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Non-Steroidal Anti-Inflammatory Drugs: *A Suitable Case for Treatment?*

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DISCUSSION PAPER 133

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: A SUITABLE CASE FOR TREATMENT?

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April 1995

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Acknowledgements

The authors would like to thank Professor Michael Drummond, at the Centre for Health Economics; Dr Chris Hawkey, Professor of Gastroenterology at Queen's Medical Centre, Nottingham; Dr Peter Noyce, Professor of Pharmacy at the University of Manchester and Dr Ian Watt, Senior Research Fellow at the NHS Centre for Reviews and Dissemination, for their helpful comments on an earlier draft of this paper. Any errors and omissions of course remain the responsibility of the authors.

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are used widely throughout the world to relieve the symptoms of musculoskeletal disorders, in particular osteoarthritis and rheumatoid arthritis. These drugs produce significant side effects, including gastro-intestinal ulceration and the associated complications of perforation and bleeding.

The relative toxicity of competing forms of branded and generic NSAIDs vary considerably. Their cost also varies considerably, often with the relatively more toxic formulations being more expensive. These characteristics, differing toxicity and cost, offer the possibility of reducing both adverse effects to patients and pharmaceutical expenditure if doctors' behaviour can be changed.

A tentative exploration of alternative patterns of NSAID use demonstrates that it may be possible to reduce expenditure below the 1994 level of around £175 million and reduce adverse events. An illustrative model shows that if prescribing was reduced by 25 per cent, average dose reduced by 10 per cent and patients switched to less toxic NSAIDs, up to £86 million could be saved, the number of serious adverse events per year reduced by 189 and the number of gastrointestinal complications reduced by 127. Such results may be achieved without reductions in the quality of life of patients using these drugs.

Available clinical and economic information about NSAIDs is limited, with numerous published studies of poor quality which corrupt the knowledge base. Despite these problems there appears to be enough evidence to indicate that expenditure on NSAIDs could be considerably reduced and significant adverse effects could be avoided if general practitioners can be persuaded to change their prescribing behaviour. Inefficient and inappropriate prescribing of these often beneficial but sometimes dangerous drugs appears to be wasting scarce NHS resources and harming patients.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed throughout the world. Their use imposes high costs on all health care systems and on patients. The resource consequences of NSAID use do not result purely from the price charged but also from the prevention and treatment of the significant side effects which occur as a result of their use.

This exploratory analysis will investigate how the prescribing of NSAIDs can be made more cost effective. NSAIDs are associated with considerable purchase costs and also a significant rate of side effects. Both of these costs (monetary and non-monetary) vary greatly depending on which NSAIDs are used. Health care purchasers wish to be able to identify clearly those patient groups for which NSAIDs are suitable, to avoid those types of NSAID which result in a higher cost and incidence of side effects. This will allow them to minimise the costs imposed on their health care system and on its patients and carers.

In the first section of this paper some of the epidemiological evidence of the use of NSAIDs and the incidence of side effects will be investigated. Section 2 will explore how this situation can be changed, to prevent side effects and challenge the current use of NSAIDs and the evidence upon which this use is based. Section 3 tentatively explores the potential impact of a number of possible scenarios for changes in usage of NSAIDs, and Section 4 concludes with a summary of the need for improvements in the efficiency of NSAID prescribing, and the research base upon which prescribing decisions are made.

1. Epidemiological Background

1.1. What are NSAIDs used for?

Non-steroidal anti-inflammatory drugs are widely used to relieve the symptoms of musculoskeletal disorders, particularly osteoarthritis and rheumatoid arthritis. In

addition, they are prescribed to relieve the pain and inflammation of acute musculoskeletal injury (sprains and strains, and sports injuries) and menstrual disorders. They may also have a small role in the management of patent ductus arteriosus in the neonate (Wynne and Campbell 1994).

Arthritis is a common and chronic disease, which, according to the World Health Organisation, affects one in ten of the world population (WHO 1990). Arthritis and rheumatism are the most frequent self reported conditions in Great Britain, with a rate of 80 per 1000 females and 40 per 1000 males (OPCS 1989).

Wynne and Campbell (1994) suggest that half of all prescription use of NSAIDs is for the management of pain associated with degenerative conditions, particularly osteoarthritis. Approximately fifteen per cent of NSAIDs are taken for rheumatoid arthritis. This leaves around 35 per cent of NSAID use for other conditions.

The overall efficacy of different NSAIDs appears to be relatively similar - consistent differences in clinical effectiveness of individual NSAIDs has not been demonstrated (Wynne & Campbell 1994) although there is considerable variation in individual patient response (British National Formulary 1991). However, there are considerable differences between NSAIDs in the incidence and severity of side effects.

1.2. Side effects of NSAIDs

In the UK, 5 per cent of all prescriptions are for NSAIDs, and some NSAIDs are available in pharmacies without prescription. They account for 25 per cent of voluntary reports of suspected adverse effects to the UK Committee on the Safety of Medicines (CSM 1986). This level of side effects illustrates the need for safer and more efficient use of NSAIDs.

