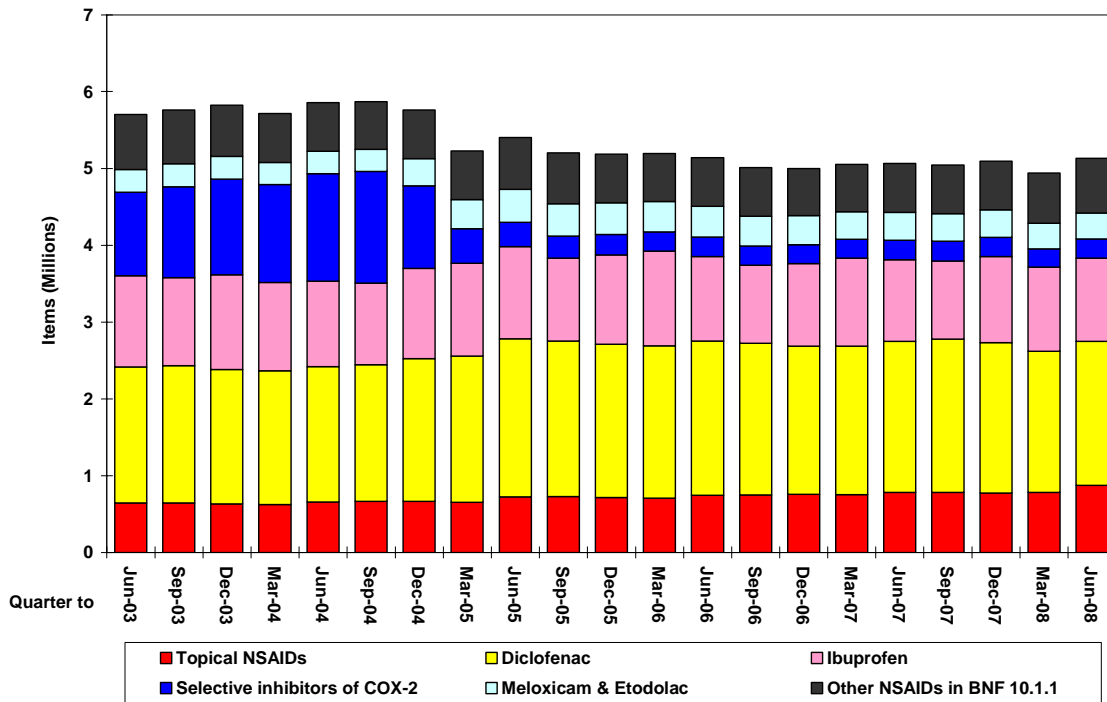
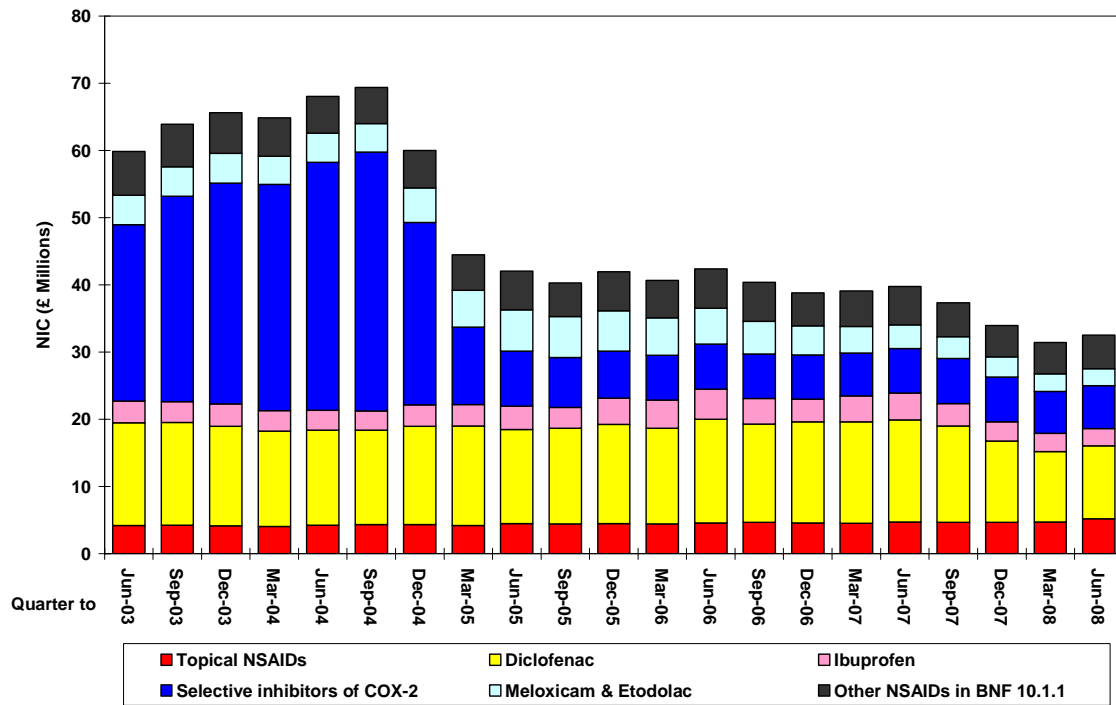


Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase enzymes and are used to manage a variety of acute and chronic conditions associated with pain and/or inflammation. All NSAIDs inhibit both COX 1 and 2 enzymes but most of the NSAIDs that have been developed in recent years show greater activity as inhibitors of COX 2.¹ These newer NSAIDs are often referred to as selective COX-2 inhibitors or simply as ‘coxibs’. Selective inhibitors of COX-2 as defined in this article, meet the Medicines and Healthcare products Regulatory Agency (MHRA) definition of selective COX-2 inhibitors (celecoxib, etoricoxib, rofecoxib, valdecoxib and lumiracoxib), all other NSAIDs are classed as non-selective.² In 2006 the MHRA issued advice following a Europe-wide review of the cardiovascular (CV) safety of the selective inhibitors of COX-2 that suggested there was small increased risk of thrombotic events compared with placebo which increased with dose and duration.³ This article explores the patterns in NSAID prescribing since the publication of the MHRA review and the withdrawal of licensed products from the UK market, but excludes the use of both oral and topical NSAIDs bought as ‘over the counter’ products.

Trends in Prescribing of NSAIDs in General Practice in England (Chart 1)



Trends in Spending on NSAIDs in General Practice in England (Chart 2)



A standard approach to symptomatic pain management should follow the principles of the World Health Organization (WHO) three-step analgesic ladder. Paracetamol and/or an NSAID can be used from step one of the WHO pain ladder onwards. Analgesics should be started at the ‘step’ most appropriate to the patient’s level of pain, and doses should be titrated following regular re-assessment of response. Treatment of the underlying disease causing the pain may reduce the need for analgesics. Non-drug treatments should be maximised, particularly in chronic pain where psychological and psychosocial factors are important. The National Institute for Health and Clinical Excellence (NICE) recommends regular dosing with paracetamol as first-line analgesia for osteoarthritis (OA).⁴ It is effective for short-term mild to moderate pain and is less likely than NSAIDs to cause gastrointestinal (GI) adverse effects. In patients with knee or hand OA, NICE also recommends use of a topical NSAID before an oral NSAID. Systematic reviews have found no important differences in efficacy between different NSAIDs in the management of musculoskeletal disorders⁵ therefore, when prescribing an NSAID, assessing differences in risk must be considered as well as patient preference and cost.

Risk factors for upper gastrointestinal adverse effects

People are at high risk of serious NSAID-induced GI adverse events if they have one or more of the following risk factors: age 65 years or older (the risk is twice as high in men as in women); history of GI ulcer, bleeding, or perforation; concomitant use of drugs that increase the risk of GI adverse events; serious comorbidity, such as CV or renal disease; requirement for prolonged NSAID use; and use of the maximum recommended dose of an NSAID.⁶ A systematic review and meta-analysis investigated NSAIDs and serious GI complications.⁷ Pooled relative risks were calculated for different risk factors. NSAID users with advanced age or a history of peptic ulcer disease had the highest absolute risks for upper GI tract bleeding or perforation. Compared with patients aged 25 to 49 years, 60 to 69 year olds had 2.4 times the risk of a GI bleed or perforation, 70 to 80 years had 4.5 times the risk, and patients over 80 years had 9.2 times the risk. Potentially hazardous drug interactions may occur with NSAIDs. For example, people who are taking warfarin should ideally avoid taking NSAIDs, and people taking a selective serotonin

