NSAIDs and adverse effects Bandolier (1999)

NSAIDs are recognised as effective analgesics in acute and chronic pain and this is reflected in the NNT league table and in individual reviews. The evidence of effectiveness for NSAIDs is overwhelming when the test is comparison against placebo in acute or chronic conditions. But when it comes to which NSAID is the best in chronic conditions, we are in trouble. There are two

Cochrane reviews of NSAIDs in hip and knee disease. That on osteoarthritis of the hip [1] found 43 randomised comparisons, but the lack of standardisation of case definition and outcome assessments, together with multiple different comparisons meant that no conclusions could be drawn about which NSAID was best. The other similarly could not help us in choosing between NSAIDs for effectiveness in knee osteoarthritis [2]. There is also the interesting question of why the drugs should perform differently on knee and hip. NSAIDs are associated with a number of adverse effects. These include effects on the kidney, and exacerbating asthma in some people, but the most important adverse effect of NSAIDs and aspirin is that on the gastrointestinal tract. NSAIDs and aspirin cause gastric erosions which can become ulcers. These can cause symptoms of an ulcer in some people, the ulcers may bleed, and indeed some people may die of a bleeding ulcer caused by NSAIDs.

Balance benefits and harms

In using NSAIDs, we try to balance their benefits and harms. Most guidance stresses the use of simple analgesics, like paracetamol (acetaminophen) as a first line treatment for chronic conditions, with NSAIDs used later, perhaps with some protective agent to try to prevent gastrointestinal harm in those most at risk. This essay tries to bring together evidence on NSAID adverse effects and updates stories first published in **Bandolier** 52 **and** **53** .

What is missing is a comprehensive vision of the relative efficacy of NSAIDs and simple analgesics in osteoarthritis, rheumatoid arthritis, and other chronic pain conditions. The evidence is just not there yet, but as it emerges over the next few years (we hope), it will be added to the Oxford Pain Site pages.

Use of analgesics

A complicating factor with analgesics is that people self-prescribe because many of the drugs are available without prescription, in addition to taking them as prescription medicines. This complicates any analysis of the impact of these drugs on a population in terms of their adverse effects. An insight into the use of both prescription and non-prescription analgesics in Sweden is provided by a recently published paper looking at data collected in 1988/9 [3].

The survey was based on a random sample of the Swedish population aged 16 years and older, who were asked specific questions relating to analgesic use. The participation rate was 79%, and information was available from just under 12,000 people.

Results of the survey

In a report full of detail, the following picture emerges. Overall, 7% of men and 12% of women used prescription analgesics, while 20% and 30% used non-prescription analgesics. Use of prescription analgesics increased with age in men

and women (Figure 1), but use of non-prescription analgesics was similar in all age groups.

Figure 1: Prescription and non-prescription analgesic use in men and women in Sweden

Deeper analysis showed some fairly obvious relationships. For instance, headache and musculoskeletal pain were associated with increased use of analgesics, as were high levels of physical work stress, poor physical fitness and perceived poor health. In the previous 12 months, 13% of men and 20% of women had visited alternative therapists.

Prescribers' knowledge of NSAIDs

Medicine is a complex business. Audit can tell us about many of our activities in medicine, but occasionally more direct methods may be tried in order to assess the appropriateness of decision-making processes. To evaluate the extent to which NSAIDs are prescribed unnecessarily and how well NSAID-related adverse effects are diagnosed, a rather ingenious study was undertaken in Montreal [4].

Method

Two clinical scenarios were devised. One was of a 67-year-old person with a history of stiffness and pain in the right hip that radiated to the groin, taking 2.6 grams of paracetamol/day, plus some paracetamol/codeine combination, and with peptic ulcer disease and intolerance to aspirin. The other was a 67 year old with three week history of intermittent mid-epigastric pain, history of peptic ulcer, history of right hip osteoarthritis, and taking naproxen 1 g daily, plus ibuprofen in the past week.

Two men and two women were trained for each case to present the essential features (much more detail available than that given above), as well as to record details of visits to a physician using a structured questionnaire. The idea was to present standardised patients for clinicians to make diagnosis and management decisions.

Invitations to participate were sent to 34 GPs in a hospital-based family medicine residency programme, 32 family medicine residents in a program at McGill University, 29 internal medicine residents in a hospital-based teaching programme and a random sample of 82 GPs. Each physician was to see one to four patients over eight months. They were invited to send reply-paid cards if they thought they had identified the standardised patients.

