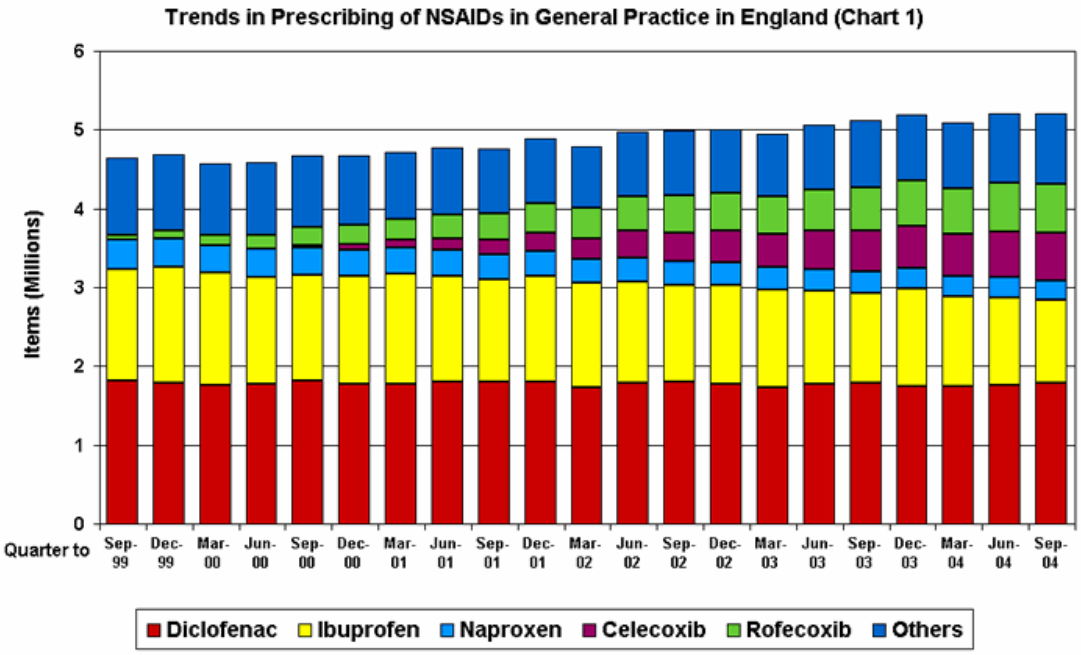
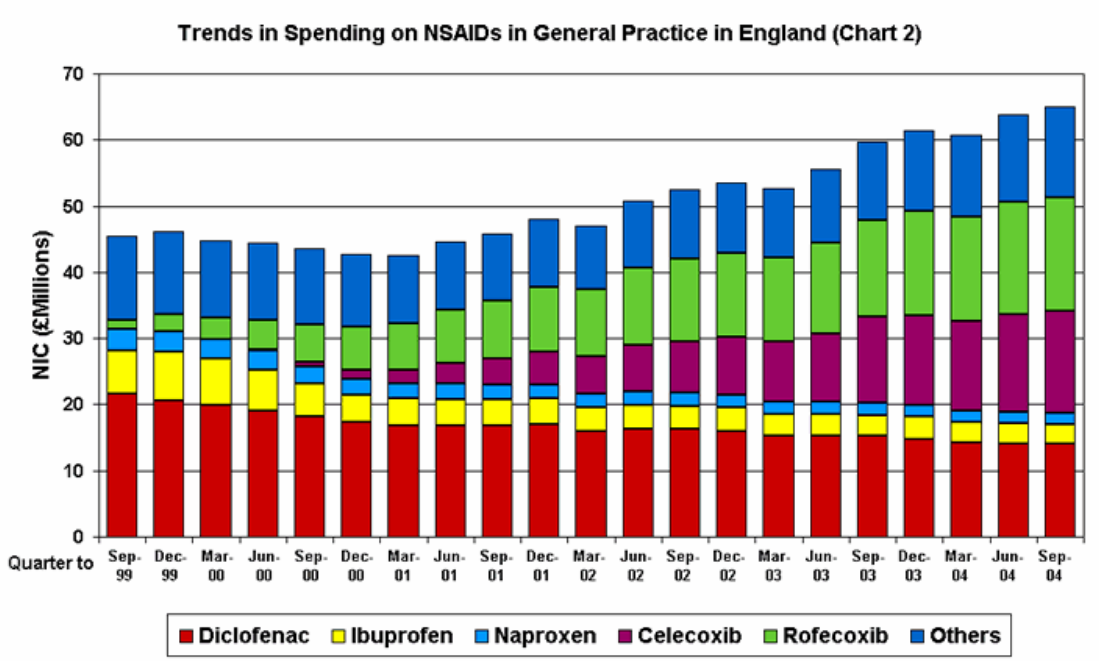
Centre Pages – NSAIDs & Analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed in primary care, mainly for osteoarthritis and back pain. Over 9 million people suffer with arthritis; osteoarthritis being the most prevalent form. On average, people visit their doctor every five months about their osteoarthritis, but a third never visit.[1] Of those patients taking medication, 32% use NSAIDs, 18% use cyclo-oxygenase II (Cox-II) selective inhibitors and 15% use paracetamol to manage their osteoarthritis pain.[1] Prescribing of NSAIDs has increased gradually over the last 5 years (Chart 1), wholly due to the rise in prescribing of Cox-II selective inhibitors. Cost has risen significantly (Chart 2) because the Cox-II selective inhibitors are more expensive than standard NSAIDs. Rofecoxib was withdrawn from the market in September 2004; it accounted for approximately 200,000 prescription items per month. Data for November 2004 show that prescriptions for celecoxib, ibuprofen and diclofenac have increased to 15%, 23% and 36% of all NSAID items respectively, compared to 12%, 21%, and 34% in September 2004. Most of the increase in prescribing of these three drugs is probably due to patients being switched from rofecoxib.