reuptake inhibitor (SSRI) plus an NSAID are advised to seek urgent medical advice and stop NSAID use if a bleeding episode occurs.^{8,9} A recently published meta-analysis found that, in people older than 50 years taking an SSRI and an NSAID with no risk factors for upper GI bleeding, for every: 411 people treated with SSRIs, one person experienced upper GI bleeding (number needed to harm [NNH] = 411), 106 people treated with an SSRI and an NSAID together, one person experienced upper GI bleeding (NNH = 106).

Prevention and management of gastrointestinal adverse effects

To prevent GI adverse effects from oral NSAIDs several recommendations have been published:

- Use an alternative to an NSAID, e.g. in patients with OA: paracetamol with or without codeine, topical NSAIDs, and physical treatments;⁴
- Use only one NSAID at a time,¹⁰ and if aspirin is needed for CV protection, its use almost always has priority over use of an NSAID;
- Use the lowest NSAID dose that is compatible with symptom relief.

In people who are at increased risk of GI adverse effects and who require an NSAID, consider use of a gastroprotective drug. Proton pump inhibitors (PPIs) are effective at reducing the risk of NSAID-induced endoscopic gastric and duodenal ulcers, and are well tolerated. In contrast, standard doses of histamine₂-receptor antagonist (H₂RA) are not very effective in reducing the risk of NSAID-induced endoscopic ulcers. Misoprostol (800 micrograms daily) is the only prophylactic drug that has been shown to reduce the occurrence of clinically important ulcer complications, but its use is associated with significant adverse effects and poor compliance, particularly at high doses. Recent trials have influenced the NICE Osteoarthritis guideline development group to recommend that when offering treatment with an oral non-selective NSAID or a selective inhibitor of COX-2 (note: etoricoxib 60mg is not recommended), the drug selected should be co-prescribed with a PPI, choosing the one with the lowest acquisition cost.⁴

Risk factors for cardiovascular and renal adverse effects

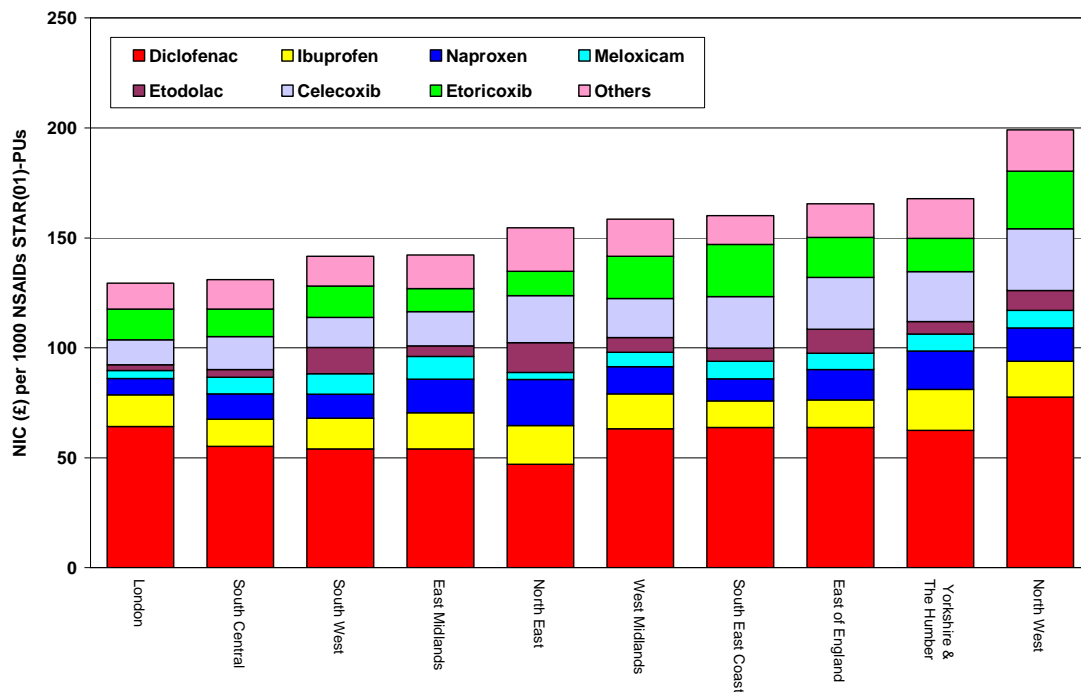
The risk of serious cardiac or renal adverse events is increased in patients: with a history of, or risk factors for, CV disease; with renal impairment (e.g. creatinine clearance less than about 20mL/min); or over 65 years of age, even in the absence of CV or renal risk factors.^{11,12} Evidence from systematic reviews suggests that many NSAIDs are associated with an increased risk of CV adverse events.¹³ The risk for individuals is associated with treatment duration and is disproportionately increased in people who are at high risk for CV disease before starting treatment. The CHM,¹¹ MHRA,¹² and the National Prescribing Centre (NPC)¹ have recently summarized the evidence for CV thrombotic risks associated with selective inhibitors of COX-2 and non-selective NSAIDs based on systematic reviews and meta-analyses and concluded that:

