

# Bandolier *Extra*

Evidence-based health care

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## NSAIDs, COXIBS, SMOKING AND BONE

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### Introduction

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*Bandolier* updates a previous review from December 2001. In the intervening years additional information has entered the literature, though little of it in the form of large, randomised, trials. The conclusion, then and now, is that apart from ketorolac, and possibly indomethacin, there is not much evidence that NSAIDs or coxibs make any difference to bone healing after surgery or trauma, unless perhaps continued for months. A more detailed look at smoking has been added. Smoking appears to have major effects on bone function, on risk of fracture, and on bone healing. The size of the effect would be a major confounding factor in investigations looking at coxibs or NSAIDs.

The main thrust of the review remains. It is directed at orthopaedic centres making decisions about the use of NSAIDs for postoperative analgesia after fractures or orthopaedic surgery, where there is concern about possible interference with bone healing. The purpose of this document is to examine the evidence for effects of NSAIDs on bone healing.

### Searching

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PubMed was searched using free text terms to detect reviews, RCTs and epidemiological reports relating to bone and fracture healing and the use of NSAIDs. This was updated in March 2004, and papers relating to smoking were also sought.

### Background

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Bone metabolism has a complex regulatory system that includes prostaglandins, produced abundantly by osteoblasts [1]. The balance of evidence from animal experiments suggests that prostaglandins favour bone formation. NSAIDs might therefore be expected to inhibit bone formation because they inhibit prostaglandin formation. The evidence for this is by no means conclusive, and some NSAIDs in some models have been shown to inhibit bone loss.

Disagreement might be a function of type of NSAID; propionic NSAIDs (ibuprofen, naproxen, ketoprofen) may prevent bone loss in some circumstances while acetic acid NSAIDs (indomethacin, diclofenac) may not. Dose and duration of use may also be factors. Experiments on rabbits (over 20 years ago) have shown that NSAIDs can inhibit fracture healing. Ketorolac has been implicated in failed bone fusion in spinal fusion experiments in rabbits.

Experimental work in animals seems, at best, to leave the role of NSAIDs and bone healing after fracture or operation uncertain. The evidence is sometimes contradictory, there are issues over drug dose and duration, and there is little evidence from clinical practice to support extrapolation to humans.

Recent interest has focused on the effects of the newer COX-2 selective NSAIDs, which are increasingly used for their better gastrointestinal tolerability. Again studies are almost all in animal models (rabbit, rat and mouse), involving fractures of the femur or tibia, spinal fusion, and a model for bone ingrowth (osteointegration), with comparisons between different COX-2 inhibitors (rofecoxib, celecoxib, parecoxib), non-selective NSAIDs (ibuprofen, indomethacin, ketorolac), and controls (water, saline, no treatment). Four studies showed no significant effect of COX-2 inhibitors compared to controls. Four other studies showed a significant effect of COX-2 inhibitors compared to controls. Ketorolac always gave the worst results, with other non-specific NSAIDs performing sometimes better and sometimes worse than the COX-2 comparator.

A real problem with experimental work in animals is that experts themselves do not agree about which model is best, and whether any model is predictive of the human experience. Extrapolation from these experiments to clinical advice about human practice is not sensible.

### NSAIDs and bone in orthodontic surgery

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Flurbiprofen appeared to increase bone formation in root-form implants in two patients [2], confirmed in a randomised study of 29 patients given flurbiprofen 200 mg a day or placebo for three months [3]. Flurbiprofen was without effect in a small randomised study after periodontal surgery [4] and naproxen did not increase bone healing in another study [5]. A more recent randomised, blind comparison of 25 mg rofecoxib daily plus enamel matrix proteins versus enamel matrix proteins alone for 14 days to promote regeneration in intrabony periodontal defects resulted in no different result [6].

In summary there is no convincing evidence that NSAIDs or coxibs have any major effects on bone in orthodontic surgery.