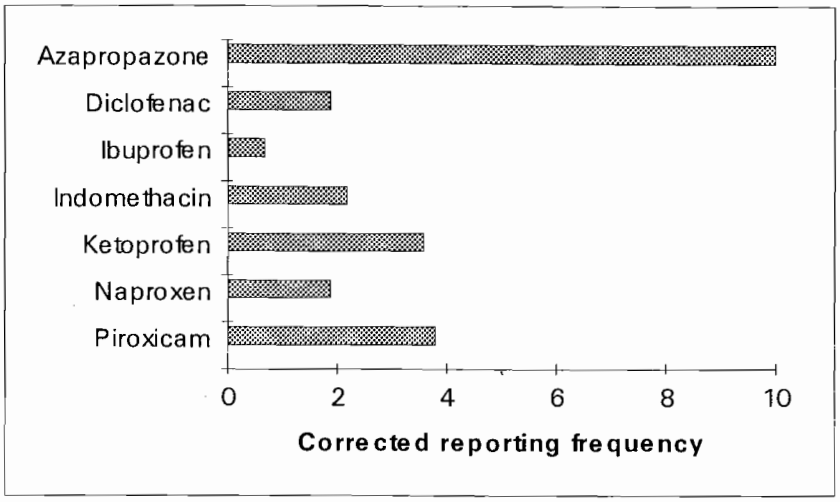
The side effects associated with treatment with NSAIDs are well known and their incidence has been reported for many years (e.g. CSM 1986, Paulus 1985). They include a variety of serious adverse reactions involving the kidney and liver, blood

disorders and allergy. Most commonly however side effects involve the upper gastrointestinal tract, including peptic ulceration and its complications of perforation and bleeding.

More recently, case control and longitudinal studies have provided information on the relative toxicity of individual NSAIDs (Fries et al 1991, Laporte et al 1991, Rodriguez & Jick 1994, Langman et al 1994). Evidence suggests that the risks of upper gastrointestinal reactions for different NSAIDs varies widely. The magnitudes of increased risk vary between studies, but there is some consistency in the rank order of risk for individual drugs. Ibuprofen is generally associated with the lowest risk of non-aspirin NSAIDs, although some newer (and more expensive) NSAIDs claim to have even lower levels of gastrointestinal risk, e.g. nabumetone (Bentkover et al. 1994). Intermediate risk drugs include diclofenac, indomethacin, naproxen and piroxicam. Azapropazone was associated with the highest risk in studies in which it was included (CSM 1994).

These epidemiological studies are supported by the 'yellow card' database of the UK Committee for the Safety of Medicines (CSM), which collects data on the frequency of adverse reactions to pharmaceutical products. The reporting frequencies for gastrointestinal reactions over the last five years are illustrated in Figure 1. Azapropazone was associated with the highest reporting frequency followed by piroxicam and ketoprofen. Lower reporting frequencies were observed with diclofenac, naproxen and indomethacin. Ibuprofen was associated with the lowest reporting frequency of gastrointestinal reactions. It is likely that due to the accepted incidence of these side effects, their reporting to the CSM is low and the actual incidence is considerably higher.

Figure 1: GI reactions 1989-1993. Reports per 100,000 prescriptions



Source: CSM 1994

Other adverse reactions tend to show a similar pattern (CSM 1994). Azapropazone is associated with the highest reporting frequencies for renal, hepatic, allergic and haematological reactions.

There is an important possibility of under-reporting with the 'yellow card' system. As NSAIDs are established pharmaceutical interventions, and the gastro-intestinal side effects are relatively well known, it is possible that UK GPs do not report every adverse reaction to NSAIDs, particularly for older established NSAIDs (including ibuprofen). This may be the case particularly since 1990, when the new GP contract was introduced in the UK, which is widely perceived to have increased GP workload and increased administration. Even at the reported level, NSAIDs have significant adverse reactions, and this is likely to be an underestimate.

Fries et al (1991) considered the relative toxicity of 11 different types of NSAIDs used in the US. Some of the drugs included (e.g. meclofenamate, salsalate) are not used in UK clinical practice. A Toxicity Index was developed, assigning weights to symptoms, laboratory abnormalities and hospitalisations both by side effect score and severity, and computing these into a single index number representing the toxicity of a particular medication. This number was then adjusted statistically for differences in length of

time on the drug regimen and for differences in characteristics of patients receiving different drugs to give a standardised toxicity index (STI score).

Applying this index to side effects reported in a study of NSAID therapy in 2,747 patients with rheumatoid arthritis receiving 5,642 courses of 11 NSAIDs over 8,481 patient years revealed startling differences in toxicity. The side effect profiles of different agents differed substantially - diarrhoea was more common with meclofenamate and tinnitus with aspirin. Combining these side-effects gave standardised toxicity index scores as follows:

Table 1: The Fries Standardised Toxicity Index Scores

Coated aspirin	1.19
Salsalate	1.28
Ibuprofen	1.94
Naproxen	2.17
Sulindac	2.24
Piroxicam	2.52
Fenoprofen	2.95
Ketoprofen	3.45
Meclofenamate	3.86
Tolmetin	3.96
Indomethacin	3.99

The authors of this study concluded that "there are substantial differences in overall toxicity between different non-steroidal anti-inflammatory drugs. The differences were clinically significant, with some drugs being 2-3 times more toxic than others. The differences were often highly statistically significant, were often larger after statistical adjustment for confounding variables, generally held across multiple data bank centers, and persisted when different weighting and scoring systems are used" (Fries et al 1991 p1358).