- All selective inhibitors of COX-2 increase the risk of atherothrombosis by about 3 events per 1,000 people per year (compared with placebo).
- Naproxen 1,000 mg daily has a lower thrombotic risk than selective inhibitors of COX-2, and overall, epidemiological data do not suggest an increased risk of myocardial infarction (MI).
- Ibuprofen may have a small thrombotic risk at high doses (i.e. 2,400 mg daily), but at lower doses (i.e. 1,200 mg daily or less) epidemiological data do not suggest an increased risk of MI.
- Diclofenac 150 mg daily has a thrombotic risk profile similar to etoricoxib (and consequently, the NPC has been encouraging prescribers to review patients taking diclofenac).
- There is less evidence for other NSAIDs, but they may all be associated with a small risk of thrombotic events.

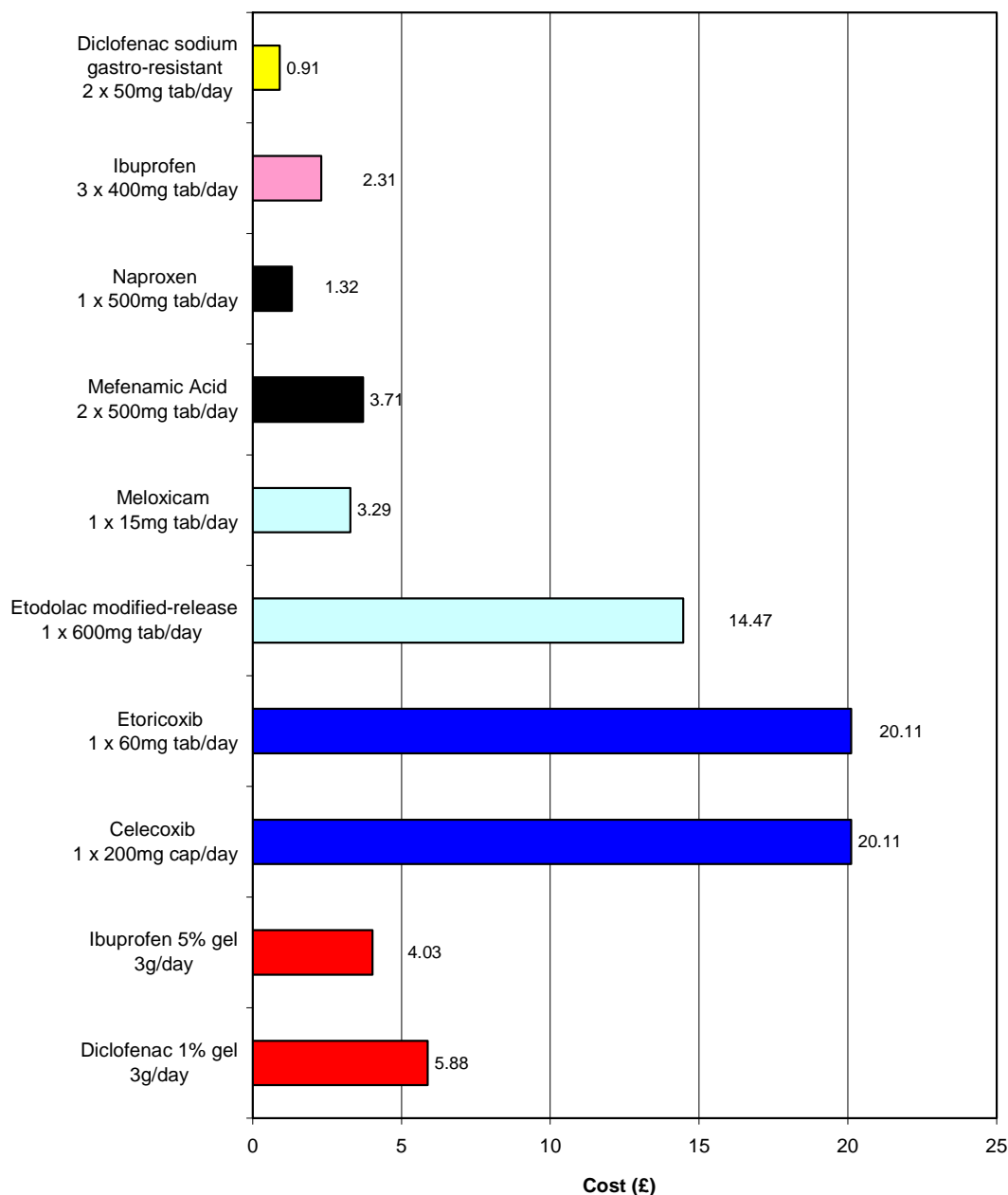
Regarding the risk of cardiorenal adverse effects (e.g. hypertension, heart failure), NSAIDs have been shown in three systematic reviews to increase blood pressure (BP) and the risk of hypertension.¹⁴⁻¹⁶ The risk of increasing BP with an NSAID is probably higher between susceptible and non-susceptible individuals than between one NSAID and another. In particular, the MHRA have advised that etoricoxib should not be initiated in people whose hypertension is not under control and careful monitoring of BP is advised.

Chart 3 shows the variation in spending on NSAIDs across strategic health authorities (SHAs) for April to June 2008. There is a two fold difference in spending between SHAs on selective inhibitors of COX-2 (celecoxib, etoricoxib) with a variation of between 18% to 29% of the total spend. Etodolac shows the greatest variation between SHAs with a five fold difference and a range of 2% to 9% of total spend.