Managing pain in osteoarthritis

Paracetamol is effective in relieving pain in osteoarthritis and should be tried first line based on its favourable safety profile compared to NSAIDs.[2] There is little evidence to suggest that NSAIDs are significantly different from paracetamol in providing pain relief. Non-drug therapies or topically applied products can be tried in addition to or as alternatives to paracetamol before trying an oral NSAID. In osteoarthritis of the knee, oral glucosamine (1500mg daily) probably provides moderate relief of symptoms and similar efficacy to NSAIDs and is another treatment option.[3] A systematic review concluded that there is insufficient evidence of benefit from chondroitin in osteoarthritis.[4] Trial evidence (although limited by reporting issues and methodology) has shown that exercise, physical therapy and acupuncture reduce pain and disability in people with knee or hip osteoarthritis.[4,5] In an Arthritis Care survey 57% of respondents used exercise to help manage their osteoarthritis.[1]

A recent meta-analysis compared topical NSAIDs with placebo or oral NSAIDs in patients with evidence of osteoarthritis.[6] In the first two weeks of treatment topical NSAIDs were superior to placebo in relieving pain due to osteoarthritis. There is no evidence to support the long term use of topical NSAIDs in osteoarthritis.[6] A review of rubefacients containing salicylates showed that they help in relieving acute pain (number needed to treat (NNT) 2.1 for at least 50% pain relief at 7 days compared to placebo). They perform less well in relieving chronic arthritic and rheumatic pain (NNT 5.3 for at least 50% pain relief at 14 days compared to placebo).[7] A meta-analysis including 23 trials with 10,485 patients (7,767 received oral NSAIDs, 3,078 received placebo) measured the change in overall intensity of pain. It showed that oral NSAIDs reduce pain in the short term for osteoarthritis of the knee, however the advantage over placebo is small.[8] Evidence is lacking for the efficacy of long term oral NSAIDs.

Cardiovascular adverse events

All NSAIDs have the potential to cause adverse effects such as fluid retention, oedema and hypertension. Caution is required when prescribing any NSAID in patients with renal, cardiac or hepatic impairment, particularly in older patients who are at higher risk of these problems. Rofecoxib was withdrawn from the market on 30th September 2004 because of concerns raised by the adenomatous polyp prevention on Vioxx (APPROVe) study, which showed increased risk of heart attack and stroke after 18 months of treatment compared with placebo. Following the withdrawal of rofecoxib, the European Medicines Agency (EMEA) is reviewing all Cox-II selective inhibitors to look at aspects of cardiovascular safety including heart attack, stroke, hypertension, oedema and cardiac failure. The EMEA recently released a statement advising patients and prescribers about the safety of valdecoxib.[9] A higher rate of cardiovascular thromboembolic events compared to placebo has been shown in studies involving coronary artery bypass graft surgery. The reported rate of serious skin reactions (some with fatal outcome) appears to be higher with valdecoxib than other Cox-II selective inhibitors.[9]

