitoring of angiotensin-converting-enzyme (ACE) inhibitor or loop diuretics, methotrexate, lithium, warfarin, and amiodarone. These drugs were chosen on the basis of medicines management difficulties that are important in overall burden and severity of iatrogenic harm in primary care.^{1, 8-9}

The computerised queries developed by the research team were used to identify at-risk patients in the PINCER trial, a robust cluster randomised controlled trial to test whether a large complex pharmacist-led IT-based intervention compared with simple feedback could reduce medication error rates within the primary care setting. In this study, 72 GP practices were randomised to receive either the PINCER intervention or simple feedback.

Those allocated to receive simple feedback were provided with computerised feedback on patients identified to be at risk from medication errors along with brief written information on the importance of each type of error. GP practices allocated to the PINCER intervention were also provided with computerised feedback on patients identified to be at risk from medication errors. In addition, they met with a pharmacist to discuss the problems identified from the computerised feedback and to agree on an action plan. The pharmacist then spent up to three days per week for the next 12 weeks working in the practice to resolve the problems identified and improve medicine management systems to avoid future errors using the principles of educational outreach and root cause analysis to bring about change. The types of activities undertaken by the pharmacists included inviting patients into the surgery for a prescription review or blood test with the aim of correcting the errors that had been identified.

The results of the trial, published in the *Lancet* in February 2012,¹⁰ showed that the PINCER intervention is an effective method for reducing a range of clinically important and commonly made medication errors in primary care.

At six months' follow-up, the general practices receiving computerised feedback and pharmacist support had significantly fewer prescribing errors than the general practices that received computerised feedback alone.

For this reason, there is much interest in rolling out the approach taken in the PINCER Trial to general practices in the UK. Not only might this approach help prevent unnecessary harm to patients, but it may also reduce the costs associated with dealing with prescribing errors, which sometimes require hospital admission. On the basis of the original research findings, and a scaling up grant award from the Health Foundation, the PINCER intervention is now being rolled out across the East Midlands, using a revised set of prescribing safety indicators (queries). This project is additionally supported by the East Midlands Academic Health Science Network, and lead by Lincolnshire Community Health Services.

The revised PINCER Query Library consists of eleven queries. This document will examine each query in turn based upon supporting research evidence.

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Aim of the PINCER Query Library/Reports

The aim of the PINCER Query Library is to identify at-risk patients in general practices who are being prescribed drugs that are commonly and consistently associated with medication errors so that corrective action can be taken to reduce the risk of occurrence of these errors. Further details of the revised PINCER Query Library are provided in Box 1.

Box 1: Revised PINCER Query Library 2015

OUTCOME: GI BLEED
Query A: In a patient aged ≥ 65 years prescription of an oral NSAID without co-prescription of an ulcer-healing drug
Query B: Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration
Query C: Prescription of an antiplatelet drug to a patient with previous peptic ulcer or GI bleed without co-prescription of an ulcer-healing drug
Query D: Prescription of warfarin or NOAC in combination with an oral NSAID
Query E: Prescription of warfarin or a New Oral Anti-Coagulant (NOAC) and an antiplatelet in combination without co-prescription of an ulcer-healing drug
Query F: Prescription of aspirin in combination with another antiplatelet drug without co-prescription of an ulcer-healing drug
OUTCOME: EXACERBATION OF ASTHMA
Query G: Prescription of a non-selective beta-blocker to a patient with asthma
Query H: Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid
OUTCOME: HEART FAILURE
Query I: Prescription of an oral NSAID to a patient with heart failure
OUTCOME: STROKE
Query J: Prescription of antipsychotics for >6 weeks in a patient aged ≥ 65 years with dementia but not psychosis
OUTCOME: KIDNEY INJURY
Query K: Prescription of an oral NSAID to a patient with chronic renal failure with an eGFR < 45

For each of the queries in the revised PINCER Query Library, the supporting evidence base has been provided based upon rapid electronic searches of the literature and respected reference sources such as the British National Formulary, Martindale and Stockley's Interactions. The queries have also been shown to the team responsible for developing the content of the British National Formulary and they have provided additional background evidence.

Additional information (added July 2018): Considering the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.

Background

The PINCER gastroprotection indicators highlight patients at a significantly high risk of gastric bleed with the aim of reducing that risk by either:

- Stopping the prescribing that is causing the high risk whenever possible.
- If this is not possible, prescribing appropriate effective gastroprotection to reduce the risk.

The PINCER indicator summaries do not dictate the medication that should be used in gastroprotection as this should be decided on an individual basis. However, the general rules of prescribing gastroprotection are still advised:

- Use the lowest effective dose
- Prescribe for the shortest time possible
- Keep prescribing under review

Evidence that long-term PPIs can be harmful

The prescribing of proton-pump inhibitors occurs frequently in primary care. Concerns have been raised regarding the possible harms from long-term PPI prescribing.

Clinical Knowledge Summaries¹ state the following long-term effects from PPIs:

- Hypomagnesaemia — symptoms include muscle twitching, tremors, vomiting, fatigue, and loss of appetite. Case reports after one year of PPI therapy, but may occur after three months. This usually improves after magnesium replacement therapy and discontinuation of the PPI
- Increased risk of fractures — especially when used at high doses for over a year in the elderly
- *Clostridium difficile* infection — due to the effect of decreasing gastric acidity.
- Rebound acid hypersecretion syndrome — may occur after stopping long-term PPI therapy, although this may be more a theoretical risk than clinical phenomenon.

However, in the literature more links have been suggested².

Gastric acid suppression is a risk factor for *Clostridium difficile* infection (CDI) and there is an emerging link between *Clostridium difficile* and PPI use. This link is not firmly established, and it remains possible that these associations are confounded by other CDI risk factors. However, PPI prescribing should be reviewed if patients have CDI or have a high risk of CDI³.

There are a number of references that provide useful summaries regarding long-term PPI treatment^{4,5,6}. With regards to CDI, the DTB bulletin⁶ summarises that there have been a number of meta-analyses of observational studies that have attempted to review the risk of CDI in PPI users. The authors of the largest meta-analysis⁷ undertook a 'speculative' assessment that estimated the number-needed-to-harm (NNH) with PPI use for the overall population was around 4,000 at one year.

However, for hospitalised patients receiving antibiotics, the NNH was 50 after two weeks of admission. The authors concluded that PPIs do not pose a risk to the general population but accepted that those at high risk of CDI should be carefully managed.

For patients who have been treated for CDI the risk of recurrence is estimated to be 20%⁶. However, in PPI users this is suggested to increase by 40⁸ to 50⁹ percent.

Should H₂ receptor antagonists be used instead of proton pump inhibitors?

The British National Formulary¹⁰ provides an unlicensed dose of ranitidine of 300mg twice daily for gastro-protection from NSAID induced duodenal or gastric ulcer. This is a high dose treatment regimen for ranitidine. There are very few studies relating to the effects of long term high dose H₂ receptor antagonists, so it is not possible to judge whether the emerging risks being noted with PPIs will also occur with H₂ receptor antagonists.

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OUTCOME: GI BLEED

Query A: In a patient aged ≥ 65 years prescription of an oral NSAID without co-prescription of an ulcer-healing drug

What is the risk to patients?

The BNF advises that all NSAIDs are associated with serious gastrointestinal toxicity and that the risk is higher in the elderly. Selective inhibitors of cyclo-oxygenase-2 are associated with a lower risk of serious upper gastrointestinal side-effects than non-selective NSAIDs.¹ Gastrointestinal effects are the most common side effects of NSAIDs and include dyspepsia, ulcer, obstruction and bleeding.

Many patients who are over 65 years will also have additional risk factors that will further increase the risk of gastrointestinal toxicity and the overall risk should be considered when prescribing an NSAID.

What evidence is there that this pattern of prescribing is harmful?

A Cochrane intervention review noted that with NSAIDs, “Common side effects such as nausea and dyspepsia correlate poorly with serious adverse GI events. While endoscopic ulcers can be documented in up to 40% of chronic NSAID users, it is estimated that as many as 85% of these never become clinically apparent. Serious NSAID induced GI complications such as haemorrhage, perforation or death is much less common, occurring collectively with an incidence of about 1.5% per year. However, the number of individuals prescribed NSAIDs and the potential for life-threatening adverse events make NSAID toxicity an important clinical and economic problem”.²

An American consensus document states “upper gastrointestinal events (UGIE), symptomatic or complicated ulcers, occur in 1 of every 20 NSAID users and in 1 of 7 older adults using NSAIDs, accounting for 30% of UGIE-related hospitalizations and deaths”.³

According to a study from the US involving patients aged 65 years or older, there is a fourfold increased risk of developing peptic ulcer disease (relative risk 4.1; 95% CI, 3.5 to 4.7) in those taking NSAIDs compared with non-users.⁴ The risk is even higher in the first month of use (relative risk, 7.2; CI, 4.9 to 10.5).

In this study, the excess risk of hospitalisations for ulcer disease was 17.4 per 1000 person-years of exposure.

Clinical Knowledge Summaries from NICE provides the guidance that patients should be considered to be at high risk of a serious NSAID- induced gastrointestinal adverse events if they have one or more of the following risk factors:⁵

- Using the maximum recommended dose of an NSAID.
- Aged 65 years or older.
- History of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation.

- Concomitant use of medications that are known to increase the likelihood of upper GI adverse events (e.g. anticoagulants, aspirin [even low-dose], corticosteroids, and antidepressants (selective serotonin reuptake inhibitors, venlafaxine, or duloxetine).
- Serious comorbidity, such as cardiovascular disease, hepatic or renal impairment (including dehydration), diabetes, or hypertension.
- Requirement for prolonged NSAID use, including people with:
 - Osteoarthritis or rheumatoid arthritis of any age.
 - Chronic low back pain and are 45 years of age or older.