Variation Between Strategic Health Authorities in Spending on NSAIDs
(Quarter to June 2008) (Chart 3)



Cost for 28 Days



Prices based on Drug Tariff November 2008. Dose based on WHO DDDs where possible, otherwise BNF stated dose. The WHO DDD is a unit of measurement based on the assumed average maintenance dose in adults. It may not necessarily reflect the actual dose used.

Prescribing Data (reporting quarter = April-June 2008, index quarter = April-June 2003)

Prescribing of NSAIDs (excluding topical) has decreased by 16% (to 4.3 million items) and costs have fallen 51% (to £27.3 million) in the last five years. Diclofenac is the most commonly prescribed NSAID, 1.9 million items per quarter (a 6% increase) costing £10.9 million (a 29% decrease). It accounts for 44% of all NSAID items and 40% of the cost. Ibuprofen accounts for 25% (1.1 million) of NSAID items (a 9%

decrease) and 10% (£2.6 million) of the cost (a 19% decrease). Naproxen items have increased by 54% to 427,000, costing £2.3 million (a 19% increase). Prescribing of selective inhibitors of COX-2 has decreased by 77% in the last five years (to 248,000 items, £6.4 million). This represents 6% of NSAID items and 23% of the cost. Prescribing of celecoxib has fallen 74% to 127,000 items, costing £3.4 million (a decrease of 67%). Etoricoxib items have increased by 36% (121,000 items, £3 million). Meloxicam items remains stable, increasing by 5% to 261,000 items with a reduction in cost of 64% (£1.3 million). Items for etodolac have increased by 66% (to 80,000) and costs by 47% (£1.3 million). Prescribing of rubefaciants has increased by 17% (to 1.3 million items) and cost has increased by 21% (to £7.5 million). Topical NSAIDs account for 872,000 of these items, £5.2 million.

