THERAPEUTICS

Non-steroidal anti-inflammatory drugs (NSAIDs)

Richard O Day,[1 2] Garry G Graham[1 2]

[1]Department of Pharmacology, University of New South Wales, Sydney, Australia
[2]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, Australia
Correspondence to: R O Day
r.day@unsw.edu.au

Cite this as: *BMJ* 2013;346:f3195
doi: 10.1136/bmj.f3195

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic for this series, please email us at practice@bmj.com.

A 70 year old obese woman asks if more can be done for her knee and low back pain, due to osteoarthritis. She used to smoke and has type 2 diabetes. Her orthopaedic surgeon does not consider the clinical presentation and radiographic changes in her knees severe enough for surgery. Her height is 160 cm, weight 85 kg, blood pressure 130/80 mm Hg, with normal renal function, plasma cholesterol concentration 5.5 mmol/L, and HDL cholesterol concentration 0.9 mmol/L. Her present drug treatment is paracetamol (4 g daily) and metformin.

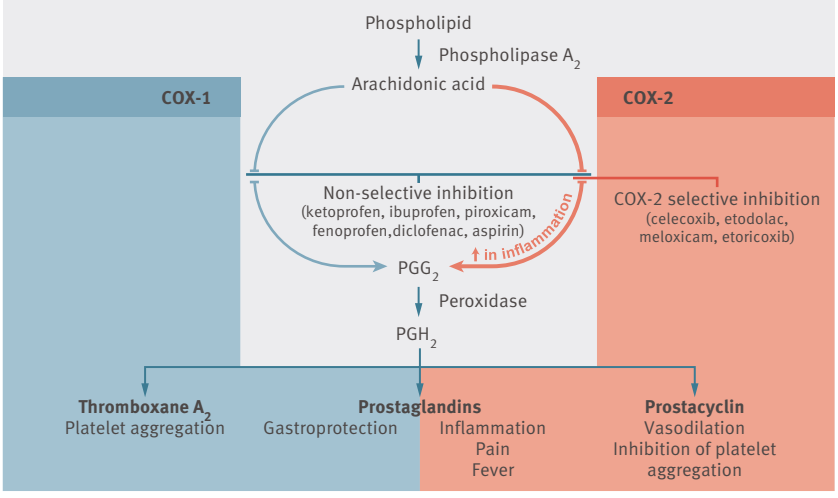
What are non-steroidal anti-inflammatory drugs (NSAIDs)?

NSAIDs act by inhibiting cyclo-oxygenase-1 (COX-1) and COX-2 enzymes, which are involved in prostaglandin synthesis, resulting in their analgesic, anti-inflammatory, and antipyretic effects (figure). Although the boundary is blurred, there are two broad groups of NSAIDs—the older, traditional, non-selective NSAIDs that inhibit both COX-1 and COX-2 and the newer, selective COX-2 inhibitors that predominantly inhibit COX-2 (figure). The non-selective NSAID aspirin is used primarily for its antiplatelet effect, thus reducing the risk of myocardial re-infarction and stroke.

How well do NSAIDs work?

Table 1 shows the indications and effectiveness of the various NSAIDs. There is little difference in their mean efficacy, although a review of individual patient data indicates that patients vary in their responses to different NSAIDs.[7] Effectiveness may vary with different conditions.

- For acute pain and dysmenorrhoea, meta-analyses indicate that both classes of NSAIDs are highly effective analgesics compared with placebo (table 1).
- For acute gout, clinical trials show that both groups of NSAIDs lead to a rapid relief of pain and inflammation, and are thus recommended by rheumatological associations.[8] Colchicine and corticosteroids are alternatives. Colchicine causes considerable diarrhoea and nausea, but a recent randomised controlled trial indicates that the new low dose (1.8 mg over one hour) for an acute attack has greatly decreased the adverse effects.[9]
- Both groups of NSAIDs play a useful but adjunctive anti-inflammatory role in rheumatoid arthritis, although disease control with antirheumatic drugs such as methotrexate and biological agents is critical.
- Both groups of NSAIDs are often used for osteoarthritis and low back pain; their effectiveness is generally small (Table 1). Patients often take either type of NSAID when osteoarthritis flares. It is generally considered that this approach reduces the risk of adverse effects. However, patients taking celecoxib, at least, report a better response without an increase in adverse effects when this is taken continuously, rather than just with flares.[10] A systematic review indicates that walking and strengthening of the quadriceps decreases pain and disability of osteoarthritis of the knee.[11] Weight loss in those who are overweight is also important for improvement in symptoms in osteoarthritis of weight-bearing joints.[4]