Additional risk factors for NSAID-induced GI adverse events include:

- The type of NSAID used. The Commission on Human Medicines (CHM; formerly Committee on Safety of Medicines) has created three categories of NSAID risk:
 - Lowest risk: ibuprofen (but serious and fatal GI adverse effects have still been reported).
 - Intermediate risk: diclofenac, naproxen, ketoprofen, piroxicam, and indometacin.
 - Highest risk: azapropazone (no longer available in the UK).
- The presence of *Helicobacter pylori* infection.
- Excessive alcohol use.
- Heavy smoking.

The Committee on Safety of Medicines (now the Commission on Human Medicines) has reviewed the relative gastrointestinal risks of NSAIDs on several occasions.

“Recently, we have highlighted the high gastrointestinal risks with piroxicam, ketoprofen, and ketorolac. Of the traditional NSAIDs, low-dose ibuprofen offers the lowest risk. Coxibs are associated with reduced gastrointestinal risk relative to most NSAIDs at equivalent doses. However, coxibs (like NSAIDs) may vary in their effects, and evidence for a reduction in the most clinically important gastrointestinal risks for etoricoxib is weak. Proton pump inhibitors reduce the gastrointestinal risks associated with NSAIDs, and may reduce the risks to a similar level as use of a coxib alone.”⁶

An American study looked at the occurrence of upper gastrointestinal events (UGIE) in veterans aged 65 years or older prescribed a Cox-2 inhibitor or a NSAID and whether the risk of a UGIE was lowered by the co-prescription of a PPI. The study included 481,980 patients, a PPI was co-prescribed in 19.8%. There were 2,753 UGIEs in 220,662 person-years of follow-up. The results showed a risk of UGIE was 1.8 with an NSAID or COX-2 inhibitor and the risk of UGIE was reduced to 1.1 on when a PPI was co-prescribed with a Cox-2 inhibitor or NSAID.⁷

Cox-2 inhibitors are associated with a lower risk of serious upper GI side effects than non-selective NSAIDs. A cohort study of patients with the first hospitalization for peptic ulcer perforation in Denmark found poorer morbidity and mortality among non-selective NSAID users compared to those using selective NSAIDs prior to index admission. "Of the 2,061 patients hospitalized with peptic ulcer perforation, 38% were current NSAID users. The 30-day mortality was 25% overall, and 35% among current NSAID users.

Compared with never-use, the adjusted 30-day mortality rate ratios (MRRs) were 1.8 (95% CI 1.4-2.3) for current use of NSAIDs alone and 1.6 (95% CI 1.2-2.2) for current use combined with other ulcer-associated drugs. The mortality increase associated with the use of COX-2 inhibitors was similar to that of traditional NSAIDs: adjusted MRR for users of COX-2 inhibitors alone and in combination, 2.0 (1.3-3.1) and 1.4 (0.8-2.5), and for users of traditional NSAIDs alone or in combination, 1.7 (1.3-2.3) and 1.6 (1.2-2.3)."⁸

According to a recent study using the CPRD database the prevalence of patients aged ≥ 65 years prescribed an NSAID without co-prescription of an ulcer-healing drug in a three month period in UK general practice is 3.44%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

NICE advises that when an NSAID or Cox-2 inhibitor is prescribed to manage pain from osteoarthritis, a proton pump inhibitor should be co-prescribed. The guideline notes that the risk of gastrointestinal problems from NSAIDs can be reduced by the use of PPIs and that it was "always more cost-effective to prescribe a PPI than to not do so".⁹

Proton-pump inhibitors (PPIs) are generally considered to be the preferred choice for gastroprotection; they are effective and well tolerated. PPIs reduce the risk of endoscopic gastric ulcers by 63% and the risk of duodenal ulcers by 81%.¹⁰

The PLUTO and VENUS studies showed that in patients taking NSAIDs there were more serious gastrointestinal adverse events in participants on placebo (12/452, 2.7%) than in participants receiving esomeprazole (9/926, 1.0%) across the two studies.⁹

Misoprostol at low dose is less effective than proton PPIs at reducing the incidence of endoscopically detected lesions, and has greater adverse effects.¹⁰ Misoprostol reduces the risk of endoscopic gastric ulcers by 75% and the risk of duodenal ulcers by 78% in people taking an NSAID.^{9,12}

The BNF advises that to reduce the risk of peptic ulceration with non-selective NSAIDs a proton pump inhibitor can be considered. If alternatives are required, H₂-receptor antagonists at twice the usual dose e.g. ranitidine, or misoprostol can be used. If there is a history of upper gastrointestinal bleeding or if the patient has three or more risk factors then the use of a Cox-2 inhibitor with a proton pump inhibitor could be considered.¹

The CONDOR trial compared celecoxib to diclofenac plus lansoprazole in patients with osteoarthritis or rheumatoid arthritis and found that the risk of clinical outcomes throughout the gastrointestinal tract was lower in patients treated with a Cox-2 inhibitor than in those receiving a non-selective NSAID plus a PPI.¹³

An evidence based review looked at the role of proton pump inhibitors in the primary prevention of NSAID/aspirin-induced, endoscopically detected gastroduodenal ulceration and found that PPI's are effective in reducing the occurrence of these lesions. (A summary of the studies reviewed can be found in Appendix 1).

See pages 6 and 7 for further information about the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.

Are there any situations where this pattern of prescribing may be considered appropriate?

NSAIDs continue to have a place in therapy in patients aged 65 years and older but there is a risk of gastrointestinal adverse events and this risk increases with further risk factors. Evidence suggests that the co-prescription of gastroprotection should always be considered in this group of patients. However, if a patient had no other risk factors than age and the GI risk was limited further by prescribing a low dose of a low GI risk agent for as short period time as possible, the absence of gastroprotection might be acceptable.

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Appendix 1

Primary Prevention of NSAID or Aspirin Use-Related Gastroduodenal Damage With PPIs (Endoscopic and Clinical Outcomes)¹²

First author (y) ^{ref}	Study type	Study population	Study groups	Duration	Primary end point	Results
Yeomans [ASTERIX study], (2008)	Randomized, double-blind, placebo-controlled	High-risk (age >60 y), ulcer-free patients requiring daily LDA	Esomeprazole 20 mg daily (n = 493) vs. placebo (n = 498)	26 weeks	Ulcer development	5.4% on placebo vs. 1.6% on esomeprazole; 6.2% vs. 1.8% ($P < .001$) by life-table estimates at 6 months
Scheiman [VENUS study], (2006)	Randomized, double-blind, placebo-controlled (United States)	High-risk ulcer-free patients requiring NSAIDs or COX-2 inhibitors	NSAID/COX-2 vs. NSAID/COX-2 + esomeprazole 20 mg (n = 281) or 40 mg (n = 282) daily or placebo (n = 281)	6 months	Ulcer development	Ulcer development: 20.4% on placebo, 5.3% on esomeprazole 20 mg ($P < .001$) and 4.7% on esomeprazole 40 mg ($P < .001$)
Scheiman [PLUTO study] (2006)	Randomized, double-blind, placebo-controlled (international)	High-risk ulcer-free patients requiring NSAIDs or COX-2 inhibitors	NSAID/COX-2 vs. NSAID/COX-2 + esomeprazole 20 mg (n = 195) or 40 mg (n = 198) daily or placebo (n = 192)	6 months	Ulcer development	Ulcer development: 12.3% on placebo, 5.2% on esomeprazole 20 mg ($P = .018$) and 4.4% on esomeprazole 40 mg ($P = .007$)
Scheiman [pooled analysis for COX-2 from VENUS and PLUTO studies] (2006)	Randomized, double-blind, placebo-controlled	High-risk ulcer-free patients requiring COX-2 inhibitors	COX-2 vs. COX-2 + esomeprazole 20 mg or 40 mg daily or placebo (total n = 400)	6 months	Ulcer development	Ulcer development: 16.5% on placebo, 0.9% on esomeprazole 20 mg ($P < .001$) and 4.1% on esomeprazole 40 mg ($P = .002$)
Regula (2006)	Randomized, double-blind, parallel-group	Rheumatic disease; high-risk;	Pantoprazole 20 mg once daily (n = 196) vs. pantoprazole	6 months	Endoscopic findings, severe GI	Remission: 90% vs 93% vs 89% (all $P = NS$)

Revised Pincer Query Library

	comparison study	continuous NSAIDs	40 mg once daily (n = 199) vs omeprazole 20 mg once daily (n = 200)		symptoms, AEs	
Stupnicki (2003)	Randomized, double-blind, multicenter, parallel-group comparison study	High-risk arthritis (>55 y age); continuous NSAID treatment	Pantoprazole 20 mg once daily (n = 257) vs misoprostol 200 µg twice a day (n = 258)	6 months	Endoscopic findings, severe GI symptoms, AEs	Remission: pantoprazole 89% vs misoprostol 70% (<i>P</i> < .001)
Pilotto (2000)	Randomized, parallel-group comparison study	Symptoms and/or a history of ulcer; elderly (>60 y); continuous NSAID treatment	Pantoprazole 40 mg daily (n = 34) vs PPI-based triple drug therapy (n = 35)	1 month	Endoscopically determined severe gastroduodenal damage	Remission: 91% vs 71% (<i>P</i> < .05)
Bianchi Porro (2000)	Randomized double blind placebo-controlled	Outpatients with RA or OA on NSAIDs (diclofenac, ketoprofen, or indomethacin) for at least 8 weeks with grade 0–2 endoscopic gastroduodenal lesions	Pantoprazole 40 mg daily (n = 70) vs placebo (n = 34)	12 weeks	Endoscopic ulcer; AE	Free of endoscopic ulcer: pantoprazole: 72% vs placebo: 59% (82% vs 55%, <i>P</i> = .036 when only considering patients with normal baseline mucosa)
Cullen [OPPULEN T study] (1998)	Randomized double-blind, placebo-controlled, parallel-group study	Continuous NSAID (any) use; not having more than mild dyspepsia	Omeprazole 20 mg daily (n = 83) vs placebo (n = 85)	6 months	Endoscopic ulcers/erosion or moderate–severe dyspeptic symptoms	Probability of remaining free of the endpoints: 0.78 for omeprazole vs 0.53 for placebo, <i>P</i> = .004
Bianchi Porro (1998)	Randomized, double-blind, placebo-controlled	Arthritis; requiring indomethacin, diclofenac, or ketoprofen	Omeprazole 20 mg once daily (n = 50) vs placebo (n = 53)	3 weeks	Endoscopic findings	Gastric ulcer-free: 100% in omeprazole groups vs 88% in placebo group (<i>P</i> < .01); no difference in duodenal ulcer rate or dyspepsia rate

