

Data focused commentary: NSAIDs and musculoskeletal disease

Introduction

All non-steroidal anti-inflammatory drugs (NSAIDs) carry the risk of side effects, which can be serious and life-threatening. Although the risks may vary between individual NSAIDs, important side effects include gastrointestinal (GI) complications (eg perforation, ulcer, bleeding) and cardiovascular (CV) events (eg stroke, myocardial infarction [MI]).¹ When deciding whether NSAIDs or alternatives such as paracetamol are most appropriate for an individual patient, at least three considerations are foremost:

- the severity of symptoms and response to treatment
- GI risk
- CV risk.¹

NICE osteoarthritis (OA) guidance states that traditional NSAIDs (eg ibuprofen, naproxen, diclofenac) and COX-2 inhibitors (coxibs: celecoxib, etoricoxib[▼]) may be regarded as a single drug class of 'NSAIDs'.² However, we continue to distinguish between the two terms for clarity, and because of the differences in side effect profile.

Gastrointestinal safety of NSAIDs¹

Of the commonly used traditional NSAIDs, ibuprofen is associated with a lower GI risk than diclofenac and naproxen. Coxibs, as a class, are associated with a lower GI risk than traditional NSAIDs. However, their GI safety advantage is diminished when co-administered with aspirin. Use of a proton pump inhibitor (PPI) with **any NSAID** significantly reduces the risk of GI side effects.

Cardiovascular and cardio-renal safety of NSAIDs

Long-term randomised controlled trials (RCTs) have demonstrated that coxibs cause a small increased risk of CV thrombotic events in comparison with placebo.¹ The excess risk is estimated to be about 3 cases per 1000 users treated for 1 year; this risk appears to increase with dose and persists throughout treatment.¹ All coxibs are now contraindicated for patients with established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.¹ An increased risk with meloxicam and etodolac can also not be ruled out, as there are insufficient data to fully examine the risks with these agents.¹

Although the CV risk associated with coxibs was already well recognised³, in June 2006 a meta-analysis of RCTs by Kearney et al⁴ raised concerns about the CV safety of traditional NSAIDs. It was suggested that high doses of diclofenac and ibuprofen, **but not naproxen**, were associated with an increased risk of CV events. In October 2006, a review of the CV safety of selective and non-selective NSAIDs, reported by the Commission on Human Medicines (CHM), identified that traditional NSAIDs may also be associated with a small increased risk of thrombotic events when used at high doses and for long-term treatment.⁵ Furthermore, they identified that not all traditional NSAIDs carried the same CV risk:

- **Naproxen** 1000mg daily may be associated with a **lower** risk of thrombotic events than coxibs. Although some risk with naproxen cannot be entirely ruled out, epidemiological evidence suggests that naproxen is not associated with an excess risk of MI.
- **Ibuprofen** may be associated with a small thrombotic risk at high doses (eg 2400 mg daily), whereas at low doses (eg 1200mg daily) evidence does not suggest an increased thrombotic risk in the short term.
- **Diclofenac** 150mg daily has a similar excess thrombotic risk to that of etoricoxib[▼] and possibly other coxibs.

Two recent epidemiological studies, reviewed in the February 2009 edition of Drug Safety Update⁶, provide further evidence that a thrombotic CV risk may apply to all NSAID users, regardless of their baseline risk, with the greatest concern being for chronic users of high doses (in particular coxibs and diclofenac).

Cardio-renal effects of NSAIDs (eg oedema, hypertension, heart failure) may also be important contributors to long-term CV risk. Clinical studies suggest that individual NSAIDs may differ in their cardio-renal effects. Etoricoxib[▼] may be associated with more frequent and severe effects on blood pressure (BP) than some other COX-2 inhibitors and NSAIDs, particularly at high doses, so the Committee on Safety of Medicines (CSM), now CHM, advised that etoricoxib[▼] treatment should not be initiated in patients whose hypertension is not under control, and that careful monitoring of BP is advised for patients taking etoricoxib[▼].³

Furthermore, the European Medicines Agency have recently advised that when prescribing etoricoxib[▼] for any indications, clinicians should be aware of the potential CV-related side effects, and have made the following recommendations:⁷