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## NSAIDs and heterotopic bone formation

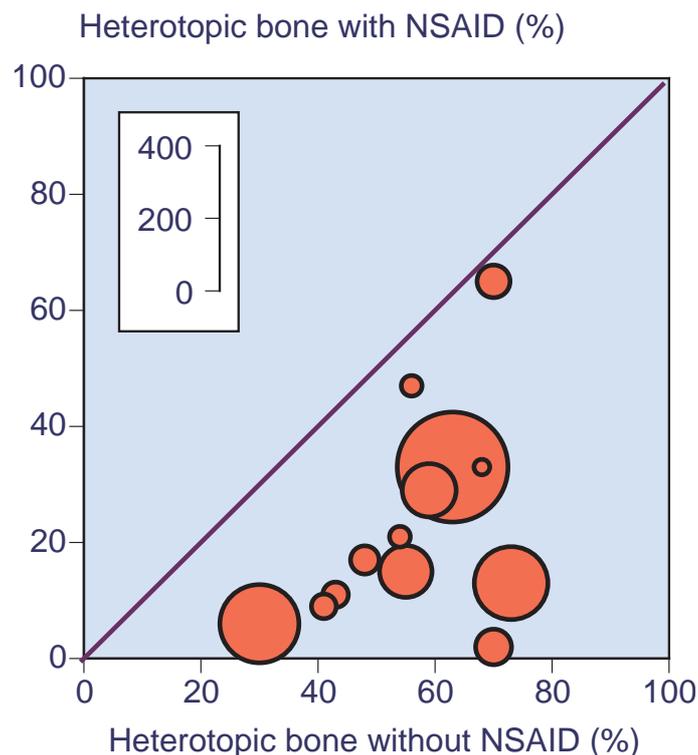
A Cochrane review has examined heterotopic bone formation after hip replacement [7]. It found 12 randomised trials, predominantly relatively small studies of medium to high dose NSAID, plus one large study of low dose aspirin. In 13 studies heterotopic bone formed in 182/806 (23%) patients with medium to high dose NSAID and 430/765 (56%) patients with control (Figure 1). The relative risk was 0.38 (0.33 to 0.44) and the number needed to treat to prevent heterotopic bone formation was 3.0 (2.6 to 3.4).

Most studies recorded heterotopic bone formation at least six months after operation. Duration, dose and type of NSAID used was not given, nor was there an analysis according to degree of heterotopic bone. Serious fatal and non fatal events were small in number (nine reported), but failure of bone healing was not mentioned. This might repay a more thorough review of these papers.

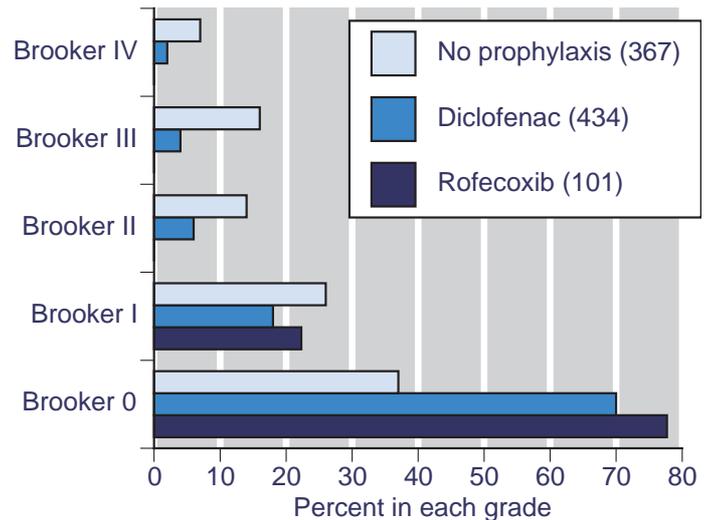
Low dose aspirin (162 mg a day) was without effect in a large (2,700 patient) trial [8]. In a detailed analysis that included NSAID use before and after operation (17% needed analgesics after the operation), there was no mention of association of NSAID use and failure of the hip replacement. Indomethacin has a similar effect on preventing heterotopic bone formation after spinal cord injury [9].

In a single randomised trial [10], a six-week course of 75 mg indomethacin a day produced similar prophylaxis as receipt of 800 cGy of local radiation within 72 hours of surgery. Another randomised study [11] found no difference between a course of 50 mg indomethacin daily and 7.5 mg meloxicam daily over 12 days.