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Ekstrom (1996)	Randomized, placebo-controlled	History of dyspepsia or uncomplicated peptic ulcer; continuous NSAID treatment	Omeprazole 20 mg daily (n = 85) vs placebo (n = 90)	3 months	Endoscopic ulcers	4.7% for omeprazole vs 16.7% for placebo
Pilotto (2004)	Cohort study	Elderly; on aspirin (low dose/regular dose) or NSAID (nimesulide, ketorolac, piroxicam, diclofenac, ketoprofen) acutely (7–30 days, 47.3%) or chronically (>30 days, 52.7%)	PPI (omeprazole 20 mg or lansoprazole 30 mg or pantoprazole 40 mg or esomeprazole 40 mg) taken for at least 7 days before EGD	At least 7 days	Endoscopic ulcer	Acute group: OR, 0.70 (95% CI, 0.24–2.04), ARR, 36.6%; chronic group: OR, 0.32 (95% CI, 0.15–0.67), ARR, 34.6%
Vonkeman (2007)	Nested case-control study	Chronic NSAID users	For cases, n = 104 and for controls, n = 284	26 months	NSAID-related complications requiring hospitalization	Concomitant PPI therapy associated with reduced risk for NSAID-related complications (adjusted OR, 0.33 (95% CI, 0.17–0.67), <i>P</i> = .002)
Lanas (2007)	Case-control study	Upper GI bleeding (confirmed by endoscopy) compared with controls	Adjusted RR of PUB in patients taking PPI (cases = 239, controls = 732)	n/a	PUB	For NSAID-related PUB: adjusted RR, 0.33 (95% CI, 0.27–0.39) and for aspirin users (all doses): adjusted RR, 0.30 (95% CI, 0.20–0.44)
Spiegel (2006)	Meta-analysis	Chronic arthritis patients	NSAID vs NSAID + PPI and COX-2 vs NSAID	n/a	Dyspepsia (epigastric pain, dyspepsia, nausea)	ARR, 9%; RRR, 66% with NSAID + PPI vs NSAIDs; ARR, 3.7%; RRR, 12% with coxibs vs NSAIDs. Conclusion: NSAID + PPI better for dyspepsia reduction

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Rostom (2002)	Meta-analysis	Adults taking NSAIDs for more than 3 weeks	PPI use vs placebo	Variable	Endoscopic ulcer detection	For duodenal ulcer: PPI vs placebo: RR, 0.19 (95% CI, 0.09–0.37), $P < .001$; for gastric ulcer: PPI vs placebo: RR, 0.40 (95% CI, 0.32–0.51), $P < .001$)
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AEs, adverse events; RA, rheumatoid arthritis; OA, osteoarthritis; EGD, esophagogastroduodenoscopy; ARR, absolute risk reduction.

(Taken from : Arora, G, Singh G, Triadafilopoulos, G. Proton Pump Inhibitors for Gastroduodenal Damage Related to Nonsteroidal Anti-inflammatory Drugs or Aspirin: Twelve Important Questions for Clinical Practice *Clinical Gastroenterology and Hepatology* 7; 2009; 725 - 735.e4)

Query B: Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration

What is the risk to patients?

All NSAIDs are associated with serious gastro intestinal toxicity. Active gastrointestinal ulceration or bleeding is a contra-indication to all NSAIDs (including Cox-2 inhibitors). There is then variation between the different medicines with piroxicam, ketoprofen, and ketorolac being contra-indicated if there has been any history of gastrointestinal bleeding, ulceration, or perforation. The BNF recommends that “other non-selective NSAIDs are contra-indicated in patients with a history of recurrent gastrointestinal ulceration or haemorrhage (two or more distinct episodes), and in patients with a history of gastrointestinal bleeding or perforation related to previous NSAID therapy”.¹

A history of previous peptic ulcer is thought to be one of the biggest risk factors for increasing the risk, by three to 13 times, of further peptic ulceration or bleeding in patients receiving a non-selective NSAID². Serious gastrointestinal events can be potentially life-threatening and frequently present with little warning.³

What evidence is there that this pattern of prescribing is harmful?

Gastrointestinal toxicity is a common side effect of long term use of NSAIDs. Risk factors for gastrointestinal toxicity whilst additive are not quantitatively similar. Previous peptic ulceration is one of the biggest risk factors with a higher relative risk than concurrent anticoagulant use, age, or high dose NSAID use.³

The Committee on Safety of Medicines provides advice on the gastrointestinal risk has of the different NSAIDs. They highlight piroxicam, ketoprofen, and ketorolac as being very high risk and that for the traditional NSAIDs, low-dose ibuprofen offers the lowest risk. “Coxibs are associated with reduced gastrointestinal risk relative to most NSAIDs at equivalent doses. However, coxibs (like NSAIDs) may vary in their effects, and evidence for a reduction in the most clinically important gastrointestinal risks for etoricoxib is weak”.⁴

NICE guidance on dyspepsia states that “in people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a COX-2 selective NSAID instead of a standard NSAID. In either case, prescribe with a PPI”.⁵

Chan et al estimate that in patients with a history of ulcer bleeding who are then given naproxen, 19% will have recurrent bleeding within six months.¹³

According to a recent study using the CPRD database the prevalence of patients with a past history of peptic ulcer or GI bleed who are subsequently prescribed an NSAID but not prescribed a PPI or H2 antagonist in UK general practice is 2.8%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

NICE advises that when an NSAID or Cox-2 inhibitor is prescribed to manage pain from osteoarthritis, a proton pump inhibitor (PPI) should be co-prescribed because the PPI reduces the risk of gastrointestinal problems and it was always more cost-effective to prescribe one.⁶

To reduce the risk of peptic ulceration with non-selective NSAIDs the BNF recommends that a proton pump inhibitor can be considered. However, H2-receptor antagonists, at twice the usual dose, e.g. ranitidine, or misoprostol can be used as alternatives. A Cox-2 inhibitor could also be considered if there is a history of upper gastrointestinal bleeding with the addition of a PPI if there are three or more risk factors for gastric bleeding.¹

PPIs are generally considered to be the preferred choice for gastroprotection; they are effective and well tolerated. PPIs reduce the risk of endoscopic gastric ulcers by 63% and the risk of duodenal ulcers by 81%.⁷

The PLUTO and VENUS studies showed a significant reduction in long term ulcers in both non-selective NSAIDs and Cox-2 inhibitors. In the PLUTO study the estimated proportion of patients who developed ulcers over six months was 12.3% on placebo, 5.2% with esomeprazole 20 mg ($p = 0.018$), and 4.4% with esomeprazole 40 mg ($p = 0.007$). In the VENUS study it was 20.4% on placebo, 5.3% on esomeprazole 20 mg ($p < 0.001$), and 4.7% on esomeprazole 40 mg ($p < 0.0001$).⁸

Misoprostol at low dose is less effective than proton PPIs at reducing the incidence of endoscopically detected lesions, and has greater adverse effects.⁹

The CONDOR trial compared celecoxib to diclofenac plus lansoprazole in patients with osteoarthritis or rheumatoid arthritis and found that the risk of clinical outcomes throughout the gastrointestinal tract was lower in patients treated with a Cox-2 inhibitor than in those receiving a non-selective NSAID plus a PPI.¹⁰

An evidence based review looked at whether PPIs were effective in secondary prevention of NSAID/aspirin-Induced, endoscopically detected gastro-duodenal ulceration and found that PPIs do effectively reduce the chance of ulceration in this high risk group of patients. (A summary of the studies reviewed can be found in Appendix 2)¹¹

See pages 6 and 7 for further information about the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.

Are there any situations where this pattern of prescribing may be considered appropriate?