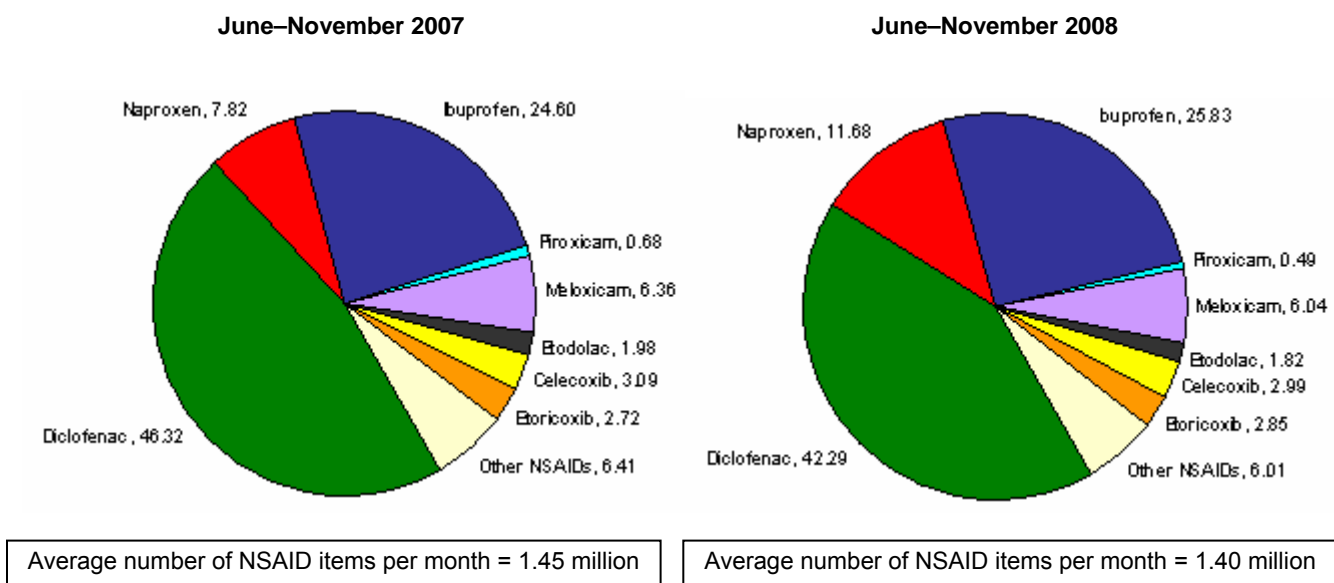
- Do not prescribe etoricoxib[▼] to patients whose BP is persistently above 140/90 mmHg and has not been adequately controlled.
- Monitor BP for 2 weeks after a patient starts etoricoxib[▼] and regularly thereafter.
- Monitor patients closely for signs and symptoms of CV side effects eg fluid retention, high BP, shortness of breath or chest pain.

The NICE OA guideline also recommends that when offering treatment with an oral NSAID/COX-2 inhibitor, etoricoxib[▼] 60mg/day (the maximum dose for OA) should not be a first-choice option.²

What do the prescribing data show?

When considering the prescribing data, we must look not only at the relative proportions of different drugs used, but also at the absolute amounts used. From a peak of over 5 million items per quarter throughout 2004, prescribing of NSAIDs in primary care in England has fallen to 4.2 million items in the quarter to November 2008. From December 2005–November 2008 there was a statistically significant reduction in the rate of NSAIDs prescribed ($P=0.017$), equivalent to a mean reduction over the 3-year period of 5.6%.

Figure 1 Proportions of NSAIDs prescribed (% of total NSAIDs) in two 6-month periods (June–November inclusive) in 2007 and 2008 in general practice in England



As shown in **Figure 1**, in the 6 months from June–November 2007, there was a decrease of 4% in the proportion of diclofenac prescribed relative to the total number of NSAID items prescribed, compared with the proportion prescribed in the same 6-month period 1-year earlier (from 46.3–42.3%). This was accompanied by a similar increase in the proportion of naproxen prescribed (from 7.8–11.7%). Although there were some changes in the quantities of other NSAIDs prescribed, the absolute changes were very much smaller, with the largest being ibuprofen (an increase of about 1%).