Eight physicians, representing different disciplines, and taking into account published guidelines for prescribing, came to a consensus about what would constitute optimal, acceptable, suboptimal and unsafe management decisions for each case (Table 1).

Table 1: Consensus on prescribing decisions for standardised patients

Quality of management **Case 1: Episodic hip pain** **Case 2: NSAID-related gastropathy**
Optimal Increase paracetamol to 4 g/day, or nonpharmacological therapy Stop therapy with both NSAIDs
Acceptable Prescribe paracetamol and codeine ("d15 mg) or codeine ("d15 mg 3-4 times a day) Stop therapy with both NSAIDs and prescribe antiulcer therapy or reduce NSAID dose by at least half and prescribe antiulcer therapy
Suboptimal Prescribe NSAID with a gastroprotective agent or codeine (>15 mg 3-4 times a day) Reduce current NSAID dose by at least half with or without gastroprotective agent
Unsafe Prescribe NSAID without protection Continue with current dose of NSAIDs

Results

Most (63%) of the physicians approached agreed to participate, ranging from 40% ofcommunity-based GPs to 100% of academic affiliated GPs. There were 312 visits to 112 physicians, and in 36 cases (12%) the physician unblinded the study by guessing that s/he was seeing a standardised patient (real patients were suspected only twice).

Case 1

In 139 blinded visits, osteoarthritis of the hip was the diagnosis made 90% of the time, with optimal/acceptable management decisions being taken in 58% of visits. Management decisions judged to be unsafe were made in 22% of cases (Figure 2).

Figure 2: Physicians' treatment decisions

Case 2

In 137 blinded visits, NSAID-related gastropathy was diagnosed 93% of the time, with optimal/acceptable management decisions being taken in 78% of visits. Management decisions judged to be unsafe were made in 10% of cases (Figure 2). In both cases, longer visit times contributed significantly to the likelihood that a relevant history would be obtained, which, in turn, contributed to the likelihood that treatment would be appropriate.

How big is the problem of NSAID GI adverse effects?

NSAIDs cause ulcers in some people. Some of those who have ulcers also have symptoms, which include bleeding. In some of those who have bleeding ulcers, the bleeding is sufficiently severe to result in hospital admission, and may cause

death. This is a fairly simplified version of events, and many of the papers in this field have as many as 10 different classifications of upper gastrointestinal complaints from which to classify an event.

Clearly, the important issue is the overall incidence of severe adverse events, including hospital admission and death, however much we might like information about the risk of any particular event happening to any particular patient. The variables are drug and dose, duration of exposure, and patient characteristics.

Most of the publications referenced in this focus have reams about the scale of the problem of NSAID-related GI problems. They make good reading, and would repay the effort if someone were to pull the information together. But for those with little time, a flavour is given in Table 2.

Table 2: NSAID-related deaths and admissions to hospital

Event	UK	USA	Canada
Annual NSAID prescriptions	25 million	70 million	10 million
NSAID-related admissions	12,000	100,000	3,900
NSAID-related deaths	2,600	16,500	365

The burden of NSAID adverse effects in the UK

There are three large-scale surveys, each looking at about 1% of the population, which tell us about

the burden of NSAID adverse events in the UK [5-7].

Blower et al

A retrospective case-control survey of emergency admissions for upper gastrointestinal disease in two English general hospitals covering 1% of the UK population (in Rotherham and Stockport) gives some good estimates [5]. Records of all community deaths attributed to upper gastrointestinal disease were also surveyed. Matched controls were identified from emergency admissions for other causes.

There were 620 emergency admissions over one year in 1990/91, with controls for 460 cases. Controls were matched for GP practice, sex, age, and date of admission. Unmatched cases were retained in the analysis.

Results

Cases and controls were well matched, except for musculoskeletal disease (24% vs 3%). Cases were more likely to be using NSAIDs (31% vs 16%), H2-receptor antagonists (20% vs 5%), ferrous sulphate (9% vs 2%) and prednisolone (7% vs 3%).

Cases presented largely (59%) as haemorrhage (Figure 3), with a small proportion presenting as perforation, and 1% dying at home. Blood transfusion was required in 36% of all cases, and in 50% of those taking NSAIDs. NSAID users needed significantly more blood transfused than non-users. NSAID users also required a significantly longer stay (24% had a hospital stay of more than 14 days). NSAID users were more

likely to die: overall mortality was 20% in NSAID users compared with 14% in non-users.