Arachidonic acid is metabolised by the cyclo-oxygenase isoenzymes COX-1 and COX-2 to intermediate prostaglandins (PGG_2, then PGH_2), which are then converted to other prostaglandins that are mediators of pain, inflammation, and fever, and are gastroprotective. Thromboxane A_2 causes platelet aggregation, and prostacyclin produces vasodilation. By blocking COX enzymes, NSAIDs inhibit the synthesis and thus the effects of prostaglandins, prostacyclin, and thromboxane A_2. The clinical effects of NSAIDs depend largely on their selectivity for these enzymes. Aspirin works by irreversibly inhibiting COX-1 mediated synthesis of thromboxane A_2, and is used to inhibit platelet aggregation

Table 1 | Indications and effectiveness for non-selective and selective NSAIDs. Comparisons are made against placebo and results are derived from systematic reviews

Clinical condition and treatment time	NSAID	Quantitative effect (95% CI)
Postoperative pain (including dental extraction); over 4-6 hours, single oral dose	Ibuprofen 400 mg	NNT 2.5 (2.4 to 2.6)[1]
	Diclofenac 50 mg	NNT 2.7 (2.4 to 3)[1]
	Naproxen 500 or 550 mg	NNT 2.7 (2.3 to 3.3)[1]
	Celecoxib 400 mg	NNT 2.5 (2.2 to 2.9)[1]
	Etoricoxib	NNT 1.9 (1.7 to 2.1)[1]
Sprains, soft tissue injury; over 7 days	Several, topical	NNT 4.5 (3.9 to 5.3)[2]
Dysmenorrhea	Several, oral	Odds ratio 4.5 (3.85 to 5.27)[3]
Osteoarthritis pain (knee); over 2-4 weeks	Several, oral, non-selective and selective	Effect size 0.29 (0.22 to 0.35)[4]
Osteoarthritis (knee); up to 12 weeks	Diclofenac, topical gel	NNT 11 (7.7 to 17)[5]
Low back pain; one week.	Several, oral	Benefit risk 1.19 (1.07 to 1.33)[6]

NNT = number needed to treat. That is, the number of patients who need to be treated with the active drug for one to respond with 50% pain relief who would not have done so with placebo. The smaller the NNT the better the treatment effect.
Effect size = difference between treated and control groups divided by the standard deviation of the groups. An effect size of 0.2 is considered small, 0.5 is moderate, and >0.8 is large.
Benefit risk = ratio of proportions of patients with >50% pain relief from active drug compared with proportion with >50% pain relief from placebo.

Table 2 | Adverse event rates for patients aged 55 at low baseline risk of gastrointestinal and cardiovascular adverse events[15]

	Mean (95% CI) adverse event rates per 10 000 patient years at risk				
Total daily dose of NSAID	Symptomatic ulcer	Gastrointestinal bleed	Myocardial infarction	Stroke	Heart failure
None	14	7	26	11	5
Diclofenac 100 mg	56 (41 to 74)	28 (19 to 39)	35 (26 to 44)	26 (18 to 34)	9 (5 to 13)
Naproxen 750 mg	112 (66 to 169)	30 (15 to 49)	26 (18 to 34)	32 (12 to 62)	34 (0 to 176)
Ibuprofen 1200 mg	80 (27 to 161)	30 (6 to 73)	61 (6 to 174)	24 (4 to 60)	34 (0 to 176)
Etoricoxib 30 mg	30 (21 to 40)	23 (14 to 33)	35 (25 to 46)	24 (16 to 34)	14 (7 to 22)
Celecoxib 200 mg	38 (11 to 80)	20 (4 to 50)	59 (8 to 162)	10 (2 to 25)	16 (0 to 87)

The adverse event rates were estimated from a model based on data from three major controlled trials on non-selective NSAIDs and COX-2 selective inhibitors on patients with rheumatoid arthritis and osteoarthritis. Note the wide confidence intervals suggesting substantial overlap between NSAIDs in their adverse event rates.