Questions for reflection

- Is this pattern of NSAID prescribing supported by the clinical evidence base?
- What is the pattern of NSAID prescribing in my practice/PBC/PCT?

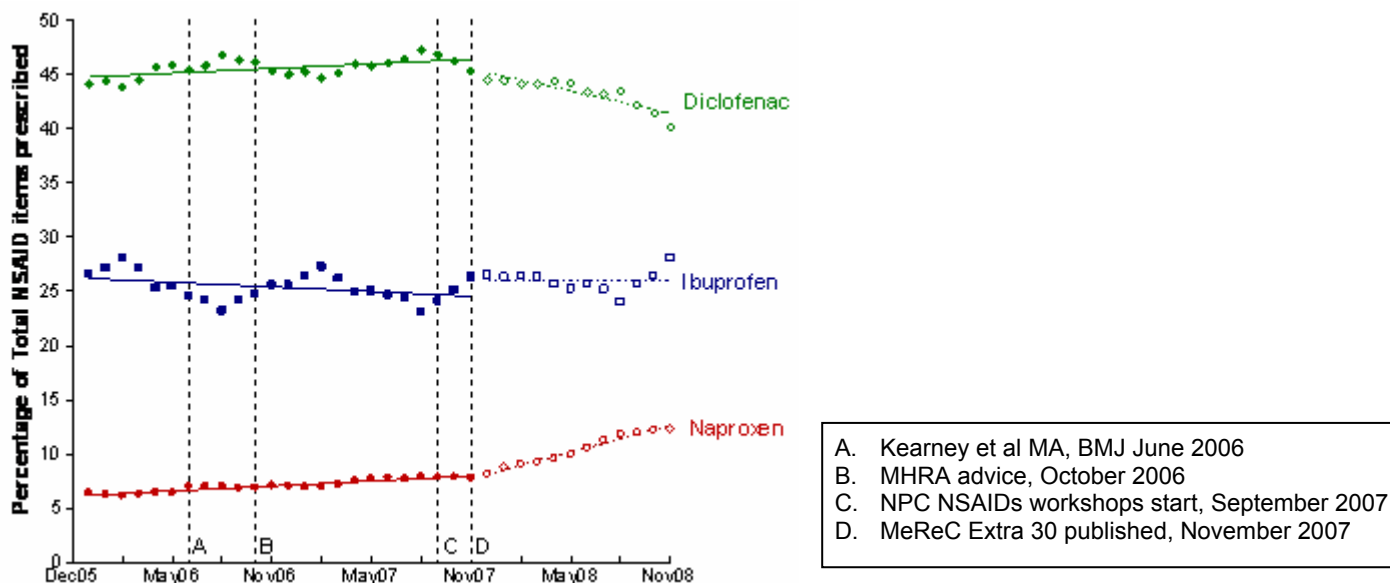
Bearing in mind that there does not seem to be a safe period over which there is no increased risk of CV events, and taking into account the high prescribing volume of diclofenac (approximately 2 million items per quarter in primary care in England) and the increased thrombotic risk being similar to that of coxibs (3 per 1000 patients per year), the prescribing of diclofenac could be associated with up to 2000 extra or premature CV events in England each year, compared with no treatment.¹

NPC initiatives

In the second half of 2007, in view of the CV risks associated with the high prescribing volume of diclofenac, here at the NPC we initiated a number of activities to raise awareness of the safety issues around the use of NSAIDs, and to encourage review of NSAID prescribing and more appropriate choice of NSAIDs, for patients based on an assessment of their CV and GI risk. In September 2007 a programme of NPC funded workshops was initiated, supported by educational materials produced by the NPC and MeReC Extra 30¹ which was published in November 2007.

Figure 2 Trends in the prescribing of diclofenac, naproxen and ibuprofen in general practice in England (December 2005–November 2008)

The lines represent the linear regression lines for the periods before and after November 2007.