The BNF provides the advice that, “While it is preferable to avoid NSAIDs in patients with active or previous gastrointestinal ulceration or bleeding, and to withdraw them if gastrointestinal lesions develop, nevertheless patients with serious rheumatic diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness. Patients at risk of gastrointestinal ulceration (including the elderly), who need NSAID treatment, particularly a non-selective NSAID, should receive gastroprotective treatment”.¹

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Appendix 2

Secondary Prevention of NSAID or Aspirin Use-Related Gastroduodenal Damage with PPIs (Endoscopic and Clinical Outcomes)

First author (y) ^{ref}	Type of study	Study population	Study groups	Duration	Primary end point	Results
Chan (2007)	Double-blind randomized controlled trial	Healed ulcers after PUB, <i>H pylori</i> negative, taking nonselective NSAIDs before, given celecoxib after ulcer healing	Celecoxib 200 mg BID + esomeprazole 20 mg daily (n = 137) vs celecoxib 200 mg BID + placebo (n = 136)	12 months	Recurrent ulcer bleeding	0% vs 8.9% ($P < .001$), adverse effects similar in both groups
Lai (2005)	Randomized controlled trial	Healed NSAID ulcer after complications; <i>H. pylori</i> eradicated	Celecoxib 200 mg daily (n = 120) vs naproxen 750 mg daily + lansoprazole 30 mg daily (n = 122)	24 weeks	Recurrent ulcer complications	Primary end point: celecoxib 3.7% vs NSAID + PPI 6.3% ($P = NS$); for dyspepsia: celecoxib 15.0% vs NSAID + PPI 5.7% ($P = .02$)
Chan (2004)	Randomized, double-blind	Healed ulcer after NSAID-ulcer bleeding; <i>H pylori</i> negative; continuous NSAID use	Diclofenac 75 mg BID + omeprazole 20 mg daily (n = 106) vs celecoxib 200 mg BID (n = 116)	6 months	Recurrent ulcer	Recurrent ulcer in: celecoxib: 18.7% vs diclofenac + omeprazole: 25.6%, $P = .21$
Graham (2002)	Randomized, double-blind, active and placebo-controlled	History of endoscopic gastric ulcer; long-term NSAID use; <i>H pylori</i> negative.	Misoprostol 800 µg daily (134), lansoprazole 15 mg (136), lansoprazole 30 mg (133), placebo (134)	12 weeks	Endoscopic gastric ulcers	Gastric ulcer-free at 12 weeks: lansoprazole 15 mg, 80%; lansoprazole 30 mg, 82%; misoprostol, 93%; placebo, 51% (lansoprazole groups vs placebo, $P < .001$; 15 vs 30 mg, $P = NS$). Compliance: lansoprazole groups: 90% vs misoprostol 73%, $P < .001$

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Olteanu (2000)	Randomized, parallel-groups comparison study	Healed gastric ulcer; continuous NSAID treatment	Pantoprazole 40 mg once daily (n = 40) vs omeprazole 20 mg once daily (n = 40) vs misoprostol 200 µg BID (n = 40)	12 months	Not specified.	Remission: 66% vs 55% (P= NS) vs 44% (P = .02)
Jensen (2000)	Prospective, randomized, parallel-group	High-risk patients (previous severe GI bleeding while on NSAIDs); continuous NSAID treatment	Omeprazole 20 mg BID (n = 23) vs misoprostol 200 µg QID (n = 23)	Not available	Treatment failure: upper GI bleeding, symptomatic ulcer recurrence, or unrelieved upper GI symptoms	Treatment failure: omeprazole 4.4% vs misoprostol 30.4% (P = .02)
Kujundzic (2000)	Randomized, parallel-groups comparison study	Healed gastric or duodenal ulcer or erosions; continuous NSAID treatment; <i>H. pylori</i> eradicated	Pantoprazole 20 mg once daily vs omeprazole 20 mg once daily vs ranitidine 150 mg BID (total n = 489)	6 months	Endoscopic findings (ulcer, >10 erosions, bleeding)	Lower rate of relapse with pantoprazole as compared with omeprazole or ranitidine (all P < .05)
Hawkey [OMNIUM study] (1998)	Randomized, double-blind, placebo-controlled, international	No ulcers, <5 erosions, no more than mild dyspepsia; continuous NSAID therapy	Omeprazole (20 mg daily, n =274); misoprostol (200 µg BID, n = 296); placebo (n = 155)	6 months	Endoscopic ulcers, withdrawals, AEs	Patients in remission at 6 months: 61% for omeprazole vs misoprostol 48% (P = .001); placebo 27% (P < .001 compared with omeprazole and misoprostol)
Yeomans [ASTRONAUT study] (1998)	Randomized, controlled, double-blind, international	No ulcers, <5 erosions, no more than mild dyspepsia; continuous NSAID therapy	Omeprazole 20 mg (n = 210) vs ranitidine 150 mg BID (n = 215)	6 months	Endoscopic ulcers	Remission: 72% for omeprazole vs 59% for ranitidine (P = .004)

BID, twice a day; QID, four times a day; AEs, adverse events.

(Taken from : Arora, G, Singh G, Triadafilopoulos, G. Proton Pump Inhibitors for Gastroduodenal Damage Related to Nonsteroidal Anti-inflammatory Drugs or Aspirin: Twelve Important Questions for Clinical Practice *Clinical Gastroenterology and Hepatology* 7; 2009; 725 - 735.e4)

Query C: Prescription of an antiplatelet drug to a patient with previous peptic ulcer or GI bleed without co-prescription of an ulcer-healing drug

What is the risk to patients?

A previous history of peptic ulcer disease is known to be a predictor for future gastrointestinal adverse events. These patients are at higher risk from the administration of gastro-irritant medication.

Even at low doses of 75mg per day aspirin has a direct irritant effect on the gastric lining. As aspirin decreases platelet aggregation it prolongs bleeding times.

Clopidogrel also prolongs bleeding times and the manufacturers note that bleeding was the most common adverse event in clinical studies especially in the first month of treatment.¹

Ticagrelor and prasugrel are two antiplatelets which are prescribed in combination with aspirin. The manufacturers Efiect®(prasugrel) and Brilique®(ticagrelor) list gastrointestinal haemorrhage as a common side effect.^{2,3}

It is not uncommon to prescribe two antiplatelets together which could prolong the bleeding time further and increase the risk of clinically relevant bleeding.

What evidence is there that this pattern of prescribing is harmful?

The BNF provides advice on antiplatelets. Caution is advised with aspirin if there is previous peptic ulceration but its use is contra-indicated in active peptic ulceration. Side effects of aspirin include gastrointestinal irritation and haemorrhage (occasionally major). For clopidogrel, there is a caution in patients at risk of increased bleeding from trauma, surgery, or other pathological conditions and a contra-indication in active bleeding. Side effects of clopidogrel include dyspepsia, abdominal pain, gastrointestinal bleeding disorders and gastric and duodenal ulcers. For ticagrelor and prasugrel there is a prescribing caution for patients with an increased risk of gastrointestinal bleeding or concomitant use of drugs that increase the risk of bleeding and side effects include haemorrhage.⁴

In the PLATO trial for ticagrelor, patients who had had gastrointestinal bleeding within six months were excluded from the trial.³ In the TRITON trial for prasugrel patients at an increased risk of bleeding were excluded from the trial.²

Stockley's interactions warns that there is a further increased risk of bleeding if other antiplatelets are prescribed with low dose aspirin and warns that the risk with prasugrel appears to be greater than that with clopidogrel.⁵

Clopidogrel carries a similar gastrointestinal bleed risk to aspirin and NSAIDs with a 2.3-2.8 fold increase in risk. When given with non-selective NSAIDs or aspirin, clopidogrel has a synergistic effect on GI bleeding and increases blood loss.⁶

Aspirin causes gastrointestinal toxicity and this risk is not significantly reduced by reducing the dosage. Low dose aspirin can double the risk of major bleeding risk although the actual risk remains low (833 patients on antiplatelet therapy for one additional major bleed per year). However the risk increases if there are underlying gastrointestinal risk factors.

Of all the NSAIDs, studies have shown that aspirin has been consistently linked with the most severe gastric mucosal lesions.⁷

British guidelines⁸ on oral anticoagulation use the following table:

Annual rates for bleeding event (fatal or non-fatal requiring hospital admission) following acute myocardial infarction (MI), according to anti-thrombotic therapy

Antithrombotic regimen	Bleeding admission rate (% per year)
Aspirin	2.6
Clopidogrel	4.6
Warfarin	4.3
Aspirin + clopidogrel	3.7
Aspirin + warfarin	5.1
Clopidogrel + warfarin	12.3
Aspirin + clopidogrel + warfarin	12.0

In the CAPRIE study the overall incidence of bleeding for either clopidogrel or aspirin was 9.3% with the case being severe in 1.4% of clopidogrel cases and 1.6% of aspirin cases.¹

According to a recent study using the CPRD database the prevalence of patients with a past history of peptic ulcer or GI bleed who are subsequently prescribed an antiplatelet but not prescribed a PPI or H2 antagonist in UK general practice is 11.5%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

Proton pump inhibitors (PPIs) are recommended when needed to reduce the risk of gastrointestinal bleeding in patients taking aspirin for cardiovascular indications.⁷

An evidence based summary⁶ reviewed the following studies which showed the effectiveness of an aspirin/PPI combination and that this combination was more effective than clopidogrel alone in preventing recurrence of gastric ulcer.

Study authors	Patients involved	Study arms	Outcome
Lai et al	123 who had taken low dose aspirin for >1 month and had an ulcer and H.Pylori infection	H. Pylori was eradicated then given lansoprazole 30mg + aspirin 100mg or placebo and aspirin 100mg for 12 months	A significantly lower percentage in the lansoprazole group (1.6% vs 14.8%, adjusted hazard ratio, 9.6; 95% CI, 1.2–76.1) had a recurrence of ulcer complications
Chan et al	320 patients with ulcer bleeding	Ulcer healing and H pylori eradication, then given clopidogrel 75 mg + placebo or aspirin 80 mg daily + esomeprazole 20 mg twice daily for 12 months	The cumulative incidence of recurrent ulcer bleeding was 8.6% (4.1–13.1%) in the clopidogrel group versus 0.7% (0–2.0%) in the aspirin + esomeprazole group. The difference between the two groups was highly significant
Lai et al	170 patients who had ulcer bleeding after low dose aspirin	After ulcer healing and H.Pylori eradication given esomeprazole 20mg + aspirin 100mg or clopidogrel 75mg for 12 months	The cumulative incidence of recurrent ulcer complication was 0% in the esomeprazole group versus 13.6% in the clopidogrel group (absolute difference, 13.6%; 95% CI, 6.3%–20.9%; P = .002)
Ng et al	129 patients with aspirin induced peptic ulcer disease who were being treated with omeprazole 20mg daily	Continue on aspirin plus omeprazole 20mg or Clopidogrel 75mg plus omeprazole 20mg	Endoscopically defined outcomes determined at eight weeks showed no difference between the two groups

Clopidogrel inhibits the liver enzyme CYP2C19 and so the combination of clopidogrel with other CYP2C19 inhibitors, such as omeprazole and esomeprazole, should be avoided. Other PPIs can be co-prescribed.⁹

See pages 6 and 7 for further information about the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.