New data from a trial of celecoxib showed that the risks of a major fatal or non-fatal cardiovascular event were 2.5 and 3.4 times higher than placebo at 400mg and 800mg doses respectively. A second celecoxib trial did not appear to confirm the same level of risk.[10] The Medicines and Healthcare products Regulatory Agency (MHRA) has advised prescribers to switch patients treated with any Cox-II selective inhibitor who have established ischaemic heart disease or cerebrovascular disease to alternative treatment (non Cox-II selective) as soon as convenient. In all patients alternative treatment should be considered in light of assessment of risks and benefits of Cox-II selective inhibitors.[10] NICE recommends that Cox-II selective inhibitors should not be used in preference to standard NSAIDs in people with cardiovascular disease or in those taking low dose aspirin.[11]

Gastrointestinal adverse events

Before prescribing an NSAID (including Cox-II selective inhibitors) the risk of a gastrointestinal (GI) adverse event versus the benefit of treatment should be assessed. In a meta-analysis the pooled relative risk of serious upper GI complications associated with NSAIDs was 3.8 (95% confidence interval 3.6-4.1).[12] The burden of adverse drug reactions (ADR) as a cause of hospital admissions was investigated in an observational study. NSAIDs were implicated in 30% (363 cases) of admissions due to an ADR. Aspirin was associated with the most adverse events, rofecoxib and celecoxib also caused ADRs resulting in admission.[13]

Factors associated with a high risk of GI adverse events from NSAIDs include:

- age over 65 years
- use of other medicines known to increase the chance of upper GI adverse events
- serious co-morbidity
- prolonged use of maximum recommended doses of standard NSAIDs
- previous history of peptic ulcer disease /dyspepsia.[11]

Cox-II selective inhibitors should only be considered instead of standard NSAIDs in people with rheumatoid arthritis or osteoarthritis who may be at high risk of developing serious GI problems. The alternative is to prescribe a standard NSAID with gastroprotection. Misoprostol reduces serious upper GI complications in high risk patients compared to placebo and significantly reduces NSAID associated gastric and duodenal ulcers found on endoscopy.[14] Proton pump inhibitors or double dose H_2-receptor antagonists also reduce the risk of endoscopic gastric and duodenal ulcers.[14] Eradicating *Helicobacter pylori* before commencing an NSAID is useful in patients with previous history of or at high risk of peptic ulcer disease.[12]