### Figure 1: Heterotopic bone formation with and without NSAID after hip replacement



### Figure 2: Brooker grades with no NSAID, with diclofenac, and with rofecoxib.



But a note of caution has been raised by a possible link between bone non-union with indomethacin in patients with concomitant long bone fractures with hip replacement [12]. Patients at risk of heterotopic ossification were randomised to receive either radiation therapy or indomethacin. Of these, 112 had sustained at least one concomitant fracture of a long bone; 36 needed no prophylaxis, 38 received focal radiation and 38 received indomethacin. Fifteen patients developed 16 nonunions. When comparing patients who received indomethacin with those who did not, a significant difference was noted in the rate of nonunion (26% v 7%). Patients with concurrent fractures of the acetabulum and long bones who receive indomethacin had a significantly greater risk of nonunion of the fractures of the long bones compared with those who receive focal radiation or no prophylaxis. The problem is that this is one study with a small number of fractures. It could be just the random play of chance, or the presence of confounding factors like smoking, but it is important that it be independently confirmed.

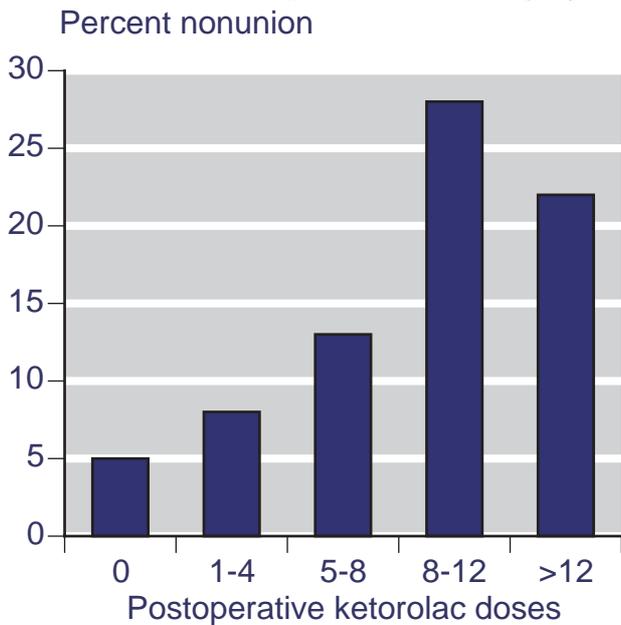
Selective cyclo-oxygenase-2 inhibitors also reduce heterotopic bone formation. We do not have randomised studies as yet, but brief reports indicate similar results with rofecoxib as with diclofenac [13] (Figure 2). With 101 patients treated with rofecoxib 25 mg daily for about a week, only Brooker grades 0 (no periarticular ossification) or I (bony islands within the periarticular soft tissue) were seen.

### NSAIDs and spinal fusion

The effect of ketorolac after spinal fusion was studied in a retrospective review of 288 cases [14] in a single centre. Patients had posterior spinal fusion between 1991 and 1992, and there was a minimum two-year follow up. Ketorolac was administered as a 60 mg intramuscular loading dose followed by 30 mg every 6 hours as needed. Seven patients given ketorolac had 2-20 (mean 8) additional 10 mg oral doses as needed.

Ketorolac was given to 167 patients, and no NSAID to 121. Patients having ketorolac received between one and 39 doses (mean 10) of ketorolac after surgery. The two groups were demographically similar.

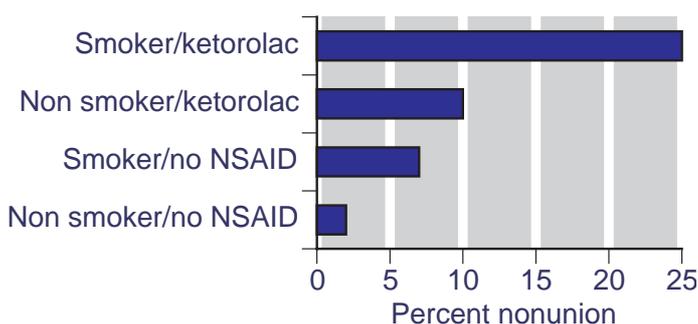
**Figure 3: Nonunion rate and postoperative ketorolac doses after spinal fusion surgery**