Are there any situations where this pattern of prescribing may be considered appropriate?

Previous peptic ulceration or gastric bleeding is an important risk factor for gastrointestinal effects from aspirin and other antiplatelets. The addition of clopidogrel, prasugrel or ticagrelor to aspirin may increase the risk of bleeding further. However, risks from aspirin and other antiplatelets can be reduced by gastric protection using a medication such as a proton pump inhibitor.

In patients at risk of a cardiovascular event or stroke the benefits of antiplatelet treatments generally outweigh the risks, but gastric protection should be offered to patients with a history of peptic ulcer. There may be rare situations in which a patient is intolerant of all ulcer healing drugs and a decision is made that the benefits of prescribing an antiplatelet (without an ulcer healing drugs) outweigh the risks even in a patients with a history of peptic ulcer.

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Query D: Prescription of warfarin or NOAC in combination with an oral NSAID

What is the risk to patients?

NSAIDs are known to cause upper gastrointestinal ulceration and bleeding. In anticoagulated patients this may increase the severity of upper GI bleeding. Many NSAIDs also have antiplatelet activity which can prolong bleeding times.

What evidence is there that this pattern of prescribing is harmful?

“In a retrospective cohort study of patients hospitalised for peptic ulcer disease, the current use of both oral anticoagulants and NSAIDs was associated with a large increase in the risk of haemorrhagic peptic ulcer disease of 12.7 (95% confidence interval 6.3 to 25.7). This was much higher than the risk associated with NSAIDs alone or oral anticoagulants alone (both about a 4-fold increased risk). In this study, about 10% of the hospitalisations for haemorrhagic peptic ulcer disease in patients taking anticoagulants were attributed to the concurrent use of NSAIDs”.¹

Cox-2 inhibitors given with warfarin were found to have a similar increase in bleeding as NSAIDs given with warfarin in the available comparative epidemiological studies when they were given with warfarin. Celecoxib may have a pharmacokinetic interaction with warfarin that can raise the INR.¹

In the RE-LY study the concurrent use of NSAIDs increased the risk of bleeding by 50% in both the dabigatran and warfarin groups.²

The combination of edoxaban with an NSAID increases the risk of clinically relevant bleeding and the “chronic use of NSAIDs with edoxaban is not recommended” by the manufacturer.³

The BNF states a major interaction between coumarins and NSAIDs due to possibly enhanced anticoagulant effect. There is also a major interaction between dabigatran and NSAIDs due to a possible increased risk of bleeding.⁴

“For the most commonly used NSAIDs; ibuprofen, diclofenac and naproxen, there does not seem to be an alteration in the anticoagulant control. However, there have been isolated cases of overanticoagulation.”¹

A Canadian nested case-control analysis over one year studied 98,821 patients over 66 years old who were continuously prescribed warfarin; 361 of these were admitted to hospital with upper GI haemorrhage and found to be more “likely to be also taking nonselective NSAIDs (OR, 1.9; 95% confidence interval [CI], 1.4-3.7), celecoxib (OR, 1.7; 95% CI, 1.2-3.6), or rofecoxib (OR, 2.4; 95% CI, 1.7-3.6) prior to hospitalization relative to controls”. The study concluded that the combination of warfarin with a non-selective NSAID or a Cox-2 inhibitor does increase the risk of upper GI haemorrhage by a similar amount.⁵

A study reviewing records in the United Kingdom General Practice Research Database (GPRD) from 2000 -2005 identified patients over 18 years old who had been diagnosed with their first gastrointestinal bleed. 4028 patients were identified. The results showed that prescribing warfarin with a NSAID increased the gastrointestinal bleeding risk (RR 4.60, 95% CI 2.77–7.64) compared with each drug alone.⁶

According to a recent study using the CPRD database (which is a more recent version of GPRD) the prevalence of patients prescribed warfarin or a NOAC in combination with an antiplatelet (without co-prescription of an ulcer-healing drug) in UK general practice is 5.5%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

In our rapid review we found no studies evaluating the effects of stopping an NSAID in a patient receiving warfarin or a NOAC, although the evidence presented above suggests that correcting this pattern of prescribing is likely to lead to a reduction in patient harm.

We did not find specific evidence to evaluate the benefits of prescribing ulcer healing drugs to patients receiving combined treatment with warfarin or a NOAC with an NSAID. Nevertheless, there is strong evidence that proton pump inhibitors protect against gastrointestinal bleeding with NSAIDs and this protection is likely to reduce the risk of bleeding if an NSAID is given with either warfarin or a NOAC.

Are there any situations where this pattern of prescribing may be considered appropriate?

There is convincing evidence that NSAIDs and Cox-2 inhibitors can cause gastrointestinal irritation and bleeding that could be severe if the patient is anti-coagulated. They can also prolong bleeding times. It is advisable to avoid this combination whenever possible. Unlike antiplatelets, which are used in the secondary prevention of cardiovascular disease, there are likely to be very few situations where the likely benefits outweigh the risks when prescribing NSAIDs in combination with anticoagulants. In rare situations where it is considered necessary to prescribe this combination, an NSAID of low gastrointestinal risk should be chosen and gastroprotection prescribed.

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Query E: Prescription of warfarin or a New Oral Anti-Coagulant (NOAC) and an antiplatelet in combination without co-prescription of an ulcer-healing drug

What is the risk to patients?

Even at low doses e.g. 75mg per day, aspirin is known to be a gastric irritant that can cause gastric bleeding and as it reduces platelet aggregation, aspirin prolongs bleeding times. When an antiplatelet dose of aspirin (75-325mg daily) is given with warfarin, the risk of bleeding is increased by 1.5-2.5 folds.¹

The addition of aspirin or clopidogrel to warfarin increases the risk of bleeding. If more than one antiplatelet is prescribed with warfarin the risk of bleeding may increase further.

The combination of warfarin and a NOAC is contra-indicated. The combination of a NOAC and an antiplatelet has a prescribing caution due to the increased risk of bleeding.

What evidence is there that this pattern of prescribing is harmful?

The STOPP tool² uses criteria which describes an odds ratio of 1.9 for hospital admission with an upper GI bleed if taking both aspirin and warfarin. The BNF advises that aspirin should be used in combination with warfarin after discussion with a cardiologist and an assessment of the patient's bleed risk. The duration of dual therapy (e.g. aspirin and warfarin) or triple therapy (e.g. aspirin with clopidogrel and warfarin) should be kept to a minimum. There is a lower risk of bleeding with aspirin and warfarin compared to clopidogrel and warfarin.³

The combination of aspirin and warfarin is associated with an increased risk of bleeding 1.5- to 2.5-fold compared to either drug used alone, although the absolute risk is small. Stockley advises that patients on combination treatment, who are at risk of gastrointestinal bleeding should receive gastroprotection".⁴

The use of NOACs is increasing rapidly and we are likely to learn more about the importance of gastroprotection when they are used in combination with antiplatelets as experience grows. However, from trials we know that the pharmacokinetics and pharmacodynamics of apixaban are not altered by aspirin, but there is an increased risk of bleeding if it is combined with aspirin or clopidogrel. The pharmacokinetics of rivaroxaban is not changed by aspirin or clopidogrel and there is no clinically relevant change in anticoagulant effect. However there may be a minor increase in bleeding time if rivaroxaban is taken with aspirin or clopidogrel.¹ Dabigatran is known to have a pharmacodynamic interaction with aspirin or clopidogrel. The RE-LY trial showed double the bleed rate in when the combination is used.⁴

The manufacturers for edoxaban warn that combination with antiplatelets can increase the risk of bleeding. High dose aspirin (≥ 325 mg per day) increases the steady state C_{max} of edoxaban by 35% whereas low dose aspirin (≤ 100 mg) did not affect the peak or total exposure of edoxaban either.

Low dose aspirin (≤ 100 mg/day) given with edoxaban is associated with a two-fold increase in major bleeding.⁵

A study reviewing records in the United Kingdom General Practice Research Datalink (CPRD) from 2000 -2005 identified patients over 18 years old who had been diagnosed with their first gastrointestinal bleed. 4028 patients were identified. The results showed that prescribing aspirin with warfarin was associated with a greater risk of gastrointestinal bleeding than that observed with each drug alone (adjusted RR 6.48, 95% CI 4.25–9.87).⁷

BCSH guidelines on oral anticoagulation with warfarin⁶ advise that trials clearly show when warfarin is prescribed with aspirin or clopidogrel there is a clear increase in the risk of major bleeding. This risk is higher with clopidogrel and warfarin than aspirin and warfarin. The guidelines give us the following table:

Annual rates for bleeding event (fatal or non-fatal requiring hospital admission) following acute myocardial infarction (MI), according to anti-thrombotic therapy

Antithrombotic regimen	Bleeding admission rate (% per year)
Aspirin	2.6
Clopidogrel	4.6
Warfarin	4.3
Aspirin + clopidogrel	3.7
Aspirin + warfarin	5.1
Clopidogrel + warfarin	12.3
Aspirin + clopidogrel + warfarin	12.0

According to a recent study using CPRD the prevalence of patients prescribed warfarin or a NOAC (rivaroxaban, apixaban, dabigatran) in combination with an oral NSAID in UK general practice is 0.8%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

In our rapid literature review we did not find specific evidence to evaluate the benefits of prescribing ulcer healing drugs to patients receiving combined treatment with warfarin and aspirin. Nevertheless, there is strong evidence that proton pump inhibitors protect against gastrointestinal bleeding with NSAIDs and this is likely also to be the case for patients receiving an antiplatelet with either warfarin or a NOAC.