The differences in risk of severe adverse reactions between individual NSAIDs has been supported in more recent studies. Langman et al (1994) compared previous use of NSAIDs in 1144 patients aged 60 and over admitted to hospitals with peptic ulcer bleeding, and in 1126 hospital controls and 989 community controls matched for age and sex. Their results showed that peptic ulcer bleeding was strongly associated with the use of NSAIDs of any type during the three months before admissions. The authors also calculated odd ratios of individual NSAIDs, finding odds ratios for peptic ulcer bleeding were lowest for ibuprofen (2.0 [95% confidence interval 1.4-2.8]) and diclofenac (4.2 [2.6-6.8]), and intermediate for indomethacin, naproxen and piroxicam (11.3 [6.3-20.3], 9.1 [5.5-15.1], and 13.7 [7.1-26.3]. Azapropazone and ketoprofen carried the highest risks (31.5 [10.3-96.9] and 23.7 [7.6-74.2]).

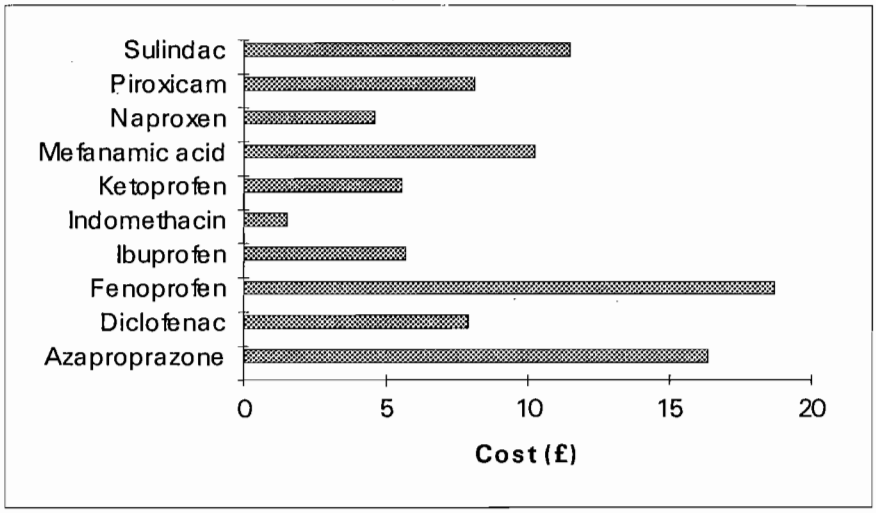
Rodriguez & Jick (1994) carried out a population based retrospective case control study to assess the variation in risk of upper gastrointestinal bleeding and perforation associated with various individual NSAIDs. Users of azapropazone and piroxicam were found to have the highest risk among the NSAIDs studied (23.4 [6.9-79.5] and 18.0 [8.2-39.6])

1.3. Costs of NSAIDs

The costs of NSAIDs are made up of the price charged for the drugs and also from the prevention and treatment of side-effects resulting from their use. The overall cost of NSAID prescriptions alone is considerable: in the UK in 1990 the number of anti-rheumatic scripts (mainly NSAIDs) totalled 23.3 million, at a cost of £219 million, that is approximately one in 20 NHS prescriptions.

The prices charged for individual NSAIDs vary considerably. Figure 2 (from Wynne & Campbell 1994) illustrates the approximate costs of 28 days' treatment with a selection of the individual NSAIDs available in the UK, at a typical daily dose. This shows a greater than tenfold difference in the price of non-aspirin NSAIDs, from £1.54 for 28 days treatment with indomethacin, to £18.73 for 28 days treatment with fenoprofen.

Figure 2: Approximate costs of 28 days treatment with individual NSAIDs in the UK



Source: adapted from Wynne & Campbell 1994.
Note: typical daily doses used: Sulindac 400mg; Piroxicam 20mg; Naproxen 500mg; Mefanamic acid 1500mg; Ketoprofen 400mg; Indomethacin 100mg; Ibuprofen 1800mg; Fenoprofen 1800mg; Diclofenac Sodium 75mg; Azapropazone 1200mg.

The purchase price of a drug does not however give a good reflection of its overall cost. In the case of NSAIDs, there are considerable costs associated with the prevention and treatment of side effects, particularly gastrointestinal side effects. For example, costs of treating gastric ulcer include endoscopy, biopsy, surgical interventions, hospital inpatient admission and use of medical treatments such as H_2 antagonists. Bentkover et al (1994) in a comparison of nabumetone and ibuprofen (with and without misoprostol) over three months in elderly patients with osteoarthritis suggest that the most cost-effective treatment does not necessarily require the use of the least costly drug.

Preventive measures such as prophylactic treatment with misoprostol alongside NSAID use can also incur considerable costs, but may, if appropriately targeted, prove cost-effective. Knill-Jones et al (1990) estimated that 3 months prophylactic treatment with misoprostol cost between £39 and £78 (depending on dose), and in 1994, the purchase price of the drug alone (Cytotec) is still £13 to £26 per month. The price of a combination drug including diclofenac and misoprostol (arthrotec) is also relatively

costly at around £15 for a 30 day pack. Misoprostol does however reduce the incidence of ulcers, and Knill Jones et al. (1990) found that under baseline assumptions, the use of prophylactic misoprostol actually reduced the overall cost of therapy over a three month period. Economic studies of misoprostol (among other antiulcer drugs) have been reviewed by Tucker and Nash (1994). Two other short term studies (Hillman & Bloom 1989, Gabriel et al. 1993) also showed misoprostol to be cost saving or cost neutral. However all three short term studies are sensitive to changes in parameters. A study of longer treatment duration (1 year) (Edelson et al. 1990) showed cost increases from misoprostol, and a high incremental cost-effectiveness ratio for misoprostol as primary prevention. The cost effectiveness of prophylaxis relies on targeting: misoprostol is likely to be more cost effective in high risk groups (such as the elderly or those with previous gastrointestinal bleeds), and the cost implications of using misoprostol for all NHS patients on NSAIDs are considerable.