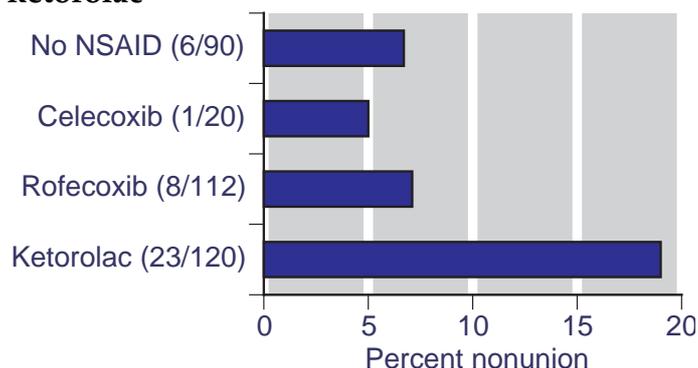
Nonunion occurred in 5/121 (4%) of patients having no NSAID and 29/167 (17%) of those receiving ketorolac. The odds ratio was 4.9 (1.8 to 17). The same degree of increased risk was seen in all subgroups. There was a dose-dependent relationship between nonunion rates and ketorolac doses (Figure 3).

There was an apparent relationship between postoperative use of ketorolac and cigarette smoking. The nonunion rate was 2% in those who neither smoked nor had ketorolac, 7% for those who smoked but did not have ketorolac, 10% for nonsmokers having ketorolac and 25% for those who both smoked and had ketorolac (Figure 4). In another study [15] smoking doubles the rate of nonunion in lumbar spinal fusion.

**Figure 4: Nonunion rate by smoking and ketorolac status**



**Figure 5: Nonunion rates with coxibs and ketorolac**



Reuben [15] had a low nonunion rate of 4.7% in 106 patients with posterior spinal fusion treated with rofecoxib 50 mg postoperatively for five days. Another analysis [16] showed no difference in success rates for spinal fusion between patients not treated with NSAIDs and those treated with COX-2 inhibitors rofecoxib or celecoxib in a retrospective study of 342 patients. There was no increased non-union rate with rofecoxib or celecoxib compared with non NSAID at about 5-7%, but ketorolac was significantly worse at 19% (Figure 5).

### NSAIDs and Colles' fracture

A randomised double-blind study of postmenopausal women with displaced Colles' fractures examined an eight week regimen of 20 mg daily piroxicam and placebo on recovery [18]. There was no effect on bone mineral density, and no decrease in fracture healing with piroxicam.

### Fracture nonunion and NSAID

A case-control study from Leeds of 32 patients with nonunion of fractured femur, and 67 comparable patients whose fracture had united, reported an association between use of NSAIDs after injury and delayed healing and nonunion [19]. There was evidence of increased non-union in long-bone fractures in patients given indomethacin for prophylaxis against heterotopic bone formation [12], but no effect of piroxicam in Colles' fracture [18]. The only other obvious literature reference was a single case report of indomethacin-induced delayed fracture healing from 30 years ago [20].

Several other studies of bone healing after fracture make no mention of NSAIDs:

- Nonunion among 67 ankle fusions in Houston was associated with open trauma, and with smoking, alcohol, diabetes or illegal drug use [21].
- A survey of 165 elderly patients with femoral neck fractures in Oslo noted technical issues associated with disturbed healing, but did not mention NSAIDs [22].
- A meta-analysis of the effect of reamed versus nonreamed nailing of lower leg bone fractures [23] examined a number of factors for nonunion, with higher nonunion rates being associated with studies of lower quality.
- Risk of nonunion for tibial shaft fractures in 100 consecutive patients from Gothenburg noted that high-energy trauma has a relative risk of 2 and open fractures one of 8. NSAID use was not mentioned [24].

### Smoking, fractures, and bone

We know that smoking is bad for us in many ways, and one of the ways is to decrease bone mineral density. Interference in bone healing, especially union after spinal fusion surgery, has already been seen in one analysis, and has been explored further in another [25] that retrospectively identified 357 patients who underwent a posterior instrumented fusion at either L4-L5 or L4-S1. Clinical out-

come and fusion status was analyzed in relation to preoperative and postoperative smoking parameters. The nonunion rate was 14% for nonsmokers and 27% for patients continuing to smoke after surgery. Patients who quit smoking after surgery for longer than six months had a nonunion rate of 17%. The nonunion rate was not significantly affected by either the quantity that a patient smoked before surgery or the duration of preoperative smoking abatement. Return-to-work was achieved in 71% of nonsmokers, 53% of nonquitters, and 75% of patients who quit smoking for more than 6 months after surgery.