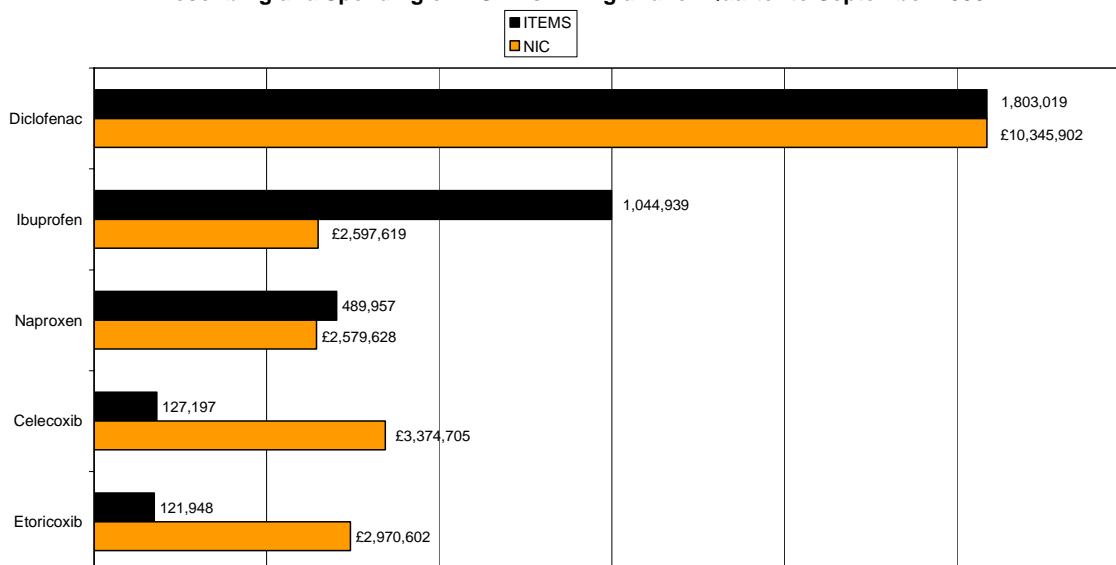
Prescribing of paracetamol and paracetamol combination products has increased by 8% (8.8 million items) and costs have risen by 62% (£35.4 million). Paracetamol is the most commonly prescribed at 4.2 million items, an increase of 48%. The cost has more than trebled to £10.1 million. Paracetamol with codeine has increased by 49% (3.5 million items, £19.7 million). Prescribing of paracetamol with dihydrocodeine increased by 6% (1 million items), cost increased 18% (£3 million). Prescribing of co-proxamol has reduced by 95% to 92,000 items following the withdrawal of its licence, with spending decreasing by only 7% (£2.6 million).

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SUMMARY

- If a person is at high risk of developing an adverse effect, ideally an alternative to an oral NSAID should be found e.g. paracetamol alone or with codeine, topical NSAIDs and physical treatments. Failing this use one NSAID at a time at the lowest dose compatible with symptom relief.
- People are at high risk of upper GI adverse events if they are aged 65 years or older; have a history of GI ulcer, bleeding or perforation; take other drugs that increase the risk of GI events; require prolonged use of NSAIDs or a maximum dose of a NSAID.
- PPIs are the most effective drugs for reducing the risk of NSAID-induced endoscopic gastric and duodenal ulcers, taking into account adverse effects and compliance issues.
- Most NSAIDs are associated with an increased risk of cardiovascular adverse events. The risk increases with increased treatment duration and in those people who already have cardiovascular disease before starting treatment.

Prescribing and Spending on NSAIDs in England for Quarter to September 2008



Quarter to September 08

National

	ITEMS/1000 PUs	NIC/1000 PUs
Diclofenac	25.27	£145.03
Ibuprofen	14.64	£36.41
Coxibs (selective inhibitors of COX-2)	3.49	£88.95
Other NSAIDs	15.43	£105.36