See pages 6 and 7 for further information about the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.

Are there any situations where this pattern of prescribing may be considered appropriate?

Prescribing of an anticoagulant in combination with aspirin or clopidogrel is not common but does occur when advised by a cardiologist. If the combination is used it is essential to have a clear indication and duration of therapy.

Whenever combination therapy is required aspirin and warfarin has a lower bleed risk than clopidogrel and warfarin. Gastroprotection should always be considered and offered when combination therapy is indicated.

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Query F: Prescription of aspirin in combination with another antiplatelet drug without co-prescription of an ulcer-healing drug

What is the risk to patients?

“Aspirin has a direct irritant effect on the stomach lining and can cause gastrointestinal bleeding, even in doses as low as 75 mg daily. It also decreases platelet aggregation and prolongs bleeding times.”¹

The Plavix® (clopidogrel) SPC² states “bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.” Clopidogrel also prolongs bleeding time.

Ticagrelor and prasugrel are two antiplatelets which are prescribed in combination with aspirin. The SPC states for Efient®(prasugrel)³ and Brilique®(ticagrelor)⁴ list gastrointestinal haemorrhage as a common side effect.

Two antiplatelets are commonly co-prescribed and as they prolong the bleeding time the risks may be additive and increase the risk of clinically relevant bleeding.

What evidence is there that this pattern of prescribing is harmful?

The BNF lists side effects for clopidogrel and aspirin that indicate that they cause gastroirritation e.g. gastrointestinal bleeding, gastric and duodenal ulcers and gastrointestinal haemorrhage.¹

For ticagrelor and prasugrel the BNF gives a prescribing caution for patients with an increased risk of gastrointestinal bleeding or concomitant use of drugs that increase the risk of bleeding.¹ In the PLATO trial for ticagrelor, patients who had had gastrointestinal bleeding within six months were excluded from the trial⁴. In the TRITON trial for prasugrel patients at an increased risk of bleeding were excluded from the trial.³

The risk of bleeding is increased if a second antiplatelet is prescribed with low dose aspirin. The risk with prasugrel and aspirin appears to be greater than with clopidogrel and aspirin.⁵

Clopidogrel has a gastrointestinal bleeding risk that is 2.3 - 2.8-fold higher than in non-users, which is similar to the increased risk seen with aspirin and NSAIDs.

Clopidogrel causes a synergistic increase in the risk of GI bleeding when given to patients on aspirin.⁶

It is commonly known that aspirin causes gastrointestinal toxicity. Lowering the dose of aspirin to less than 300mg per day does not significantly lower the risk of bleeding. There have been reports of gastrointestinal injury with doses of 10mg per day.

Aspirin up to 325mg a day increases the risk of gastrointestinal bleeding two-fold compared to placebo (one additional major bleed for 833 patients on low dose aspirin). However, the risk of bleeding varies depending on underlying gastrointestinal risk factors e.g. old age. Aspirin has consistently been associated with the most severe gastric mucosal lesions when compared to other NSAIDs.⁷

British guidelines⁸ on oral anticoagulation use the following table:

Annual rates for bleeding event (fatal or non-fatal requiring hospital admission) following acute myocardial infarction (MI), according to anti-thrombotic therapy

Antithrombotic regimen	Bleeding admission rate (% per year)
Aspirin	2.6
Clopidogrel	4.6
Warfarin	4.3
Aspirin + clopidogrel	3.7
Aspirin + warfarin	5.1
Clopidogrel + warfarin	12.3
Aspirin + clopidogrel + warfarin	12.0

In the CAPRIE study, the overall incidence of any bleeding with clopidogrel or aspirin was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for aspirin.²

According to a recent study using the CPRD database the prevalence of patients prescribed aspirin in combination with another antiplatelet drug (without co-prescription of an ulcer-healing drug) period in UK general practice is 3.87%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

Proton pump inhibitors (PPIs) are recommended when needed to reduce the risk of gastrointestinal bleeding in patients taking aspirin for cardiovascular indications.⁷ An evidence based summary⁶ reviewed the following studies which showed the effectiveness of an aspirin/PPI combination and that this combination was more effective than clopidogrel alone in preventing recurrence of gastric ulcer.

Study authors	Patients involved	Study arms	Outcome
Lai et al	123 who had taken low dose aspirin for >1 month and had an ulcer and H.Pylori infection	H. Pylori was eradicated then given lansoprazole 30mg + aspirin 100mg or placebo and aspirin 100mg for 12 months	A significantly lower percentage in the lansoprazole group (1.6% vs 14.8%, adjusted hazard ratio, 9.6; 95% CI, 1.2–76.1) had a recurrence of ulcer complications

Chan et al	320 patients with ulcer bleeding	Ulcer healing and H pylori eradication, then given clopidogrel 75 mg + placebo or aspirin 80 mg daily + esomeprazole 20 mg twice daily for 12 months	The cumulative incidence of recurrent ulcer bleeding was 8.6% (4.1–13.1%) in the clopidogrel group versus 0.7% (0–2.0%) in the aspirin + esomeprazole group. The difference between the two groups was highly significant
Lai et al	170 patients who had ulcer bleeding after low dose aspirin	After ulcer healing and H.Pylori eradication given esomeprazole 20mg + aspirin 100mg or clopidogrel 75mg for 12 months	The cumulative incidence of recurrent ulcer complication was 0% in the esomeprazole group versus 13.6% in the clopidogrel group (absolute difference, 13.6%; 95% CI, 6.3%–20.9%; P = .002)
Ng et al	129 patients with aspirin induced peptic ulcer disease who were being treated with omeprazole 20mg daily	Continue on aspirin plus omeprazole 20mg or Clopidogrel 75mg plus omeprazole 20mg	Endoscopically defined outcomes determined at eight weeks showed no difference between the two groups

The liver enzyme CYP2C19 is inhibited by clopidogrel and therefore the combination of clopidogrel with omeprazole and esomeprazole (also CYP2C19 inhibitors) should be avoided. Other PPIs can be co-prescribed.⁹

See pages 6 and 7 for further information about the potential harm from long-term proton pump inhibitors (PPIs) when using the PINCER gastroprotection indicators.

Are there any situations where this pattern of prescribing may be considered appropriate?

The addition of clopidogrel, prasugrel or ticagrelor to aspirin may increase the risk of bleeding. However, risks from aspirin and other antiplatelets can be reduced by gastric protection using a medication such as a proton pump inhibitor. Therefore, for patients at risk of a cardiovascular event or stroke the benefit of combination antiplatelet therapy **plus gastric protection** may outweigh the risk of bleeding.

There are very few situations in which it would be considered appropriate **not** to prescribe gastric protection in patients receiving aspirin along with another antiplatelet agent. In patients unable to tolerate ulcer healing drugs a decision would be needed about whether the benefits of the two antiplatelets outweigh the increased risk of GI bleed. In these circumstances, it might be safer to give just one antiplatelet agent.

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Outcome: Exacerbation of Asthma**Query G: Prescription of a non-selective beta-blocker to a patient with asthma****What is the risk to patients?**

In susceptible patients with asthma, beta-blockers can precipitate acute attacks of bronchospasm or worsen daily symptoms of asthma resulting in increased morbidity and mortality. This effect can also occur with beta-blocker eye drops. The BNF advises that:

“beta-blockers can precipitate bronchospasm and should therefore usually be avoided in patients with a history of asthma. When there is no suitable alternative, it may be necessary for a patient with well-controlled asthma, to receive treatment with a beta-blocker for a co-existing condition (e.g. heart failure or following myocardial infarction). In this situation, a cardioselective beta-blocker should be selected and initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects. Atenolol, bisoprolol, metoprolol, nebivolol, and (to a lesser extent) acebutolol, have less effect on the beta₂ (bronchial) receptors and are, therefore, relatively cardioselective, but they are not cardiospecific. They have a lesser effect on airways resistance but are not free of this side-effect.”¹

The Committee on Safety of Medicines² issued the following advice:

“... β-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease, unless no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.”

What evidence is there that this pattern of prescribing is harmful?

Beta-blockers vary in their affinity for beta₁- and beta₂-adrenoceptors, and are divided into two groups, cardioselective (greater affinity for beta₁), and non-cardioselective (greater affinity for β₂).

Table 1: Relative selectivity of commonly used cardioselective and non-cardioselective beta-blockers.

Cardioselective beta-blockers (relative selectivity for β₁- adrenoceptors)³	Non Cardioselective beta-blockers (relative selectivity for β₂- adrenoceptors)³
Acebutolol (2.4)	Labetalol (2.5)
Atenolol (4.7)	Propranolol (8.3)
Bisoprolol (13.5)	Sotalol (12.0)
Metoprolol (2.3)	Timolol (25.7)

“The greatest risk from beta-blockers in people with asthma follows initial exposure.”¹⁵ A recent meta-analysis¹⁶ reviewed the effect of acute beta-blocker exposure in people with asthma and found that non-selective beta-blockers (the evidence reviewed was primarily for propranolol), caused an average reduction in FEV1 of 10%. However, a reduction in FEV1 of $\geq 20\%$ was seen in one in 8 patients and symptoms of bronchospasm were experienced by one in 13 patients. The review also notes that “non-selective b-blockade completely attenuated b₂-agonist response relative to placebo” meaning that if non-cardioselective beta-blocker-induced bronchospasm occurs, bronchodilator therapy would not be as effective. The authors noted that whilst there have been deaths following ocular exposure to beta-blockers in asthma there was a lack of data to review. Ocular exposure has the potential to be riskier than oral due to rapid systemic absorption. From the data reviewed, a fall in FEV1 of 14.2% was noted with timolol eye drops and 9.6% with betaxolol eye drops.