There is growing evidence that smoking delays or inhibits bone healing after surgery or trauma. It delayed tibial shaft fracture healing, increasing median time for healing from 136 to 269 days [26], as well as after ulna-shortening surgery [27], though not all studies show dramatic differences [28]. Evidence that current smoking increases nonunion is seen in open tibial fractures [29] and hind foot fusions [30], and rates of non-union are often doubled in smokers.

Smokers have significantly reduced bone mass at all bone sites, averaging one-tenth standard deviation at all sites [31]. Deficits were especially pronounced at the hip, where bone mass of current smokers was one-third of a standard deviation unit lower than never smokers. Effects were greatest in men and the elderly, and were dose-related. This and another meta-analysis [32] showed that women who were current smokers were at increased risk for hip fracture. A new analysis [33] extends that analysis to men, to former smokers, and looks at where we live. It examined PubMed and EMBASE up to mid 2002 for any type of study relating to smoking and fracture that reported relative risk or odds ratio in smokers compared with non-smokers. If subjects had other major diseases they were not included. Smokers were categorised as current smokers (smoking daily), previous smokers (irrespective of when they stopped), and ever smokers, a combination of both.

The outcome was the occurrence of a fracture, with division into any fracture, or hip, wrist, or spine. Analysis was by age, gender and geographical region as well as by smoking status.

Fifty-one studies with 512,000 people were included in the analysis. Current smoking was associated with higher risk of any fracture, and hip and spine fractures, but not wrist fractures. Previous smoking was associated with increased risk only of hip fracture. Studies reporting on the amount smoked reported higher risk estimates the more that was smoked. Hip fracture risk was the same in men and women, for current and previous smoking.

**Table 1: Percentage of fractures attributable to smoking at different levels of smoking in a population**

Current smokers as % of population	Fractures (%) attributable to smoking		
	Hip	Spine	All
20	7	13	5
50	16	28	12

Latitude was a major influence (Figure 6). Studies in current smokers from northern Europe in had a higher risk for hip fractures than those from more southerly latitudes. Studies near the equator had no increased risk, and the risk from southern Europe, the USA and Mexico showed no statistically increased risk.

A clinically important fraction of fractures may be related to smoking (Table 1). Reducing current smoking would help prevent hip and spine fractures.

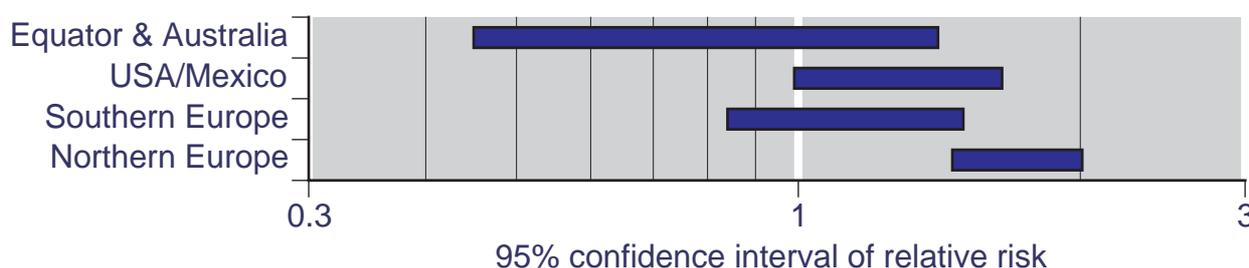
### NSAID and bone mineral density

Laboratory exploration of the effect of NSAIDs on bone metabolism has demonstrated that bone resorption can be affected through prostaglandin inhibition. One implication is that NSAIDs potentially could reduce bone loss and hence fracture risk.