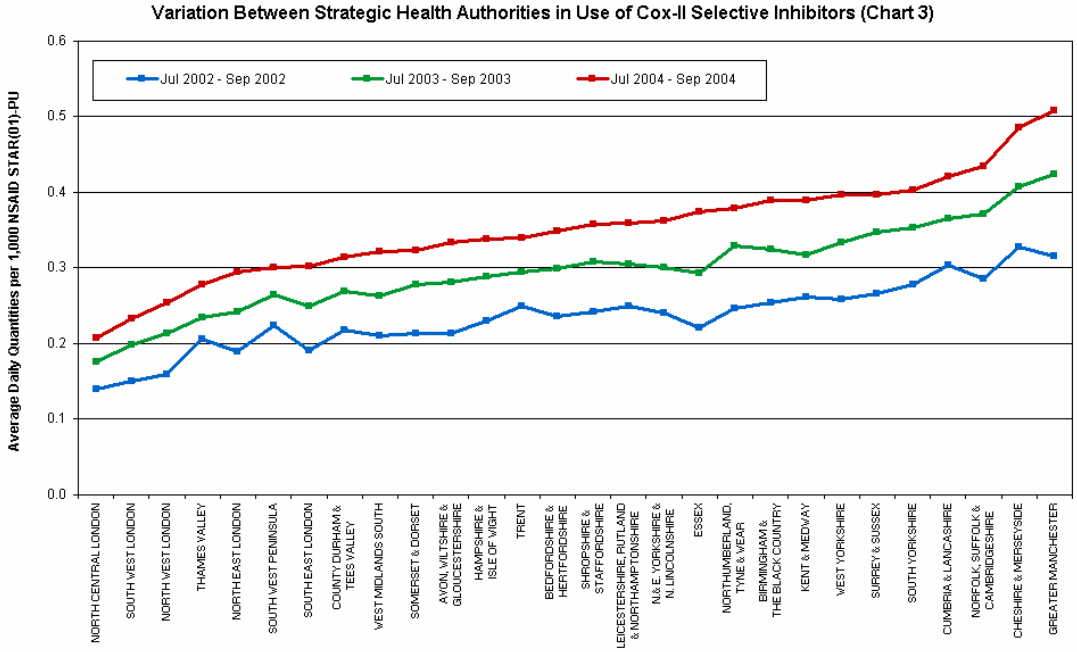
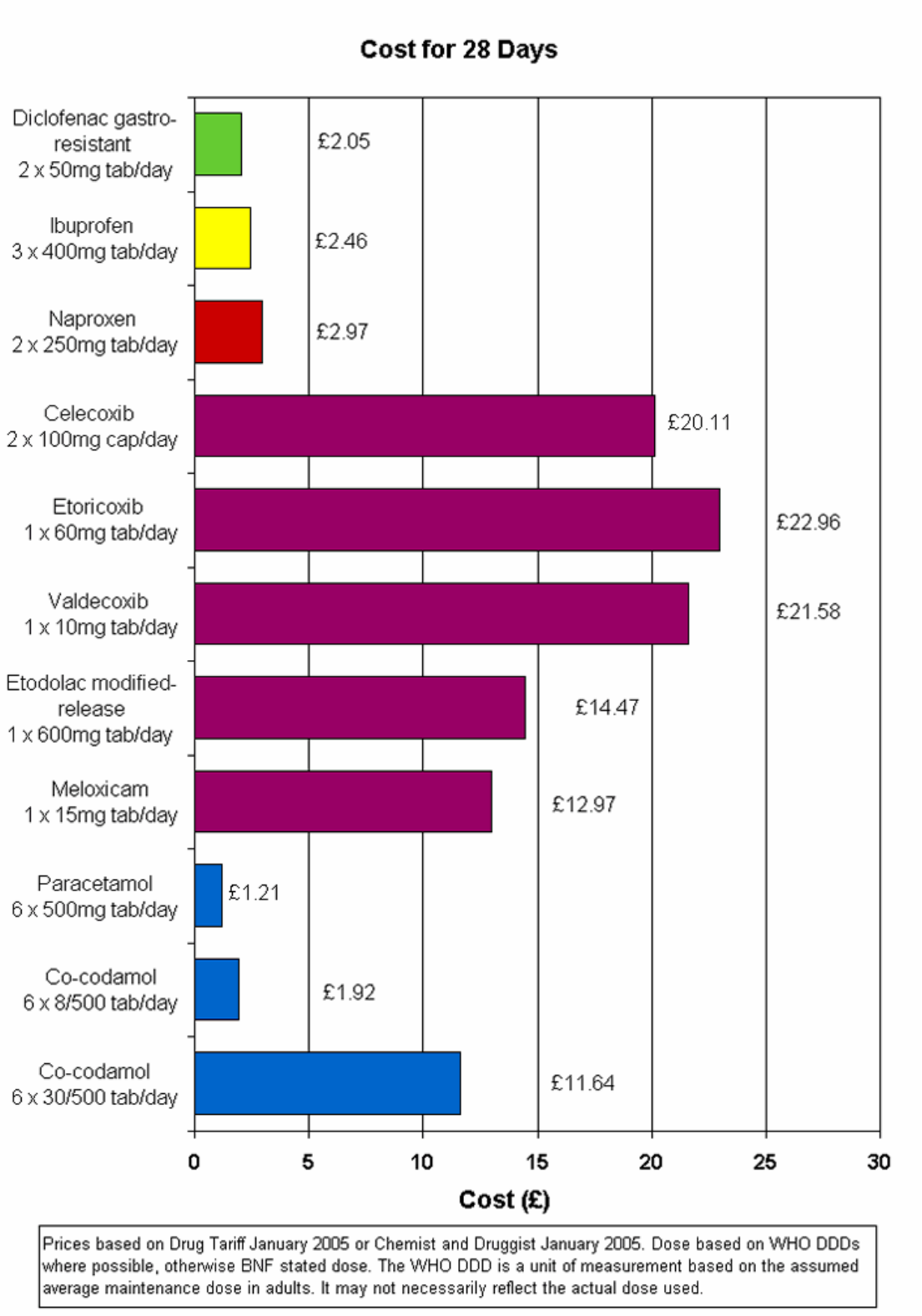


Chart 3 shows the year on year increase in prescribing of Cox-II selective inhibitors for Strategic Health Authorities for the last three years. There is a 2.5 fold variation in prescribing of Cox-II selective inhibitors across Strategic Health Authorities.