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Previous articles in this series

- Carbapenem antibiotics for serious infections (*BMJ* 2012;344:e3236)
- Bisphosphonates in the treatment of osteoporosis (*BMJ* 2012;344:e3211)
- Maintenance drugs to treat opioid dependence (*BMJ* 2012;344:e2823)
- Cholinesterase inhibitors and memantine for symptomatic treatment of dementia (*BMJ* 2012;344:e2986)
- Antimuscarinic drugs to treat overactive bladder (*BMJ* 2012;344:e2130)

Topical NSAIDs

Creams, solutions, gels, sprays, and patches of non-selective NSAIDs are widely used for their local effects, low systemic absorption, and considerable safety. For acute soft-tissue injuries (sprains, minor injuries, etc), systematic reviews have shown that topical products are more effective than placebo products (table 1). For effects on osteoarthritis, the most comprehensive data have been obtained with diclofenac. Although the results of clinical trials are variable, systematic reviews indicate that the available gel formulations of diclofenac provide greater relief of pain than placebo, though the improvement is small (table 1). They are recommended by the UK National Institute for Health and Care Excellence (NICE) for patients with mild or moderate osteoarthritis of the hand and knee, particularly for elderly patients.[12]

How safe are NSAIDs?

Harm from both types of NSAID is a major problem in osteoarthritis because of their prolonged use in the treatment of this disease. The absolute risk of adverse effects increases substantially in patients over 70 years old and with duration of use and size of dose, and is affected by individual risk factors, particularly for cardiovascular or gastrointestinal harm.[13-16]

Gastrointestinal adverse effects

A major adverse effect of the non-selective NSAIDs is serious injury to the upper gastrointestinal tract (perforations, ulcers, bleeding) (table 2).[13-15] The COX-2 selective inhibitors are also associated with upper gastrointestinal toxicity (table 2), but large controlled and observational studies and meta-analyses indicate this is significantly less than with non-selective NSAIDs.[13-16] The risks of serious gastrointestinal adverse effects, and in general the advantage of COX-2 selective inhibitors over non-selective NSAIDs (table 2), are less in patients with low background risks but increase with dose for both groups.[14] Modelling indicates that adding a proton pump inhibitor to an NSAID reduces the rate of upper gastrointestinal adverse effects, and (because of the small cost of adding a proton pump inhibitor and the savings from not having to treat gastrointestinal adverse effects) this is cost effective for both non-selective and selective COX-2 inhibitors in the UK at about £1000 per quality adjusted life year (QALY) based on UK prices for 2009.[15]

Despite the cost-benefit analysis, the routine use of a proton pump inhibitor with any NSAID is still controversial. If either type of NSAID is used long term in treating osteoarthritis, NICE recommends the concomitant use of a proton pump inhibitor,[12] whereas an advisory group recommends a proton pump inhibitor only for patients at high risk of toxicity in the upper gastrointestinal tract.[17]

Aspirin decreases the gastrointestinal tolerance of selective COX-2 inhibitors, although a selective COX-2 inhibitor plus aspirin may still be better tolerated than a non-selective NSAID alone.[16 18]

Dyspepsia is common with both types of NSAID, although a meta-analysis indicates that the risk is slightly smaller (12%) with the selective COX-2 inhibitors.[16] Many patients have decreasing dyspepsia despite continuing treatment with either type of NSAID.[16] It should be noted that the presence of dyspepsia does not predict peptic ulceration, bleeding, or perforation.

Long term treatment with both classes of NSAIDs may also cause bleeding and possible obstruction in the small intestine beyond the duodenum, even when taken with a proton pump inhibitor.[19] This problem is largely hidden, but in individuals taking NSAIDs long term, iron deficiency anaemia may indicate damage to the small intestine in the absence of damage to the stomach. There is now good evidence that both classes of NSAID exacerbate ulcerative colitis and Crohn's disease[19] and may injure the large intestine.