A large study of aspirin and NSAID use on bone mineral density in 7,768 white women older than 65 years in the USA [34] concluded that bone mineral density was higher in users of these drugs. Risk of fracture was unaffected. The study had the benefit of being large, but aspirin and NSAID users were different from non-users. Osteoarthritis, rheumatoid arthritis, back pain and other conditions were much more common in NSAID users than nonusers. Adjustment of results for potential confounding can be difficult in circumstances where subjects and controls differ markedly. NSAID use did not affect the rate of excretion of markers of bone resorption [35], but bone mineral density at some sites was again found to be affected by proprionic acid NSAIDs in 84 older women [36].

We now also have a study on 2,800 older adults (mean age 74 years) that tells that concomitant use of cox-2 selective inhibitors and aspirin was associated with higher bone mineral density [37]. Whole body density was increased by 4%, hip by 5%, trabecular bone by 34% and cortical spine by 13%.

**Figure 6: Fracture risk and current smoking at different latitudes**



**Table 2: Fracture type, rates and relative risk for regular NSAID users versus controls (about 215,000 each group)**

Fracture type	Regular NSAID use		Control		Relative risk (95%CI)
	Number of fractures	Rate per 100 years	Number of fractures	Rate per 100 years	
Vertebral	808	0.1	192	0.03	2.9 (2.5 to 3.4)
All nonvertebral	10505	1.5	5793	1	1.5 (1.4 to 1.5)
Forearm	2516	0.3	1556	0.3	1.3 (1.2 to 1.4)
Hip	973	0.1	686	0.1	1.1 (0.98 to 1.2)

## NSAID and fracture risk

A large retrospective cohort study to examine NSAID use with fractures was conducted using the GPRD [38]. It looked at fracture risk in people using NSAIDs and compared that with people who did not use NSAIDs.

NSAID users fulfilling one or more prescriptions for an NSAID from 1987 up to end 1997 were included, and divided arbitrarily into those receiving three or more prescriptions and those receiving one or two prescriptions. A control group of people never having a prescription for NSAIDs was created by matching for sex, age, and practice (where possible). Systemic corticosteroid use was an exclusion criterion for users and controls. Information on about a dozen possible confounding conditions, and about a dozen possible confounding drug treatments was collected for each case and control.

After a prescription was filled follow up was until fracture or 91 days after the last prescription. Nonvertebral fractures were assessed by ICD codes and vertebral by radiography.

NSAIDs were prescribed for 501,000 patients, with 215,000 having three or more prescriptions for a median 3.4 years (regular users), and 287,000 having one or two having one or two prescriptions for a mean of 0.7 years (incidental users). There were 215,000 controls. Back pain and rheumatoid arthritis were more common in NSAID users than in controls. Incidental users were about 10 years younger than the mean age of 54 years for regular users and controls.

Nonvertebral fractures occurred more frequently in older women and the oldest men (Figure 7). For women fracture rates rose substantially after age 64.

Fracture rates with regular NSAID users were certainly not lower than controls. If anything, they were somewhat higher (Table 2) for vertebral and all nonvertebral fractures. Regular users had fracture rates no different from incidental users.

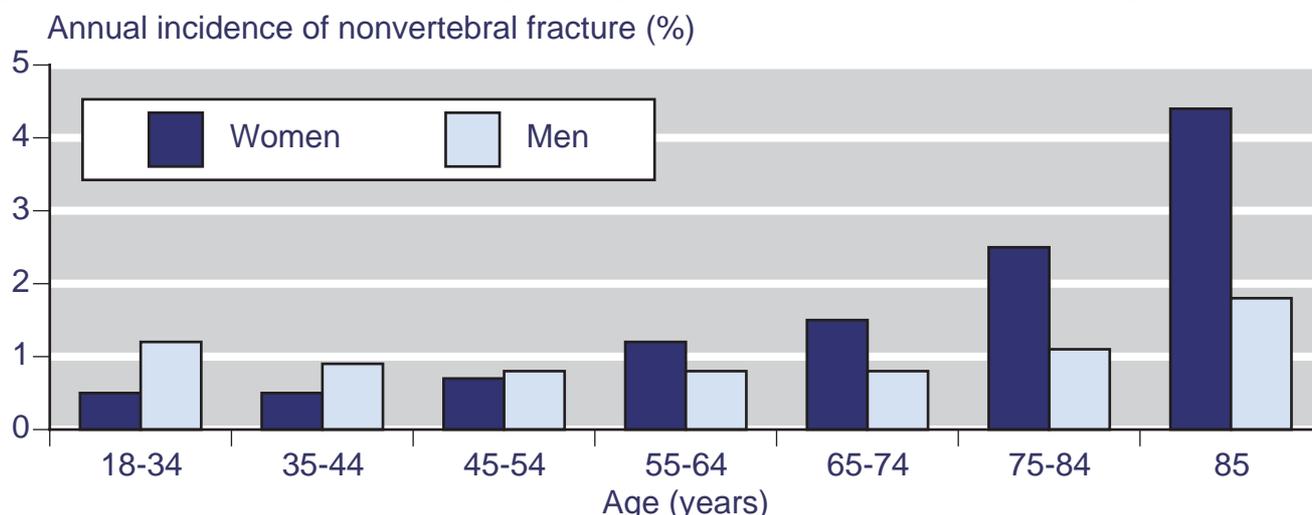
No NSAID was associated with higher or lower rates of fracture. Restricting analysis to patients with a history of arthropathy reduced the difference between regular users and controls for nonvertebral fractures, with a relative risk of 1.2 (1.1 to 1.3).