2. How can side effects and costs be reduced?

There are four potential methods for the reduction of side effects resulting from NSAID use, and / or the overall costs of NSAIDs. These can be used individually or in combination, and are:

- discontinuing the use of NSAIDs in some patient groups;
- reducing the dose of NSAIDs;
- switching to less toxic NSAIDs; and
- use of prophylactic therapies.

The background to each of these potential policy options is set out in this section. In the next section the implications of some changed treatment scenarios are explored.

2.1. Reduction of the overall use of NSAIDs

There are some questions regarding the effectiveness of the use of NSAIDs in treatment of osteoarthritis. Evidence suggests that "analgesics are the mainstay of treatment for osteoarthritis with NSAIDs used only if analgesics prove to be ineffective" (OHE 1992). However, in practice half of the overall prescriptions of NSAIDs are used for osteoarthritis. This suggests that perhaps a total of over 10 million NSAIDs prescriptions are written in the UK for alleviating the symptoms of osteoarthritis. Is it possible that this total, with the associated cost and risk of severe adverse reactions, could be reduced?

Dieppe et al (1993) suggested that research into the treatment of osteoarthritis with NSAIDs has been misdirected. "We still know very little about the causes, diagnosis, natural history and appropriate management of osteoarthritis. Instead of a broad programme addressing these issues, research has focused almost exclusively on drugs, especially NSAIDs ..... Yet osteoarthritis has only a minor inflammatory component, and this inflammation is unlikely to contribute substantially to pain generation. The models adopted to develop osteoarthritis are irrelevant to osteoarthritis, but patients with this disorder are now the main recipients of these drugs" (Dieppe et al, page 353).

Simple analgesics offer an alternative to NSAIDs, with fewer side effects and at considerably lower cost. However, almost all trials of NSAIDs compare one NSAID against another: Dieppe et al (1993) could find only five peer-reviewed clinical trials of paracetamol against either NSAID or placebo in osteoarthritis (all of which did favour the NSAID), but trials comparing different NSAIDs are abundant. The authors suggested that the paucity of comparative studies of simple analgesics and NSAIDs "must be in the vested interests of the pharmaceutical industry" (ibid page 354).

Bradley et al (1991) carried out a randomised controlled trial where 184 patients with chronic knee pain due to osteoarthritis were given either 1200mg or 2400mg of ibuprofen per day or 4000 mg of acetaminophen (paracetamol) per day. Their results after four weeks showed improvements in all major outcome variables (pain scores,

walking distance and time, disability scores, physician impression) in all three groups. However, the magnitude of improvements between the groups did not reach statistical significance in most scores, including the walking pain score ($p=0.1$), and only just reached significance in the rest pain score ($p=0.05$). The authors concluded that in short-term symptomatic treatment of osteoarthritis of the knee, the efficacy of paracetamol was similar to that of ibuprofen, whether ibuprofen was administered in an analgesic or an anti-inflammatory dose. The authors of this study do not support the use of NSAIDs in the treatment of some types of osteoarthritis, particularly as their side effect profile suggests far greater gastrointestinal risks than those associated with the use of simple analgesics such as paracetamol.

Jones et al (1992) studied prospectively five hundred consecutive emergency admissions to a ward for the elderly in the UK. Their data suggested that for one in five of the patients presenting at a health care for the elderly ward, "NSAIDs could be implicated as a causative or exacerbating factor in the presenting condition" (Jones et al 1992 page 47). They argued that "one third of patients claimed to have derived no benefit from their use and indeed in some cases the original indication was no longer valid" (ibid. page 47). In this study, 75 per cent of the elderly patients on NSAIDs were successfully withdrawn from NSAIDs. Following cessation, 34 per cent of patients noticed no symptoms requiring intervention. The remaining patients received alternative treatments including analgesics (paracetamol / coproxamol) (60 per cent); local physiotherapy (11 per cent); muscle exercises (9 per cent) and appliances (8 per cent). This study supports the view that alternatives to NSAIDs should be considered and used, and if NSAIDs are necessary, regular review of their continuing requirement is essential, particularly in this high risk group (Jones et al 1992).

In rheumatoid arthritis (for which around 15 per cent of NSAIDs are consumed) treatment with NSAIDs appears to be more justifiable. Patients with mild and intermittent pain should however be treated with analgesics taken when needed, unlike NSAIDs which need to be regularly maintained in adequate doses to obtain their full therapeutic effect (OHE 1992). The efficacy of NSAIDs in alleviating symptoms in rheumatoid arthritis is the subject of a large number of reported studies.