Small-scale safety studies, detailed in Table 2, confirm that **non-cardioselective** beta-blockers *do* cause bronchoconstriction, which can be severe in some asthmatics. There are also a small number of case reports of beta-blockers causing bronchoconstriction in patients with a past-history of asthma.⁴

A study reviewing medical records in America¹⁴ showed that non-selective beta blockers in patients with asthma (with or without COPD) were associated with a 147% increase in hospital admissions compared to placebo. The number needed to harm, compared to placebo, was 56 patients for one additional hospital admission and 26 for one additional visit to an emergency department.

Table 2: Summary of studies of the effects of non-cardioselective beta-blockers on airway function in asthmatics.

Beta-blocker	Effect on airways	Type of study
Carvedilol ⁵	6/12 (50%) patients with asthma withdrew from therapy secondary to wheezing.	Open-label study of carvedilol in patients with CHF and COPD or asthma.
Oxprenolol ⁶	Worsening airway obstruction in 6/11(55%) patients without airways disease, and 7/12 (58%) patients with bronchitic asthma.	Double-blind controlled trial in COAD and non-COAD patients.
Pindolol ⁷	Pindolol caused a significant a significant fall in FEV ₁ in > 50% of patients.	Placebo controlled study in asthmatics.
Pindolol ⁸	No significant reduction in pulmonary function at rest or on exercise with Pindolol. However, a trend towards a reduction in airway function was observed.	Safety trial in mild to moderate controlled asthmatics.

Propranolol ⁹	Worsening of pulmonary function following propranolol 40mg, lasting for over four hours compared to placebo (p<0.01).	Randomised, double blind crossover, placebo controlled trial.
Sotalol ¹⁰	Sotalol induced a significant reduction in FEV ₁ .	Placebo controlled, double blind, single-dose, crossover study in asthmatics.
Timolol ¹¹	Asthmatic patients suffered bronchoconstriction following topical timolol eye drops, accompanied by a 32% reduction in FEV ₁ . No change was seen in non-asthmatics.	Double blind, randomised, cross over trial in mild asthmatics and non-asthmatics.
Timolol & Betaxolol ¹²	Significant reduction in FEV ₁ seen with timolol eye drops, but no change seen with betaxolol (a cardioselective beta-blocker) eye drops.	Double blind, randomised, cross over trial in patients with reactive airway disease.
Timolol & Betaxolol ¹³	Significant reduction in FEV ₁ seen with timolol eye drops, and reduction in response to bronchodilator. No change seen with betaxolol (a cardioselective beta-blocker) eye drops.	Double blind cross over study in asthmatics.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

In our rapid review we found no studies evaluating the effects of stopping a non-selective beta-blocker in a patient with asthma.

Are there any situations where this pattern of prescribing may be considered appropriate?

“Although some people with asthma may tolerate acute exposure to non-selective beta-blockers, risk is greater and rescue therapy is less effective suggesting their risk probably outweighs any potential benefits for existing clinical indications and should be avoided.”¹⁵

Overall, there is little justification for use of non-selective beta-blockers in patients with asthma, mainly because other safer treatment options are available i.e. cardioselective beta-blockers for cardiovascular disease and other pharmacological and non-pharmacological treatments for anxiety.

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Query H: Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid

What is the risk to patients?

Long acting beta agonists (LABAs) are useful in the management of chronic asthma but should be used in line with the British Thoracic society BTS step-wise approach at step 3.¹ The use of a LABA without a steroid may put the patient at risk of sudden or chronic deterioration of their asthma.²

What evidence is there that this pattern of prescribing is harmful

The BNF³ recommends that for safety, in asthma patients, LABAs should only be used if the patient is taking a regular inhaled corticosteroid. It also refers to Commission of Human Medicines (CHM) advice which recommends that in chronic stable asthma a LABA should be added when asthma remains uncontrolled despite regular use of standard-dose inhaled corticosteroids. If the patient has rapidly deteriorating asthma, a LABA should not be initiated.

Concerns about LABAs were raised as a result of the Salmeterol Multi-Centre Asthma Research Trial (SMART)⁴, conducted in the United States. This study “found a small but statistically significant increase in respiratory-related and asthma-related deaths or life-threatening episodes in the total population receiving salmeterol compared with placebo”.⁵ The study was stopped early but half of the participants were not taking inhaled corticosteroids.

“Systematic reviews of regular treatment with salmeterol or formoterol for chronic asthma found an increased risk of serious non-fatal adverse effects compared with placebo. In contrast, subsequent reviews of regular treatment with salmeterol or formoterol plus inhaled corticosteroids found no difference in serious adverse effects when compared with inhaled corticosteroids although results were not sufficient to conclude that there was no increased risk. Additionally, the number of deaths was too small to allow a firm conclusion to be reached on the effect of long-acting beta₂ agonists on mortality”.⁵

Long-acting β₂ agonists should not be used without also taking regular corticosteroids. When used alone, long-acting β₂ agonists have been associated with a, sometimes severe, worsening of asthma in some patients.⁶

The British Thoracic Society asthma guidance¹ does not recommend the use of a LABA without an ICS and advocates the use of combination inhalers to avoid improve adherence and reduce the risk of a patient taking using a LABA without an inhaled corticosteroid (ICS).

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

The National Review of Asthma Deaths report⁷ looked at 195 cases where the patient's death was thought to be due to asthma over a three year period. "There have been major concerns over the prescription of LABA inhalers without ICS (i.e. LABA monotherapy), a treatment that has been associated in controlled trials with increased mortality and is without a licence or guideline endorsement.

LABAs can be provided either as part of a single ICS/LABA combination inhaler, which ensures that LABA therapy cannot be prescribed as monotherapy without ICS, or as a LABA inhaler, which allows the possibility of differential adherence to ICS and LABA components. Of those who died from asthma, 27 were prescribed LABA as a single-component inhaler device. The panels reported that, in eight cases, LABA therapy without concomitant ICS was a factor in the asthma death. However, on closer scrutiny, only five were actually on LABA monotherapy (i.e. without ICS)".

A systematic review by Rodrigo⁸ found that LABA used in conjunction with inhaled corticosteroids reduced the incidence of asthma related morbidity and mortality when compared to patients receiving LABA alone: the combination of LABA and inhaled corticosteroids reduced risks of exacerbation of asthma (relative risk = 0.73; 95% CI, 0.67–0.79).

Are there any situations where this pattern of prescribing may be considered appropriate?

In the management of asthma, a LABA should never be prescribed without an inhaled corticosteroid. The preference is to provide the LABA and ICS in a single combination inhaler.

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Outcome: Heart Failure

Query I: Prescription of an oral NSAID to a patient with heart failure

What is the risk to patients?

Heart failure is a risk factor for cardiac and renal events in patients taking NSAIDs or COX2-Inhibitors. To varying degrees, there is an increase in thrombotic risk associated with all NSAIDs and Cox2- inhibitors.¹ This risk is more likely in long term NSAID users.²

“Although prostaglandins have both vasodilator and vasoconstrictor actions, the overall effects of NSAIDs are to raise systemic vascular resistance and to reduce renal perfusion in susceptible individuals. In some individuals with impaired ventricular function, these mechanisms can exacerbate their tendency to develop congestive heart failure (CHF).”³ NSAIDs have also been shown to lead to persistently elevated blood pressure in older patients, which can exacerbate or increase the likelihood of developing heart failure.

What evidence is there that this pattern of prescribing is harmful?

The BNF advises that in severe heart failure, all NSAIDs are contra-indicated. “Diclofenac, aceclofenac and the selective inhibitors of cyclo-oxygenase-2 (celecoxib, etoricoxib, and parecoxib) are contra-indicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and mild to severe heart failure. They should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, in patients with oedema for any other reason, and in patients with other risk factors for cardiovascular events. Other non-selective NSAIDs should be used with caution in uncontrolled hypertension, heart failure, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, and when used long term in patients with risk factors for cardiovascular events”.¹

Cox-2 inhibitors may cause a slight increase in the risk of cardiovascular events such as heart attack or stroke. Rofecoxib was withdrawn in 2004 due to this risk. Based on available evidence in a general population, Diclofenac and Cox-2 inhibitors may result in about three extra thrombotic events per 1000 patients per year.⁴

Naproxen at any licensed dose and ibuprofen at doses ≤ 1200 mg a day are thought to have a lower risk of heart attacks or strokes than selective Cox-2 inhibitors. However, higher doses of ibuprofen are thought to have a small increased thrombotic risk.⁴ An MHRA⁹ release in June 2015 confirmed that ibuprofen at doses ≥ 2400 mg/day has a similar cardiovascular risk to Cox-2 inhibitors and diclofenac. The advice re-iterates that ibuprofen is contra-indicated in severe heart failure and advises that ibuprofen at high doses should be avoided in congestive heart failure (New York Heart Association [NYHA] classification II-III).

“The recent use of NSAIDs has been associated with an increased risk of developing heart failure in elderly patients. A case-control study found that the use of an NSAID in the previous week doubled the odds of being admitted to hospital with heart failure; this risk was increased tenfold in those with a history of heart disease. The study also suggested an association between both high-dose and long drug plasma half-life and an increased risk of heart failure”.⁵

Patients with impaired circulation e.g. heart failure, elderly, may rely on increased prostaglandin production to improve renal blood flow by vasodilation. NSAIDs can inhibit this effect and worsen renal function.⁵

According to a recent study using the CPRD database the prevalence of prescribing and oral NSAID to a patient with heart failure in UK general practice is 3.87%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

Evidence from a recent study shows that patients with chronic heart failure who continued to take NSAIDs regularly had a significantly higher risk of mortality and cardiovascular related morbidity than those who stopped taking NSAIDs.⁷ The ten year follow up study of over 100,000 patients in Denmark also showed that there was a dose-dependent increase in risk of death and increased risk of hospitalisation because of myocardial infarction and heart failure.