- A. Kearney et al MA, BMJ June 2006
- B. MHRA advice, October 2006
- C. NPC NSAIDs workshops start, September 2007
- D. MeReC Extra 30 published, November 2007

Analysis of the changes in the proportions of NSAIDs prescribed each month before and after November 2007 identified a statistically significant change in rates of prescribing of both diclofenac and naproxen (both $p < 0.0001$). Before November 2007 there was a significant **increase** in the rate of diclofenac prescribing (0.07%/month; $p = 0.003$), whereas after November 2007 there was a significant **decrease** (0.33%/month; $p = 0.0002$), see **Figure 2**. There was a significant **increase** in the rate of naproxen prescribing both before (0.08%/month; $p < 0.0001$) and after (0.40%/month; $p < 0.0001$) November 2007. These changes are equivalent to a shift in prescribing rates of -4.9%/year for diclofenac and +3.9%/year for naproxen, relative to the total quantity of NSAID items prescribed. There was no statistically significant change in the rates of prescribing of ibuprofen before and after November 2007 ($p = 0.06$ and $p = 0.97$ respectively). However, there was an indication of a small upward shift (about 1%) in the prescribing of ibuprofen after November 2007 compared with the period before November 2007 ($p = 0.02$).

Figure 3 Prescribing of diclofenac in general practice in England (Dec 2005– Nov 2008)

The lines represent the linear regression lines for the proportion of diclofenac prescribed in England overall, before and after November 2007.

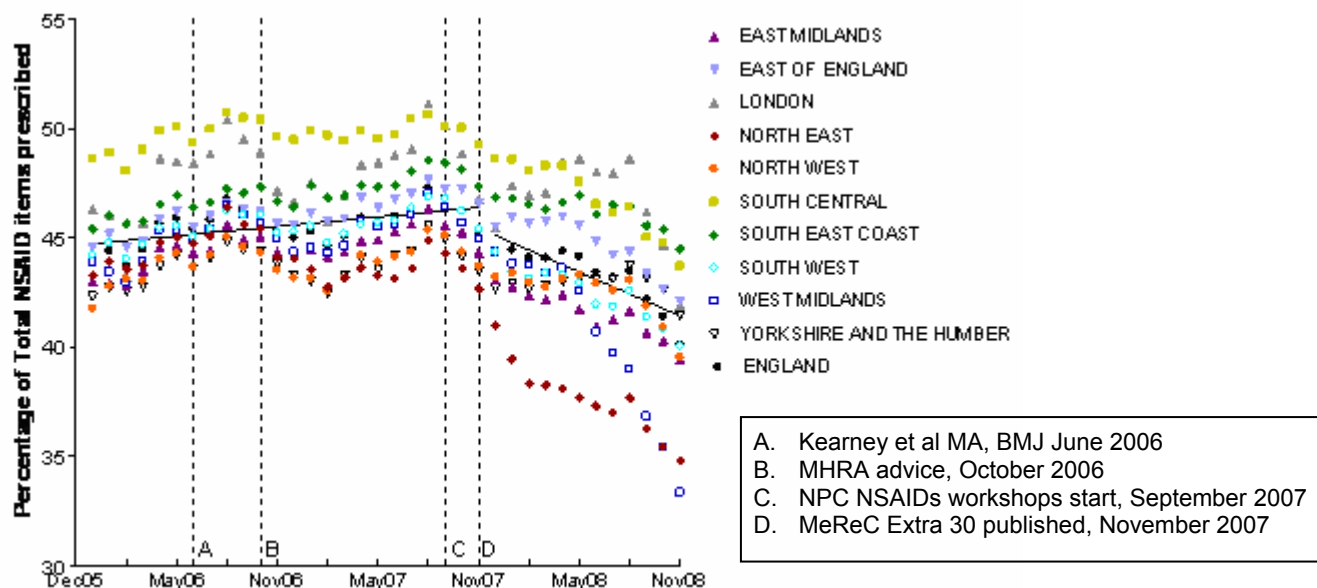
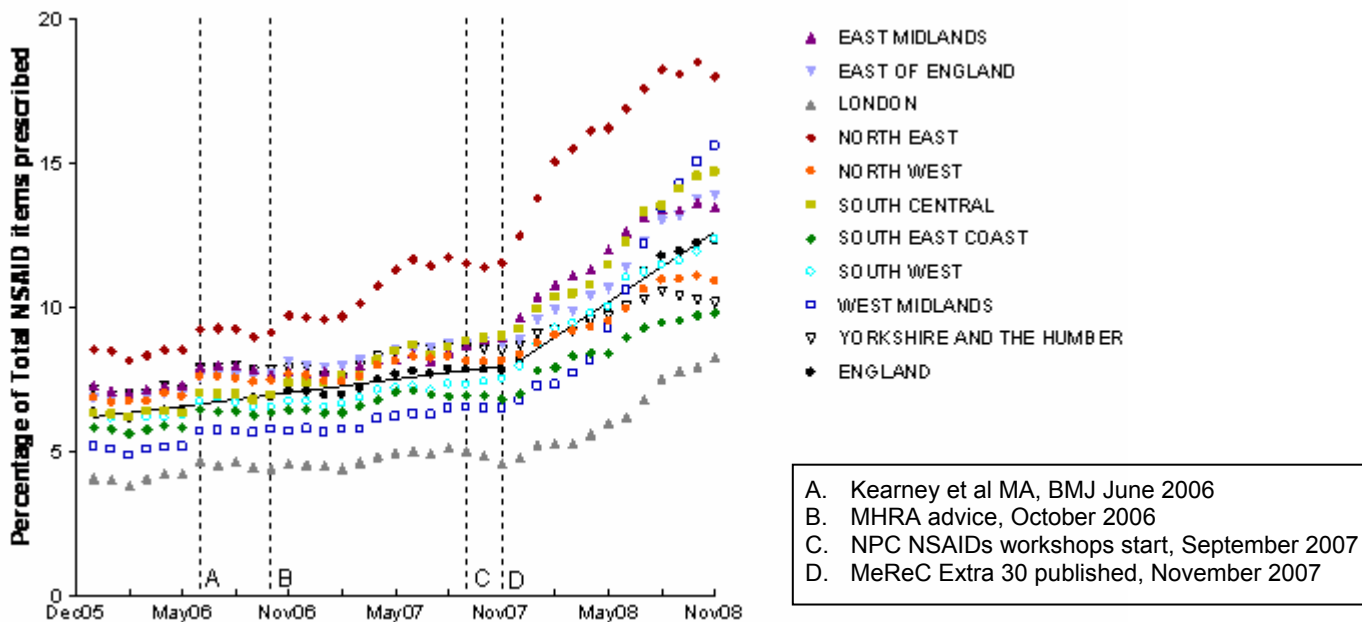