Figure 3: Presentation of cases by number and percent of total

Extrapolation to the UK

These results suggest an overall incidence of upper gastrointestinal emergencies in the UK of 147 per 100,000 of the adult population, with an incidence of gastrointestinal haemorrhage of 87/100,000. This would indicate about 65,000 such crises a year in the UK. The study estimated that 1.9% of NSAID users in the Rotherham and Stockport area were admitted to hospital each year with upper gastrointestinal emergencies. The NSAID-attributable number of NSAID-associated emergency admissions in the UK would be about 12,000, with about 2,500 deaths.

The data from this study also gave age-related NSAID-specific incidence figures which have been used [8] to calculate the burden of hospital admissions for an average Primary Care Group of 100,000 people (Table 3). It shows that there would be 24 emergency admissions, and about five deaths, in any one year.

Table 3: Calculations of NSAID-related admissions for an average PCG

Age range (years)	Percent of total population	Number	Percent prescribed NSAIDs	Number prescribed NSAIDs	Annual incidence of upper GI crisis (%)	Annual number admitted to hospital from an average PCG	Annual UK total admissions
16-45	42	42000	5	2100	0.071	**802**	**2641**
45-64	19	19000	17	3230	0.146	**5**	**2224**
65-74	12	12000	19	2280	0.187	**4**	**1540**
>75	7	7000	22	1540	0.904	**14**	**6514**
				24	**12181**		

Data from Blower et al [5]; PCG - Primary Care Group of average size 100,000 people

Hawkey et al

Another study in Nottingham [6] prospectively interviewed 500 patients aged over 60admitted to the city's two hospitals with peptic ulcer bleeding over a five-year period. A structured questionnaire was used to determine NSAID use. General practice prescribing was also examined for patients admitted, looking at 103 general practices responsible for half a million people.

Results

Overall NSAID prescribing varied greatly, by about six-fold from lowest to highest prescribing practices, even when patient mix was taken into account. NSAID prescribing was the main determinant of emergency GI admissions from practices (Figure 4). Raw prescribing rates were

between 137 items per 1000 population and 833 items per 1000.

Figure 4: Relationship between NSAID-prescribing and rate of ulcer bleeding in the over 60s

The average admission rate for bleeding peptic ulcer was 15 per 100,000 per year. Analysis indicated a 0.23% (95%CI 0.08 to 0.31%) increase in the rate of ulcer bleeding of all causes in the elderly for each increase of 1 NSAID prescription per 1000 patients. This is equivalent to one episode of ulcer bleeding in the elderly per 2,823 (95%CI 2095 to 8116) prescriptions.

MacDonald et al

This cohort study from Scotland [7] looked at the relative risk of hospital admission for 52,000 people over 50 who received at least one NSAID prescription and 74,000 control patients who did not. About 2% of the NSAID cohort were admitted to hospital with a gastrointestinal event over three years, compared with 1.4% of controls - suggesting that about 0.2% of the over 50s population can be admitted in any one year because of NSAID-related gastrointestinal events. The risk of gastrointestinal bleeding or perforation was similar at all times after first day of NSAID exposure. There was therefore no evidence that

risks were higher with either acute use or with chronic exposure.

The cost of NSAID adverse events

For the NHS this has been explored in a recent economic analysis [8]. There are two main costs - those of hospital admissions with NSAID-related gastrointestinal bleeding, and the use of co-prescribing with acid-suppressing medicines. This paper used data from Blower et al [5] to provide the natural history of a person with NSAID-related hospital admission. It performed a literature search to estimate co-prescribing (which ranged between 17% and 34%, with an average of about 25%).

By using a range of possible co-prescribing rates and different percentages of histamine antagonists and proton pump inhibitors, the paper estimated the cost to a Primary Care Group, to the UK, and for any patient prescribed an NSAID (Table 4).

Table 4: Annual NHS costs for NSAID-related gastrointestinal adverse effects

	Primary Care Group		
	Low	**Medium**	**High**
	£,000		
Co-prescribing	220	365	563
Hospital costs	70	70	70
Total	290	435	633
	United Kingdom		

	Low	Medium	High
	£ million		
Co-prescribing	130	215	331
Hospital costs	36	36	36
Total	166	251	367
	Patient prescribed NSAID		
	Low	**Medium**	**High**
	£		
Co-prescribing	24	40	62
Hospital costs	8	8	8
Total	32	48	70

Who needs protection?