However, the quality of many of these studies is questionable. Gøtzche (1989) attempted to carry out a meta-analysis of 196 trials of NSAIDs in rheumatoid arthritis, but found that the quality of methodology was inadequate and trials were often biased. Appendix 1 lists factors that may increase the number and the proportion of significant results favouring a new drug (Gøtzsche 1989). Rochon et al (1994) studied manufacturer-supported trials of NSAIDs in the treatment of arthritis including randomised controlled trials (RCTs) published between September 1987 and May 1990. Their results showed that the manufacturer-associated NSAID was almost always reported as being equal or superior in efficacy and toxicity to the comparison drug, but claims were often not supported by trial data. Support for the use of NSAIDs, even in rheumatoid arthritis, may therefore be questionable if clinical studies are methodologically inadequate if not biased.

Some prescribing of NSAIDs, particularly in the treatment of some patients with osteoarthritis, may be inappropriate and unnecessary. It has been suggested that many patients with osteoarthritis could be managed as well or better with simple analgesics such as paracetamol (Dieppe et al 1993). If the overall consumption of NSAIDs could be considerably reduced, this would reduce expenditure on both drugs and on the amelioration of their gastrointestinal side effects. In some patients it may be necessary to replace NSAIDs by other less toxic drugs (such as paracetamol) or by non-medical interventions such as physiotherapy. The assertion that the use of NSAIDs could be significantly reduced is contentious and requires further study.

2.2. Reductions in NSAID dose

The risk of gastrointestinal adverse reactions to NSAIDs have been consistently shown to be dose-related, and recommendations suggest that to reduce the risks of adverse reactions, the lowest effective dose should be used (CSM 1994). The cost of NSAIDs is also dose-related. Gøtzsche (1989) carried out a review of dose-response studies of NSAIDs in treating rheumatoid arthritis. Many of these studies suggested that most of the analgesic benefit of NSAIDs is obtained at low doses, with minimal increases in

benefit thereafter. This suggests that low doses of NSAIDs represent a better ratio of benefit to hazard.

Langman et al (1994) showed that in addition to the differences in risk of peptic ulcer associated with individual NSAIDs, risk also increased with drug dose (odds ratio [95% confidence interval]: low dose 2.5 [1.7-3.8], intermediate 4.5 [3.3-6.0] and high 8.6 [5.8-12.6]).

Kvien et al (1991) compared a standard fixed dose regimen and a patient determined dose regimen of naproxen for 396 patients with knee and hip osteoarthritis in a multicentre controlled trial. Efficacy measures included pain, stiffness, a functional index and patients' and doctors' overall assessments. Similar improvements were seen in both groups, but highly significant differences between groups in drug consumption was observed. The variable dose group had 20-30 per cent lower consumption than the fixed dose group. The authors concluded that "similar efficacy and possibly better tolerance was obtained with a lower drug consumption by a variable dosing regimen compared to a fixed regimen" (Kvien et al 1991).

It may therefore be possible to reduce the average doses of patients on NSAIDs, by ensuring that patients are started on the lowest possible dose. Such practice would reduce expenditure and the incidence of side effects resulting from NSAID use.

2.3. Switching to less toxic NSAIDs

Fries et al. (1991) clearly illustrated the substantial differences in the toxicity of individual NSAIDs. This has been supported in more recent studies (Rodriguez and Jick 1994, Langman et al 1994). The UK Committee on the Safety of Medicines recommends that drugs associated with low risk of adverse reactions should generally be preferred (CSM 1994).

The very large differences in the drug prices and the incidence of side effects of the individual NSAIDs (see Figures 1 and 2) creates scope for reducing costs and side

effects, even without reducing use or dose of NSAIDs, just by switching patients to less toxic drugs. The large variations in individuals' response to NSAIDs means that it may be inappropriate to use the least toxic drug in all patients, but as there are a number of less toxic NSAIDs, switching patients between a number of relatively less toxic drugs should be possible. A tentative illustrative example is explored below (Section 3).

2.4. Prophylactic therapies

The incidence of gastrointestinal side effects associated with NSAIDs has stimulated the development of therapies to prevent GI damage, including misoprostol and the use of prophylactic H_2-receptor antagonists such as ranitidine and famotidine. Wynne and Campbell (1994) review the cost of prophylaxis alongside NSAID use. Trial results suggest that standard doses of H_2 receptor antagonists may be effective in preventing duodenal ulcer but are much less effective in healing or preventing gastric erosion or ulcer formation induced by continuous NSAID therapy (Roth et al 1987, Ehsanullah et al 1988). French et al. (1994) carried out a meta-analysis of six placebo controlled studies to evaluate the use of ranitidine as prophylaxis for NSAID related duodenal and gastric ulceration. After four weeks of NSAID therapy, there was a significantly reduced frequency of duodenal ulceration in the patients taking ranitidine, but no significant reduction in gastric ulceration (which are more commonly caused by NSAIDs).

Prostaglandin E_1 analogues (such as misoprostol) do appear to have a significant mucosal protective effect against NSAID-induced complications (Aadland et al 1987, Graham et al 1988, Birnie et al 1988). They are effective when NSAIDs are continued. However, as there are some side effects to their use, particularly diarrhoea, as many as 25-30% of patients may discontinue their use.