Figure 4 Prescribing of naproxen in general practice in England (Dec 2005– Nov 2008)

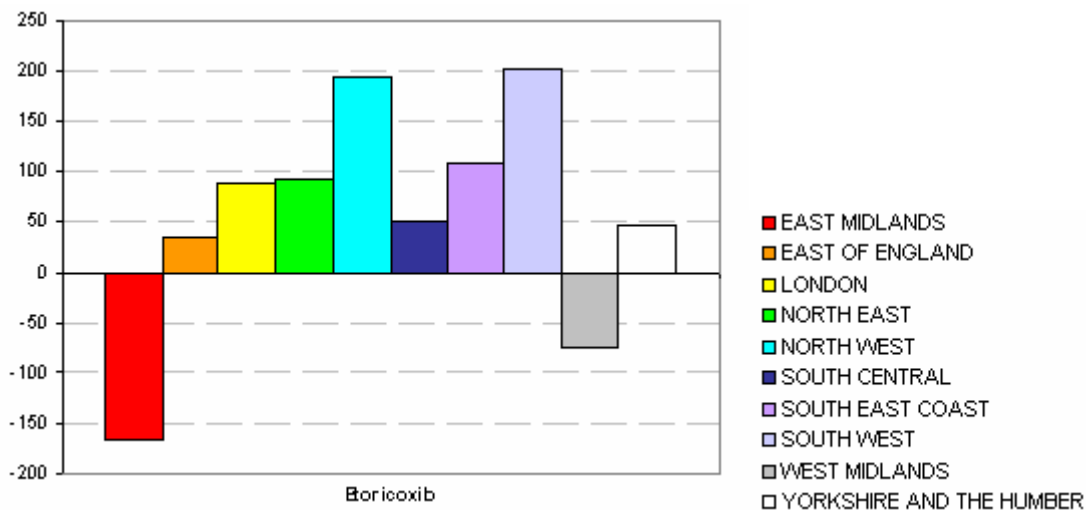
The lines represent the linear regression lines for the proportion of naproxen prescribed in England overall, before and after November 2007.