We know that NSAIDs cause ulcers. The average risks for gastric ulcers were 3.6% and 6.8% with <2 weeks and >4 weeks use of NSAIDs, and for duodenal ulcers the average risks were 3.0% and 4.0% with <2 weeks and >4 weeks use respectively [9] (**Bandolier 39**). The risk of developing serious GI injury was higher in a large clinical trial [10] which used a multiple linear regression model with 18 potential risk factors. It showed that risk factors for serious complications with oral NSAIDs were age 75 years or more, history of peptic ulcer, history of gastrointestinal bleeding and history of heart disease (Bandolier 25).

The model predicted that for patients with none of the four major risk factors, the one-year risk of a complication was 0.8%, for patients with any single risk factor it was 2%, and for patients with all four factors it was 18%. With combinations of

three of the factors, the one-year risk was 8 - 10%.
Age and sex were also highlighted as important determinants of risk of serious GI complications with NSAID use in a large case-control study [11]. Figure 5 shows the increasing odds ratios with age for all patients (60% men), and the increased risk for women over men.

Figure 5: Odds ratios for major gastrointestinal complications with NSAIDs by age and sex

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Are some NSAIDs safer?

Three reports indicate that some NSAIDs are associated with more harm than others [7, 12, 13]. One [12] is a meta-analysis of case-control studies, another [7] is a cohort study of about 130,000 people over 50 years in Scotland, and the third is a case-control study from Italy in which the source population was 780,000 people. They give somewhat different magnitudes of difference, but the direction is similar (Table 5).

Table 5: Relative risk of gastrointestinal complications with

NSAIDs, relative to ibuprofen or non-use (shaded)

Drug	Case-control studies [12]	Cohort study [7]	Italian case-control [13]
Nonuse	1.0		
Ibuprofen	1.0	1.0	2.1 (0.6 to 7.1)
Fenoprofen	1.6 (1.0 to 2.5)	3.1 (0.7 to 13)	
Aspirin	1.6 (1.3 to 2.0)		
Diclofenac	1.8 (1.4 to 2.3)	1.4 (0.7 to 2.6)	2.7 (1.5 to 4.8)
Sulindac	2.1 (1.6 to 2.7)		
Diflusinal	2.2 (1.2 to 4.1)		
Naproxen	2.2 (1.7 to 2.9)	1.4 (0.9 to 2.5)	4.3 (1.6 to 11.2)
Indomethacin	2.4 (1.9 to 3.1)	1.3 (0.7 to 2.3)	5.4 (1.6 to 18.9)
Tolmetin	3.0 (1.8 to 4.9)		
Piroxicam	3.8 (2.7 to 5.2)	2.8 (1.8 to 4.4)	9.5 (6.5 to 13.8)
Ketoprofen	4.2 (2.7 to 6.4)	1.3 (0.7 to 2.6)	3.2 (0.9 to 11.9)
Azopropazone	9.2 (2.0 to 21)	4.1 (2.5 to 6.7)	
Ketorolac		24.7(9.6 to 63.5)	

Note that the Italian case-control study (shaded) compares risk of gastrointestinal event with non-use, while the other two reports make the comparison with ibuprofen.

There are clear differences in risk with different NSAIDs, and some clearly are associated with

higher risks of upper gastrointestinal bleeding than others. The Italian study [13] demonstrates a particularly high risk with ketorolac, for instance. The Italian study also clearly demonstrates the fact that dyspepsia or antiulcer drug use, and previous ulcer diagnosis are major risk factors for upper gastrointestinal bleeding with NSAIDs (Table 6).

Table 6: Risk factors for upper gastrointestinal bleed with NSAID

Risk factor	Relative risk
No history of ulcer or antiulcer drug	1.0
Dyspepsia or antiulcer drug use	3.7 (3.2 to 4.2)
Ulcer without complication	5.3 (4.2 to 6.7)
Ulcer with complication	20 (14 to 28)

How effective are anti-ulcer treatments with NSAIDs?

In ***Bandolier*** 25, we gave the NNT for misoprostol to prevent one bleeding event compared with placebo in one year, the number-needed-to-treat as 83 (95%CI 55 - 160) in one large randomised trial. In ***Bandolier*** 39 we highlighted a systematic review which looked at gastric and duodenal lesions with NSAIDs and how misoprostol and histmaine antagonists affected them. Misoprostol was found to be effective at reducing gastric ulcers caused by NSAIDs (NNT 8 for less than 2 weeks

treatment), but was ineffective for duodenal ulcers. Histamine antagonists did not reduce the rates of gastric or duodenal ulcers in any clinically meaningful way (NNT about 30 in long-term trials).