Prescribing data

Diclofenac is the most commonly prescribed NSAID, 1.8 million items (34% of all NSAIDs) in the quarter to September 2004, followed by ibuprofen, 1.1 million items (20%). Prescribing of ibuprofen has decreased significantly (25%) over the last 5 years with diclofenac prescribing falling only slightly (2%). The amount spent on ibuprofen has more than halved (£2.9 million,

quarter to September 2004) while spending on diclofenac has fallen by 35% (£14.1 million per quarter). In the quarter to September 2004 one-third of all NSAID prescriptions (1.7 million items) and 66% of cost (£42.7 million) were for the Cox-II selective inhibitors (rofecoxib, celecoxib, etoricoxib, valdecoxib, etodolac and meloxicam).

Overall the number of non-opioid analgesics items (8.4 million, quarter to September 2004) has shown little change over the last 5 years. 97% of non-opioid analgesics items and 98% of cost are for paracetamol and paracetamol combination products. Prescriptions for paracetamol and paracetamol with codeine have both risen by about 25% in the last 5 years (2.9 million and 2.5 million items per quarter, £3.4 million and £14.2 million respectively). Prescriptions for paracetamol with dextropropoxyphene and paracetamol with dihydrocodeine have decreased by 26% and 4% respectively to 1.8 million and 1 million items per quarter, while cost has fallen by 38% and 12% respectively (£2.5 million and £2.6 million, quarter to September 2004). The increase in paracetamol with codeine items over the last 5 years is due to greater prescribing of preparations containing at least 30mg codeine (up by 57% to 1.3 million items, £10.8 million in the quarter to September 2004).The cost of 28 days treatment for preparations of paracetamol combined with 30mg codeine is 1.25 times the cost of prescribing these two drugs separately.

Total prescribing of rubefacients and topical NSAIDs has decreased by 11% and cost has fallen by 9% over the last 5 years. Topical NSAIDs account for 0.67 million items and topical rubefacients 0.45 million items, quarter to September 2004, while their cost is £4.3 million and £2.2 million respectively. Movelat® accounts for more than half of all topical rubefacient items, 0.26 million (58%) and £1.4 million per quarter. Over the counter sales of topical products are not included in these figures and these may be substantial.

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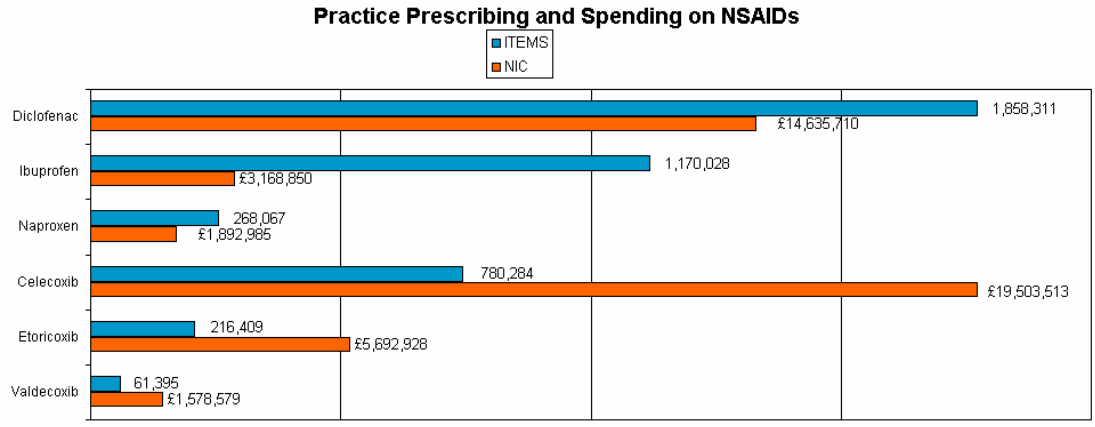
Summary

- Paracetamol should be prescribed first for pain in osteoarthritis before trying an NSAID.

- Rubefacients and topical NSAIDs can be useful to relieve osteoarthritic pain in the short term.

- Patients with ischaemic heart disease or cerebrovascular disease taking Cox-II selective inhibitors should be switched to a non Cox-II selective alternative.

- Misoprostol prescribed with a standard NSAID can reduce the risk of serious GI adverse events in patients at high risk.

- In those with a previous history of or at high risk of peptic ulcer disease eradication of *Helicobacter pylori* is useful before starting a patient on an NSAID.

	Quarter to December 04	
	National	
	Items/1000 PUs	NIC/1000 PUs
Diclofenac	26.64	£209.82
Ibuprofen	16.77	£45.42
Naproxen	3.84	£27.13
Cox-II Inhibitors	20.44	£463.13
Other NSAIDs	5.21	£51.99