Graham et al. (1993) carried out a multicentre randomised controlled trial of 638 patients with inflammatory and noninflammatory arthritis taking NSAIDs without gastric or duodenal ulceration at screening endoscopy. After 12 weeks, duodenal

ulcers were detected (by endoscopy) in 0.6 per cent of misoprostol patients and 4.6 per cent ($p=0.002$) of the placebo group. Gastric ulceration was found in 1.9 per cent of misoprostol patients and 7.7 per cent of the placebo group. The authors concluded that misoprostol significantly lowers the frequency of both duodenal and gastric ulcer development in patients who require long term therapy with NSAIDs. However, it is important to note that ulcers detected by endoscopy will not always result in symptoms and would not therefore always need therapy. Soll (1989) suggested that 40 per cent of endoscopically detected lesions greater than 0.5cm would not require treatment. For a pragmatic clinical study and for an economic evaluation, the relevant endpoint is symptomatic ulcers requiring therapy.

Silverstein et al. (1994) reported the preliminary results of the MUCOSA trial (Misoprostol Ulcer Complications Outcomes Safety Assessment). In this large randomised controlled trial around nine thousand patients requiring NSAIDs were randomised to misoprostol or placebo for six months. In the preliminary analysis of the intent to treat group, 67 gastrointestinal endpoints occurred, 42 in the placebo group and 25 in the misoprostol group ($p<0.05$). These authors also concluded that misoprostol significantly reduces gastrointestinal complications in patients taking NSAIDs for rheumatoid arthritis.

Hillman and Bloom (1989) evaluated the cost effectiveness of prophylactic use of misoprostol. Using assumptions of a 60 per cent compliance rate, 40 per cent silent ulcer rate and cost of medicine of less that $US 1.74 per day (1988 terms) the medication was cost saving for the first three months of prophylaxis, but data is unavailable after three months. Knill-Jones et al (1990) suggested that cost savings to the UK NHS could be obtained, but this is also a short term (three month) study. These economic studies were limited by the short duration of the clinical trials upon which they were based. A one year study by Edelson et al. (1990) showed additional costs resulting from use of misoprostol, with a high incremental cost effectiveness ratio for misoprostol used as primary prevention, decreasing if it is restricted to those who had experienced a gastrointestinal bleed in the previous year.

Wynne and Campbell (1994) point out that since about 22 million prescriptions for NSAIDs are written in Britain each year, the cost of co-prescribing misoprostol or ranitidine with each would exceed £600 million per year. This is clearly excessive, and the data sheet for misoprostol (Cytotec, Searle Laboratories, in ABPI 1990) suggests that misoprostol is indicated for the healing of duodenal and gastric ulcers including those induced by NSAIDs, and in addition it can be used for the prophylaxis of NSAID-induced ulcers. If it is used for prophylaxis, it is possible to identify other risk factors associated with gastrointestinal problems in patients receiving NSAIDs, including age, previous history of peptic ulcer, previous gastrointestinal bleeds and prior cardiovascular disease. It should therefore be possible to target prophylactic therapies at high risk patients. This will improve the cost-effectiveness of prophylactic medication.

3. An exploration of alternative NSAID usage

Whilst the clinical knowledge background is incomplete, it seems agreed that NSAID use could be reduced without loss of pain control and with considerable reductions in treatment side effects and costs. The purpose of this section is to explore a series of tentative scenarios which save significant sums of money and, from the literature, seem likely to reduce side effects whilst maintaining pain control. All these scenarios are exploratory, and represent potentially contentious changes in clinical practice, but they reveal the need for further study of appropriate NSAID prescribing.

3.1. Reduction in the overall use of NSAIDs

Table 2 shows the overall number of prescriptions of NSAIDs in the year to March 1994, and the overall expenditure on NSAIDs, highlighting the 'top 10' prescribed brands. In addition, using data from CSM 1986, the predicted number of side effects resulting from this level of prescribing is analysed.

In the year to March 1994, total expenditure on NSAIDs for musculoskeletal conditions was £173 million, with ten drugs comprising £127.6 million (around 75 per

cent of the total). This expenditure was made up of 23 million prescriptions. From this level of prescribing, there would be an expected 503 serious adverse reactions resulting from the use of the 'top 10' NSAIDs, 315 of these being gastrointestinal. For example, Voltarol (diclofenac) has a rate of adverse events of 39.4 per million scripts (CSM 1986). With 2.9 million prescriptions written during the year to March 1994, this gives 115 predicted adverse reactions.

Table 2: Current use of NSAIDs in the UK

	Sales £000	%	Scripts 000	%	ARs per million	GIs per million	Predicted ARs	Predicted GIs
Voltarol	52460	30.27	2922	12.58	39.4	20.9	115	61
Naprosyn	12723	7.34	845	3.64	41.1	32.8	35	28
Brufen	12308	7.10	1499	6.45	13.2	6.6	20	10
Oruvail	12073	6.97	631	2.72	38	33.2	24	21
Ibuprofen	8380	4.84	6188	26.64	13.2	6.6	82	41
Diclofenac	6703	3.87	2525	10.87	39.4	20.9	99	53
Surgam	6500	3.75	457	1.97	80	75	37	34
Lederfen	5878	3.39	298	1.28	69.4	35.7	21	11
Naproxen	5523	3.19	1719	7.40	41.1	32.8	71	56
Arthrotec	5076	2.93	530	2.28	?	?	?	?
Sub-total	127624	73.65	17614	75.84			503	315
Others	45658	26.35	5612	24.16				
Total	173282	100	23226	100				

Note: AR's - serious adverse reactions, GI's - serious gastrointestinal reactions

Approximately 50 per cent of all prescribed NSAIDs are used to reduce pain and inflammation from osteoarthritis (Wynne & Campbell 1994). Evidence tends to suggest that much of this prescribing is inappropriate, and the first line treatment for osteoarthritis should be analgesics such as paracetamol (OHE 1992, Bradley et al 1991). In certain patient groups, it seems likely that NSAID use in arthritis could be discontinued altogether (Jones 1992).