Two further large RCTs have compared omeprazole with misoprostol, and with ranitidine and placebo. The first study [14] randomly assigned 935 patients who needed continuous NSAID therapy and who had ulcers or erosions to 20 or 40 mg omeprazole once daily, or 200 É g misoprostol four times a day. Healing over 4 to 8 weeks was assessed, and then patients with healed ulcers or erosions were randomly re-assigned to maintenance therapy of 20 mg omeprazole or misoprostol, or placebo, for six months. The second study [15] had a similar design, but with 20 and 40 mg omeprazole daily and 150 mg ranitidine twice a day in the healing phase, and randomisation of 432 patients to 20 mg omeprazole or 300 mg ranitidine a day in the maintenance phase, over six months.

Omeprazole 20 mg was more effective than misoprostol 800 É g a day. Compared with placebo the NNT for omeprazole 20 mg over six months was 3.0 (2.3 to 4.1), while for misoprostol 800 É g compared with placebo the NNT was 5.8 (3.8 to 12).

For omeprazole 20 mg compared with misoprostol 800 É g the NNT was 6.0 (4.0 to 12). For omeprazole 20 mg compared with ranitidine 300 mg the NNT was 6.2 (4.0 to 15).

These NNTs are impressive compared with those obtained for misoprostol previously [10]. But these

are different studies, and the two recent omeprazole studies [14,15] use patients with established ulcers or erosions, in which the baseline risk of an ulcer with NSAID is much higher than in the complete population. Though the population studied was not particularly old (mean late 50s), all had previous symptoms or established gastroduodenal problems (see ***Bandolier*** 39) .

What about H pylori?

Both Helicobacter pylori and NSAIDs cause ulcers, so there may be some interactions. The evidence up to now has been unclear, perhaps because there are so many different things going on in epidemiological studies. A randomised trial [16] indicates that perhaps eradicating the bug in people on NSAIDs may be a good thing.
Briefly, some 200 patients who needed NSAID treatment for musculoskeletal pain were tested for H pylori. Just over half were positive, and of these H pylori positive patients 47 were randomised to naproxen without eradication therapy. Another 45 were randomised to eradication therapy (which was effective in 40) before starting on naproxen (750 mg daily in all cases. Endoscopy was performed before treatment and after eight weeks. None of the patients had an ulcer before starting naproxen. After eight weeks, 12 of 52 patients (27%) who had not had H pylori eradication, or in

which it had failed had an endoscopically evident ulcer. Of 40 patients with successful eradication, only 1 (2.5%) had an ulcer. This gives an NNT of 4.1 (2.7 to 8.8) for preventing an endoscopic ulcer at eight weeks.
Now this is but one, small, RCT. The outcomes were endoscopic ulcer, not symptomatic ulcer, and the time-scale was short, but this is a significant straw in the wind. It suggests that H pylori eradication might be considered for those at highest risk and who are being started on long-term NSAID therapy.

What's the bottom line?

This focus has been on some of the bad things that can happen with oral NSAIDs. It is worth remembering that NSAIDs are excellent analgesics and anti-inflammatories, and bring huge benefits to many people who need them. But the gastrointestinal consequences of long-term NSAID use are not negligible. A US study [17] puts the human impact of NSAID-related gastrointestinal deaths into perspective: the rate is higher than that found from cervical cancer, asthma or malignant melanoma.

Figure 6: NSAID-related deaths compared with deaths from other causes in the USA, 1994

The evidence we have is that using paracetamol as a first-line agent is sensible. It is an effective and safe analgesic at therapeutic doses. It is worth remembering that NSAIDs given by topical routes are not associated with any of the gastrointestinal adverse effects seen with the oral route [18]. Meta-analysis has also shown them to be effective, with NNTs of about 3 in chronic conditions [19]. Thereafter the rule would seem to be to use ibuprofen for preference, at the lowest effective dose, and with mucosoprotective agents for those at highest risk of developing severe adverse gastrointestinal effects.

The risks are going to be highly age-related. Data from Table 3 can be used to calculate the annual risk of GI bleed, and, if the death rate of 17% from Blower et al [5] is assumed to be similar for all ages, the annual risk of death can also be calculated. For over-75s the annual risk of GI bleed with an NSAID is 1 in 110, and the annual risk of death is 1 in 650 (Table 7, Figure 7).

Table 7:

Age range (years)	Number taking NSAID	Number with GI bleed	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAID
		Risk in any one year is 1 in:		
16-45	2100	1	2100	12353
45-64	3230	5	646	3800

65-74 2280 4 570 3353
>75 1540 14 110 647
Data taken from Blower et al, 1997, recalculated for PCG of 100,000 people (Table 3)

Figure 7:

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