Cardiovascular adverse effects

Myocardial infarction

Overall, both NSAID classes, with the apparent exception of the non-selective NSAID naproxen, are associated with a significantly increased risk of myocardial infarction and coronary death. From a recent, very large meta-analysis of individual data from randomised trials,[14] this translated to three more major vascular events (mainly major coronary events) occurring in 1000 patients taking a selective COX-2 inhibitor or diclofenac for one year than seen with placebo, one of these extra events being fatal. This risk seems to increase with dose, although some uncertainties remain about the degree of risk with individual drugs and doses. The rate ratio for major vascular events was estimated from this study to be around 1.8-fold (1.76 (95% confidence interval 1.31 to 2.37) P=0.0001 for selective COX-2 inhibitors; 1.70 (1.19 to 2.41) P=0.0032 for diclofenac) and, importantly, seems not to be affected by an individual's background risk for vascular events. Thus, the higher the background risk, the higher the absolute risk will be on exposure to one of these drugs. These conclusions are supported by a cost effectiveness analysis of data from three large controlled clinical studies on NSAIDs (table 2)[15] and a recent network meta-analysis of a large number of randomised controlled trials.[20]

Naproxen seems to be the safest NSAID, with a similar rate of myocardial infarction as with no treatment (table 2).[14 15 20] The cardiovascular safety of naproxen cannot be guaranteed in all patients, but low dose naproxen (≤750 mg per day) is recommended when NSAIDs need to be used in patients at a low to a moderate risk of cardiovascular events and the patients are not taking aspirin (see comments on interactions with aspirin below).[21] Of the non-selective NSAIDs, there is broad agreement that diclofenac seems to have the greatest risk of myocardial infarction, similar to COX-2 selective drugs.[14 15 18 20] Ibuprofen is an example of uncertainty regarding individual NSAIDs: the recent meta-analysis shows a significantly increased risk of myocardial infarction at high

doses of about 2400 mg daily,[14] while modelling data from three trials found a statistically non-significant increase at 1200 mg daily for patients aged 55 years and at low risk of cardiovascular events (table 2).[15] This trend of no significant cardiovascular toxicity at low doses of ibuprofen but significant toxicity with higher doses was also evident in a systematic review of controlled, observational studies.[21]

Stroke

While controlled trials and a network meta-analysis show an increased risk of stroke with most NSAIDs (table 2),[15 20] the most recent and largest meta analysis of randomised controlled trials shows no increased risk with either COX-2 selective drugs or high dose non-selective NSAIDs.[14]

Interactions with aspirin; cardiovascular implications

The antiplatelet effect of low dose aspirin is blocked by all non-selective NSAIDs except diclofenac, provided that diclofenac is administered two hours after aspirin.[22] Selective COX-2 inhibitors do not block the antiplatelet effects of low dose aspirin. Low dose aspirin is used for patients at high risk of myocardial infarction, and there is obvious concern about the use of selective COX-2 inhibitors, which have adverse cardiovascular effects. However, low dose aspirin can be used concomitantly with, preferably, low doses of selective COX-2 inhibitors, as cardiovascular risk is considered to be lower with lower doses.[14 15 18]

Cardiac failure and renal impairment

As renal prostaglandins and prostacyclin are synthesised by both COX-1 and COX-2,[23] both classes of NSAIDs increase the risk of further renal impairment and of worsening cardiac failure (table 2)[14 15]—the latter being a particular risk for patients with renal impairment. For patients taking angiotensin converting enzyme inhibitors or angiotensin inhibitors, particularly those with impaired renal function, both classes of NSAID can lead to increased plasma potassium concentration and further deterioration in kidney function.[18]

Hypertension

All NSAIDs cause a dose dependent increase in blood pressure. The mean increase is around 2-3 mm Hg in systolic blood pressure, but it can be dramatic and may be greater in patients with hypertension or those taking angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β blockers, or diuretics.[13 24] The increases may be least in patients taking calcium channel blockers, but this is not conclusive.[24]

Aspirin induced asthma

A systematic review showed that taking aspirin reduces forced expiratory volume in one second (FEV_1) in about 20% of adults and 5% of children with asthma.[25] There is almost total cross reactivity with the non-selective NSAIDs. However, asthma has not been produced by selective COX-2 inhibitors in double blind challenge tests on asthmatic patients sensitive to aspirin,[26] although a few case reports of this exist.