Reducing the overall level of prescribing of NSAIDs by 25 per cent (half of those patients treated for osteoarthritis) could save over £43 million in the costs of NSAID drugs alone. It may also reduce the number of serious adverse reactions per year by

126, and reduce the number of gastrointestinal reactions per year by 79 patients in the UK. This may be possible without reductions in the quality of life of osteoarthritis patients if NSAID use is replaced with analgesics such as paracetamol or non-medical therapies such as physiotherapy where appropriate. These medical and non-medical therapies may increase costs, but could be cost-effective if NSAID adverse reactions were avoided.

3.2. Reducing NSAID dose

Recent studies support the view that the incidence of side effects of NSAIDs is dose related (Langman et al 1994, Rodriguez & Jick 1994). Published guidelines recommend that patients should always be started at the lowest effective NSAID dose (CSM 1994). It may therefore be possible to reduce the average dose level of NSAID prescribing, both by ensuring that new patients receiving NSAIDs are started on the lowest possible dose and by reducing the dose of selected patients, from high to medium dose, or from medium to low dose.

The purchase price of NSAIDs appears to increase proportionately with increased dose (MIMS 1994). If, it were possible to reduce the dose of certain patient groups, and start new patients at low doses, it may be possible to reduce the overall average dose of NSAIDs. For example, reducing the average dose of all NSAIDs by 10 per cent or 20 per cent could save expenditure on pharmaceuticals of £17.3 million or £34.6 million respectively in the UK. Assuming that overall numbers of side effects were reduced by 5 and 10 per cent (half the reduction in dose), 25 to 50 serious adverse reactions per year could be avoided, or 16 to 32 serious gastrointestinal reactions. Further study is required to investigate the potential for dose reduction without reducing the pain control or mobility of patients.

3.3 Switching to less toxic NSAIDs

Evidence indicates that ibuprofen is the least toxic of the non-aspirin NSAIDs (CSM 1986, CSM 1994, Fries et al. 1991, Langman et al. 1994, Rodriguez & Jick 1994).

Guidelines suggest that patients should be started on the least toxic NSAIDs (CSM 1994). While it is clear that individual patient response to the different NSAIDs varies considerably (British National Formulary 1991), it may be possible to switch patients to less toxic NSAIDs, reducing costs and side effects without reducing the use of NSAIDs or using prophylactic medications.

For example, using the UK data in Table 2 above, switching patients from more toxic drugs to generic ibuprofen has a significant impact on costs and side effects. Maintaining the current overall level of prescriptions (23.2 million per year) but switching patients so that generic ibuprofen accounts for 50 per cent of all prescriptions (from its current 26 per cent), and reducing all other brands proportionately (to 68 per cent of their current level) reduces overall drug expenditure by £45 million (26 per cent). In addition, serious adverse reactions could be reduced to 440 (by 12.5 per cent) and gastrointestinal reactions to 263 (by 16.5 per cent) per year.

The above estimates of cost savings all include only the costs of the prescribed NSAIDs. However, it is clear that direct health care costs resulting from treating the side effects of NSAIDs are considerable (Knill Jones et al. 1990, Bentkover et al. 1994 and others). If the costs of treating adverse reactions were included, cost savings from reducing NSAID use, reducing average doses or switching to less toxic NSAIDs would be even greater.

3.4. Use of prophylaxis

The use of prophylactic medications such as misoprostol or H_2 antagonists alongside NSAID prescription is becoming more widespread. Arthrotec, a combination of diclofenac and misoprostol, represented 2.3 per cent of all NSAID prescriptions in the UK in the year to March 1994. Misoprostol and other protective agents (such as H_2 antagonists) are also prescribed alongside other NSAIDs.

There have been a number of studies assessing the efficacy of ulcer prophylaxis, and studies have also attempted to assess the cost effectiveness of this preventive measure (Knill Jones et al 1990, Hillman and Bloom 1989). These short term studies show that under certain conditions prophylaxis can be cost effective or even cost saving. However, longer term studies such as Edelson et al. (1990) show increased costs from primary prevention, and illustrate the need to target prophylaxis.

To ensure the cost effectiveness of prophylactic drugs it is essential that they are targeted appropriately at high risk patients. There are a number of accepted risk factors for NSAID related ulcers, including increasing age, multiple NSAID use, male sex, smoking and history of ulcers (Rodriguez and Jick 1994). To maximise the effect of prophylaxis, this should be targeted carefully at high risk patients using accepted risk factors. Without this targeting, prophylaxis will become expensive and inappropriate.

3.5. Potential for economic benefits

Combining these recommendations (reducing prescribing of NSAIDs, reducing dose, switching to less toxic NSAIDs and using targeted prophylaxis) could have a major impact on the overall costs and benefits of NSAID use.