Absolute proportions and changes in the rates of prescribing of diclofenac and naproxen after November 2007 varied widely among individual strategic health authorities (SHAs), as shown in **Figures 3** and **4**. However, only in one case (diclofenac in Yorkshire and the Humber SHA) was there no statistically significant shift in the rates of prescribing for diclofenac (decrease) or naproxen (increase) identified before and after November 2007.

Figure 5 Change in prescribing of etoricoxib in general practice in England from June–November 2007 to June–November 2008

The bars represent the absolute change in the average number of NSAID items prescribed each month during the two 6-month periods considered.



There appears no justification for the increased prescribing of etoricoxib[▼] across all but two SHAs, on the basis of current evidence.^{1,3,7}

Question for reflection

- Are recommendations on the prescribing of etoricoxib[▼] implemented in my practice/PBC/PCT?

Implications for practice

Every prescribing decision must balance safety, efficacy, cost and individual patient preferences.⁸ The risk to an individual patient of serious GI or CV adverse effects from NSAIDs is low, but may be increased in the presence of other risk factors, such as age, previous CV or GI disease or certain concurrent medication. In attempting to avoid the CV risks associated with diclofenac, meloxicam, etodolac or the coxibs, we must take care not to increase the GI risks.

The ideal anti-inflammatory prescribing choice will vary from patient to patient, depending on individual risk factors, therapeutic response and patient preference. Patients should use the lowest effective dose, and the shortest duration of therapy necessary to control symptoms.¹

Because of the risk of adverse CV effects, coxibs would appear to have a very limited role in clinical practice. They are inappropriate to prescribe to patients who require aspirin for CV prevention because any GI benefits are diminished. They are also contraindicated in patients with any kind of existing CV disease. Co-prescription of a traditional NSAID with a PPI appears at least as effective as a coxib alone in reducing GI side effects, and is a less expensive option.¹

Although prescribing trends since November 2007 are encouraging, the use of diclofenac in the UK is widespread. There is an immediate need for reconsideration of its use ahead of low-dose ibuprofen or naproxen (with a PPI if appropriate), in people at risk of CV disease who require an NSAID.¹ Although there is nothing to indicate that diclofenac has higher risks than many other options, and the risk to an individual may be low, when used widely in the population the increased risk constitutes a significant risk to CV public health, and at the next routine review the choice of NSAID should be reviewed.¹

When reviewing the treatment of patients already receiving, for example, diclofenac, some patients, after discussion, may decide to continue treatment with their current medication. However, in some cases (especially patients with risk factors for arterial thrombotic disease) it may be appropriate to consider alternatives:¹

In summary then:

- Patients who change from eg diclofenac 150 mg daily to paracetamol 4 g daily would probably reduce both their GI and CV thrombotic risk.
- Patients who change from eg diclofenac 150 mg daily to ibuprofen 1200 mg daily would probably reduce both their GI and CV thrombotic risk, especially if the opportunity is taken to introduce a

PPI. High doses of ibuprofen (eg 2400 mg daily) are not prescribed frequently in clinical practice, and the relative risks versus diclofenac are unclear.

- Patients who change from eg diclofenac 150 mg daily to naproxen 1000 mg daily would reduce their CV thrombotic risk, but may slightly increase their risk of GI complications. However, if the opportunity is taken to introduce a PPI, the GI risks may also be reduced. There is less evidence for the balance of risks with lower doses of diclofenac and naproxen.

For patients at increased risk of GI side effects, and in whom use of an NSAID is needed for pain relief as other options have failed, low-dose ibuprofen (1200mg/day) is an appropriate first choice NSAID.

Naproxen would seem appropriate as an alternative for those at risk of CV disease.

Both should be prescribed with a PPI. The apparently increased rate of CV events with diclofenac and high dose ibuprofen (2400mg/day) suggests that, like coxibs, they are a less appropriate option for those at risk of CV disease.¹

Questions for reflection

- What processes are in place to ensure patients are reviewed at appropriate intervals?
- How can I go about improving the appropriateness and cost-effectiveness of prescribing?
- How will I know if the appropriateness and cost-effectiveness of prescribing increases?

Acknowledgment

The data used for the analysis reported in this data focused commentary was kindly supplied by the NHS Business Services Authority

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