Pregnancy

A large epidemiological study has found that both classes of NSAID may lead to abortion in the first trimester, with an odds ratio of 2.43 (95% confidence interval 2.12 to 2.79) compared with women not taking NSAIDs.[27] Both classes of NSAID may also delay labour and lead to premature closure of the ductus arteriosus, while non-selective NSAIDs may increase blood loss at delivery.[28] Pregnant patients should not take NSAIDs with misoprostol, which is a prostaglandin analogue used to prevent NSAID associated ulcers and may also induce miscarriage.

Rare adverse effects

These do not seem to be related to dose and include hepatotoxicity (particularly with diclofenac and ibuprofen). Aseptic meningitis has been reported mainly in patients with inflammatory diseases,[29] while serious skin disorders, such as Stevens Johnson Syndrome, have been reported very rarely with several NSAIDs.

How are NSAIDs taken and monitored?

Selection of NSAIDs

Discuss with patients any successes or adverse effects from previous treatments with NSAIDs. For future treatment, especially long term therapy, it is important to discuss the likelihood of success or toxicity in the light of the individual patient's background risks, signs of adverse effects, and other useful therapeutic measures, such as weight loss and muscle strengthening in the treatment of osteoarthritis (box 1). Some patients may prefer a treatment with a greater chance of efficacy than a safer treatment but with lesser efficacy. Some may prefer the converse.

Oral NSAIDs are second line drugs—For osteoarthritis and back pain, use paracetamol and topical NSAIDs before consideration of oral NSAIDs, particularly for prolonged treatment.

Elderly patients—For patients over 75 years old, advise use of topical rather than oral NSAIDs as far as possible.

Concomitant NSAIDs—Patients should be told to avoid additional oral NSAIDs, such as over the counter preparations, as increased total dose of NSAIDs is associated with higher risk of adverse reactions. Topical products and paracetamol can be used concomitantly.

High risk of gastrointestinal adverse effects—Risk factors include age >65 years; previous ulcer, gastrointestinal bleeding or perforation; other drugs known to increase upper gastrointestinal adverse events (anticoagulants, aspirin, serotonin reuptake inhibitors); corticosteroids; and serious comorbidities (hepatic, renal, or cardiac impairment, excessive alcohol intake, heavy smoking).[16] A proton pump inhibitor can be used with non-selective NSAIDs or selective COX-2 inhibitors. Misoprostol reduces the gastrointestinal adverse reactions of non-selective NSAIDs but is poorly tolerated because of diarrhoea and should not be used by women who may become pregnant.[30]

High risk of thrombosis (in patients taking aspirin)—If physical measures, paracetamol, and topical NSAIDs are insufficient, continue aspirin (emphasising compliance) and add low doses of a selective COX-2 inhibitor with proton pump inhibitor. Note that naproxen and ibuprofen block the antiplatelet effects of aspirin and diclofenac has a risk comparable to that of a COX-2 inhibitor.

TIPS FOR PATIENTS TAKING NSAIDS

- You may have used these drugs before, but it is important that you review their benefits and risks with your doctor
- Other measures such as weight loss and muscle strengthening are part of the treatment for osteoarthritis and are effective
- Make sure your doctor knows about other medications you are taking, especially blood thinners, aspirin, and any drugs that you are taking for arthritis
- Avoid other aspirin-like drugs such as ibuprofen, or combinations of ibuprofen with codeine or paracetamol. If in doubt, contact your doctor
- Make sure your doctor knows if you have had heart problems, stroke, kidney problems, or are being treated for high blood pressure, as NDAIDs may increase risk in these conditions
- Do not take more than is prescribed and use NSAIDs only as long as they are helpful
- Stop the medication and talk to your doctor if you have stomach discomfort or heartburn
- Keep an eye on your stools and report promptly to your doctor if they change colour to black as this may be due to bleeding from the gut

Cardiac failure or renal failure —Avoid all oral NSAIDs as far as possible; if considered essential, start an oral NSAID at the lowest dose and monitor cardiac and renal function closely.

Aspirin sensitive asthma—Avoid non-selective NSAIDs. Selective COX-2 inhibitors can generally be taken, although the first dose should be taken under medical supervision.[26]

Pregnancy—Avoid all NSAIDs as far as possible. Where NSAID use is essential, limit the dose during early pregnancy because of the risk of miscarriage and in late pregnancy because of the risk of delayed delivery and increased blood loss.