There is no major effect of NSAIDs on risk of fracture, though there were problems with confounding. While many confounding factors could be taken into account, but others, like diet, exercise or bone density could not. To properly take account of confounding factors you have to know what they are, and how much to adjust for them.

## Summary

Bone repair is a complex process initiated by injury and an inflammatory response. Prostaglandins mediate inflammation, influence the balance of bone formation and resorption, and are essential for bone repair. NSAIDs inhibit cyclooxygenases, which are essential for prostaglandin produc-

**Figure 7: Nonvertebral fracture rates per 100 years for women and men not using NSAID**



tion. Smoking is also a potent inhibitor of repair of bone injury, and of normal bone function, and will be an important likely confounder in any studies on the effects of NSAIDs on bone.

The animal experiments are interesting, but may not be relevant to clinical situations in men and women. For instance, the RCT on NSAIDs in Colles' fracture [18] was performed by researchers to confirm in man an inhibitory effect of NSAIDs on fracture healing seen in rats. There was no confirmation. Nor do epidemiological studies show much of an effect on NSAID or aspirin use on bone in man. If anything, bone mineral density is increased in regular users of NSAIDs or coxibs, and there is no increased fracture risk.

Those few strands of possibly pointing to clinical effects may be leading us astray and be confounded. But they have to be thought about before being dismissed.

One is NSAID use in spinal fusion surgery [14]. The problems with this retrospective survey include the choice of drug. Ketorolac, especially at the high doses given intramuscularly, is hardly representative of NSAIDs as a class. Intramuscular ketorolac at 30 mg is equivalent to 10 mg orally in analgesic effect [39], but gives a bigger body load of drug. It is particularly effective at producing gastrointestinal bleeding. Then there is the problem that patients needing ketorolac needed more postoperative analgesic, but we do not know whether that itself was a marker for some other pathology. Smoking could be an important confounder to this, and other retrospective information suggests that ketorolac may be specifically the problem, as impaired spinal fusion was not seen with selective cyclooxygenase inhibitors.

A second is studies suggesting that NSAIDs inhibit healing of fractures. A number of investigations into fracture healing fail to mention NSAIDs. Yet we have a few straws suggesting that there is an effect: the small study case-control study from Leeds suggesting that NSAIDs inhibit healing of fractured femur [19], the failure of long-bone healing with long-term indomethacin for heterotopic bone prophylaxis [12], and a single case report. These small studies might conceivably be confounded by the (apparently) much larger effect of smoking on bone healing. Unless the latter is controlled for, we can only guess about the former. The strong effect of smoking weakens any conclusions about NSAIDs.

There is no abundance of top quality evidence. None from randomised controlled trials, and what randomised trials there are show no effect, nor evidence from large good quality observational studies. The dogs not barking in the night are those from observational studies and case reports suggesting any link. Given the millions of orthopaedic operations performed and bone fractures every year, plus the frequent use of NSAIDs for postoperative analgesia, and available from pharmacists without prescription, is it credible that a major effect of NSAIDs on bone healing could be missed?

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