An earlier RCT found that patients with a history of heart failure were over two times more likely to develop myocardial infarction if treated with selective Cox-2 inhibitors than those given other NSAIDs. Patients taking other non-selective NSAIDs were still more likely to exhibit cardiovascular related morbidity than those not treated with NSAIDs.^{7,8}

Are there any situations where this pattern of prescribing may be considered appropriate?

There are no situations in which NSAIDs should be used in severe heart failure or acute heart failure. Diclofenac and Cox-2 inhibitors should not be used in any severity of heart failure. Even in milder forms of heart failure, the benefits of prescribing NSAIDs are unlikely to outweigh the risks. If a non-selective NSAID is prescribed, it makes sense to use the lowest possible dose for the shortest possible time period, and to do this with caution, including monitoring for worsening of the heart failure.

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OUTCOME: STROKE

Query J: Prescription of antipsychotics for >6weeks in a patient aged ≥65 years with dementia but not psychosis

What is the risk to patients?

Antipsychotics are sometimes used to treat the behavioural and psychological symptoms of dementia (BPSD). The Banerjee report in 2009 estimated that there are “180,000 people with dementia treated with antipsychotic medication in England per year. Of these, up to 36,000 may derive some benefit from treatment, but an additional 1,800 may die and an additional 1,620 suffer a cerebrovascular adverse event (around half of which may be severe) per year”.^{1,5}

What evidence is there that this pattern of prescribing is harmful?

The BNF advises that antipsychotics given in dementia results in a small increase in mortality, stroke or transient ischaemic attack. Elderly patients are more susceptible to the antipsychotic side-effects of postural hypotension and to hyper- and hypothermia. If antipsychotics are used then the dose in elderly patients should be at least halved in comparison to the standard adult dose and reviewed regularly.²

The dementia guidance from NICE³ states that antipsychotics should not be prescribed to patients with mild to moderate non-cognitive symptoms and:

- Alzheimer's disease, vascular dementia or mixed dementias due to the possible increased risk of cerebrovascular adverse events
- Dementia with Lewy bodies as they are at particular risk of severe adverse reactions.

“The risk of adverse effects of antipsychotics in dementia has been quantified by pooling studies. The pooled relative risk for mortality is 1.41 (a 41%) increased risk of dying over the first three months of treatment. Put another way, the numbers needed to harm (NNH) for death from antipsychotics in dementia is 100 over the first six to 12 week period of treatment. This increased risk of mortality persists for at least six months from the initial prescription, based on observational studies.

Meta-analysis of 15 trials of newer atypical antipsychotic drugs compared with placebo found robust evidence for an increase in cerebrovascular side effects of antipsychotics. The pooled relative risk was 2.57 (i.e., taking an antipsychotic makes someone with dementia two and a half times more likely to have a stroke as someone not on antipsychotic). Put another way, if 59 people with dementia were treated with antipsychotics for six-12 weeks, one of those would have a stroke; with a 50% chance this would be severe.”⁴

The Banerjee report⁵ concluded that “there is some evidence to support slightly greater efficacy for risperidone for the treatment of aggression, as opposed to non-aggressive agitation, with effect sizes in the region of 0.3. NNT to achieve clinically significant improvement in one additional behaviourally disturbed patient range from 5 to 11”.

It also found that “there is very limited evidence for the efficacy of atypical or typical antipsychotic drugs for the treatment of symptoms of psychosis in dementia. A clinically significant degree of improvement has only been demonstrated for aripiprazole, with NNT of 13.8.”

A retrospective case controlled study published in 2015⁶ found that the risk of death in due to antipsychotic use in patients with dementia is greater than previously thought. The study involved 46,008 patients. The study found that when compared with matched non-users:

Drug	Increased risk of death	Number needed to harm (NNH)
Haloperidol	3.8%	26
Risperidone	3.7%	27
Olanzapine	2.5%	40
Quetiapine	2.0%	50

If haloperidol and quetiapine are compared with antidepressant users then the increase in mortality risk is 12.3% and 3.2% (NNH is 8 and 31) respectively. A 3.5% increase in mortality was shown in the high dose atypical antipsychotic sub-group when compared to the low dose sub-group.⁶

Out of the available anti-psychotics, only risperidone is licensed specifically for up to six weeks treatment of aggression in Alzheimer’s.

According to a recent study using the CPRD database the prevalence of patients prescribed antipsychotics for more than six weeks in a patient aged ≥ 65 years with dementia but not psychosis in UK general practice is 8.7%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

A Cochrane systematic review of withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia, identified nine trials totalling 606 patients.⁷ Different antipsychotics and doses were included and withdrawal schedules varied from being abrupt to slow. The primary outcome of the review was success of withdrawal (determined as being able to remain in the study and off antipsychotics).

The review suggests that withdrawal of antipsychotic medication can be done successfully without worsening behaviour in patients with Alzheimer's dementia and that withdrawal schedules should form part of clinical practice. However, in patients with severe neuropsychiatric symptoms at baseline may benefit from continuing antipsychotic treatment. It is still unclear whether cognition or psychomotor status is improved by withdrawal of antipsychotics.

Are there any situations where this pattern of prescribing may be considered appropriate?

There is uniform agreement that antipsychotics should be considered for non-cognitive symptoms in dementia only if the person is severely distressed or there is an immediate risk of harm to them self or others. When used antipsychotics should be used at the lowest dose possible and should be reviewed after six weeks where withdrawal and discontinuation should be considered. However, there are some patients who will need longer term treatment if their symptoms re-emerge on withdrawing or their symptoms are severe. If treatment is continued, then prescribing should be under continual review e.g. three monthly with the patient/family involved. Most local areas now have thorough guidelines covering prescribing for behavioural and psychological problems patients with dementia and there is no situation where these should not be followed by primary care.

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OUTCOME: KIDNEY INJURY

Query K: Prescription of an oral NSAID to a patient with chronic renal failure with an eGFR <45

What is the risk to patients?

Non-steroidal anti-inflammatory drugs (NSAIDs, including COX-2 inhibitors) may rarely precipitate renal failure. Patients with existing renal impairment are at the highest risk of renal failure. It is estimated that NSAID use accounts for 15% of all cases of drug-induced acute renal failure.¹

“NSAIDs inhibit prostaglandins PGE2 and PGI2. Inhibition of these prostaglandins may result in sodium retention, reduced renal blood flow, and renal failure”.²

What evidence is there that this pattern of prescribing is harmful?

NSAIDs should be avoided in severe renal impairment. Manufacturers advise caution in prescribing to patients with renal impairment due to the possibility of fluid retention and oedema.³

The BNF advises that “NSAIDs should be avoided if possible or used with caution in patients with renal impairment; the lowest effective dose should be used for the shortest possible duration, and renal function should be monitored. Sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure”.⁴

A case-control study estimated an increased relative risk (3.2 [95% CI 1.8–5.8]) of acute renal failure in otherwise healthy current users of NSAIDs.¹

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines¹³ recommend the following with regards to NSAIDs:

- Avoid in people with GFR <30 ml/min/1.73 m²
- Prolonged therapy is not recommended in people with GFR <60 ml/min/1.73 m²
- Temporary discontinuation if GFR < 60 ml/min/1.73 m² who have serious intercurrent illness that increases the risk of acute kidney injury
- NSAID is one of the most common risk factors for acute decline in GFR for patients with established CKD

Several studies have found a significant association between prolonged use of NSAIDs and renal failure⁵⁻⁸. Heavier NSAID use has also been associated with an increased risk of end stage renal disease in a dose-dependent fashion⁹. Sporadic or regular use of NSAIDs has been associated with an almost two fold increase in the risk of end stage renal disease (ESRD) in older patients.⁹

According to a recent study using the CPRD database the prevalence of patients prescribed an oral NSAID with an eGFR <45ml/min/1.72m³ in UK general practice is 3.4%.

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

High cumulative NSAID exposure is associated with an increased risk for rapid chronic renal failure progression in the setting of a community-based elderly population. Cohort studies have shown faster degeneration of renal function in patients with renal failure who continue to use NSAID. "Patients who continue analgesics, those with pre-existing vascular disease and those with more advanced renal impairment at presentation, are at a significantly increased risk of reaching the combined end-point of death or end-stage renal failure requiring dialysis."¹⁰ A recent study has also showed faster degeneration of renal function over five to seven years of patients with chronic renal failure who continue to regularly use NSAIDs. The progression rate of renal failure for regular users of NSAID was higher than that for non-regular users (regular users progressed 0.93 mL/min/1.73 m² per year higher than non-regular users).¹¹ In another study that investigated the impact of NSAID use on progression of chronic kidney disease in patients aged 65 years and over, high dose NSAID users experienced a 26% increased risk of a clinically significant decrease in eGFR greater or equal to 15ml/min/1.73. A linear association between cumulative NSAID dose and change in mean GFR was also seen. No risk difference was identified between selective and non-selective COX-2 inhibitor NSAIDs.¹²

Are there any situations where this pattern of prescribing may be considered appropriate?

The appropriateness of prescribing may be dependent on the degree of renal impairment and the patient's other co-morbidities. Whilst the use of NSAIDs is usually best avoided in renal impairment, some prescribers may consider using these in patients with mild renal impairment if considered necessary for control and pain and inflammation where other options have been exhausted.

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