Lactation—Babies may be breast fed if either type of NSAID is used, as levels of celecoxib and ibuprofen are very low in breast milk.[31 32] This is likely to be the case for all NSAIDs.

Monitoring treatment with NSAIDs

Gastrointestinal adverse effects—If risk is high, monitor haemoglobin levels for 1-4 weeks after the start of treatment. At all times, measure haemoglobin if there are symptoms and signs suggestive of bleeding. If dyspepsia develops without signs of gastrointestinal bleeding, consider trying another NSAID or add a proton pump inhibitor.[15 18] Reinforce the value of taking an NSAID with food.

Hypertension—Check for increased blood pressure within 1-4 weeks if starting long term treatment with any NSAID in elderly patients or patients with hypertension.

Renal function—Check for increased plasma creatinine concentration and decreased estimated glomerular filtration rate after 1-2 weeks of starting treatment and then intermittently, especially in elderly patients and patients with cardiac failure.

Inadequate response—Check level of exercise and weight loss. Add topical NSAIDs for osteoarthritis or increase dose or change oral NSAID.

How do NSAIDs compare with other analgesics?

Paracetamol

For chronic conditions, such as osteoarthritis and back pain, paracetamol is generally recommended as first line treatment even though meta-analyses indicate that both groups of NSAID are, on average, superior in reducing pain. For example, the effect size for pain relief with paracetamol is estimated at 0.14 (95% confidence interval 0.05 to 0.22) compared with 0.29 (0.22 to 0.35) for NSAIDs (table 1). NICE recommends that combinations of paracetamol and opioids can be considered for treatment of osteoarthritis if the response to paracetamol is inadequate.[12] Paracetamol is not suitable for the treatment of acute gout or rheumatoid arthritis.

The reason for the preference of paracetamol is its superior tolerability compared with both classes of NSAID. Paracetamol has little gastrointestinal toxicity, minimal effect on blood pressure and renal function, no reported increase in the rate of myocardial infarction, and no effect on the antiplatelet effect of aspirin.[33] In patients with aspirin sensitive asthma, a systematic review indicates that paracetamol produces a mild reaction in about 7%.[25]

Opioids

These drugs should not be used as first line treatment of osteoarthritis because of their adverse effects such as constipation, drowsiness, and cognitive blunting. Use of opioids in elderly patients is also associated with a high incidence of falls and fractures. For example, the incidence of fractures was about 27 per 100 patient years in a large observational study on the use of codeine and other opioids by elderly patients (mean age 78 years) with non-malignant diseases.[34]

Alternative drugs for acute gout

Corticosteroids such as prednisolone or the old drug, colchicine, may be used when all NSAIDs are contraindicated.[8]

Case outcome

The patient is referred to a guided exercise and rehabilitation programme, given its value in increasing muscle strength and improving symptoms. Although she has no history of cardiovascular disease, her risk of myocardial infarction or stroke is still high at 30% in 10 years.[35] She is prescribed topical NSAID in addition to her full dose, regular paracetamol, as this should help reduce pain without adding to her cardiovascular risk. If her pain remains substantial, the topical NSAID could be replaced with oral naproxen (starting at low doses) because it has the lowest cardiovascular risk. A proton pump inhibitor should also be taken to protect the upper gastrointestinal tract (table 2). The patient's renal function is normal, and naproxen is thus not contraindicated. Occasional intra-articular injection of the knee with corticosteroids is also an option.

Contributors: Both authors contributed equally to the conceptualisation and writing of this article. ROD has expertise in medicine, clinical pharmacology, and toxicology. GGG has expertise in basic and clinical pharmacology. ROD is guarantor.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: ROD has been involved with consultancies with several drug companies on patents and advice on paracetamol, ibuprofen, selective COX-2 inhibitors, and other drugs used for osteoarthritis; all payments for consultancies were made to a trust fund at St Vincent's Hospital. Payment to ROD was made for expert testimony regarding a veterinary anti-arthritic product unrelated to NSAIDs. We acknowledge the assistance of the National Health and Medical Research Council programme grant (568612) for general research relating to patient safety.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

References are in the version on bmj.com.