For example, using the data on sales and side effects in Table 2, and combining the above scenarios could have a considerable impact, i.e.:

- *reducing overall levels of prescriptions by 25 per cent;*
- *reducing the average dose by 10 per cent;*
- *switching patients to less toxic drugs, so that 50 per cent of all prescriptions are for ibuprofen, reducing the level of all other NSAIDs proportionately.*

This reduces the total expenditure on NSAIDs to £86.48 million (approximately half its current UK level) and reduces the number of serious adverse reactions and gastrointestinal reactions to 314 and 188 respectively (62 per cent and 59 per cent of

their current levels). Targeting the use of prophylaxis may reduce the number of side effects even more, and increasing the proportion of generic drugs prescribed could further reduce costs.

The scenarios suggested above are summarised in Table 3. These illustrative scenarios illustrate the resource consequences of changed NSAID treatment regimes. Policy makers could usefully adapt incremental policies of changed use where the evidence about clinical efficacy is good and, in so doing, save resources to fund other more beneficial activities and reduce the incidence of side effects due to the over use of NSAIDs.

Table 3. ***Potential effects of changing behaviour***

	Current levels	Scenario 1: Reduce scripts by 25%	Scenario 2: Reduce dose by 10%	Scenario 3: Switch to 50% on ibuprofen	Scenario 4: Combine 1-3
Prescriptions (000)	23,226	17,420	23,226	23,226	17,420
Costs (£000)	173,282	129,962	155,954	128,123	86,483
Serious ARs per annum	503	377	478	440	314
Serious GIs per annum	315	236	263	263	188

4. Conclusions

Any economic evaluation of treatment options involving the use of NSAIDs is fraught with difficulty because of the poor knowledge base and the reluctance of the medical profession to translate what is known about efficacy and safety into practice protocols and more appropriate prescribing behaviour.

Altman (1994) argued that the major reason why medical practitioners became involved in the design, execution and reporting of trials was not the production of knowledge but the desire to enhance their career prospects by developing their curricula vitae!

Gøtzsche (1989) in his review of 196 NSAIDs trials has demonstrated that many clinical evaluations produce biased results: a list of biases produced in his review of the literature are presented in appendix 1. He concluded:

"Doubtful or invalid statements were found in 76% of the conclusions or abstracts. Bias consistently favoured the new drug in 81 trials and the control in only one".

Rochon et al (1994) reviewed the NSAIDs trial literature and concluded:

"Claims of superiority, especially with regard to side effects profiles, are often not supported by trial data. These data raise concerns about selective publication or biased interpretation of results in manufacturer associated trials".

This inadequate knowledge base about the clinical effectiveness of NSAIDs means that any economic evaluation must be exploratory and tentative. Furthermore, both clinicians and economists must be explicit about industry links, details of which will have to be revealed in the USA in future (New York Times, 24 September 1994).

Despite the biases in the clinical database it seems clear that the therapeutic effects of NSAIDs are similar overall even if individual patient responses may vary. It is also known that these products have differing toxicity and produce adverse reactions to differing extents.

Unfortunately this knowledge tends to be ignored. The costs and adverse reactions effects of alternative treatment scenarios in the UK are such that it seems possible that the costs of NSAID treatment could be reduced whilst at the same time adverse reactions could also be reduced. The extent of these effects needs much more careful evaluation than is presented in this exploratory analysis.

The benefits of changing physician prescribing of NSAIDs are considerable. An emerging literature also demonstrates that the prophylactic use of misoprostol and famotidine in the prevention of duodenal and gastric ulcers may be considerable. These drugs may also produce significant side effects (e.g. diarrhoea from misoprostol) which will affect patient compliance and benefit. The widespread use of such drugs in the NSAIDs population would be very expensive (e.g. £600 million in the UK) and thus they should be targeted on patients with particular risk factors (e.g. increasing age, multiple NSAID use, male sex, smoking and history of ulcers). Such policies need careful modelling and evaluation rather than ad hoc therapeutic 'innovation' by clinicians in everyday practice.

With an informed knowledge base about such policies, practice guidelines can be evolved. In a non-randomised evaluation Newton-Syms et al (1992) promoted a prescribing strategy which had ibuprofen 400/800mg as first choice, and piroxicam and indomethacin as second and third choice NSAIDs. The 'academic representative' intervention they used in 101 randomly selected GPs from Leeds did result in some changes in prescribing behaviour. There was a significant increase in the prescribing cost of ibuprofen in the intervention group, sustained over the five months after the intervention, and prescribing of piroxicam reduced in the reference group but not in the intervention group. The impact on overall prescribing costs however was small, with a reduction in the average prescribing cost of NSAIDs of only £6.60 per month in the intervention group compared with the reference group.

Others, in other therapeutic areas (e.g. Soumerai et al 1990) have used an 'academic detailing' approach, i.e. devising guidelines for prescribing based on knowledge about efficacy derived from rigorous trials. Such guidelines can be complemented by incentive arrangements.

The scope for reducing costs and improving patient pain control with appropriate use of NSAIDs which minimises side effects is considerable. The purposeful pursuit of such policies with the selective use of prophylactic therapies needs further evaluation

from both clinical and economic perspectives, and careful managerial control if resources are to be used efficiently and without avoidable morbidity and mortality.

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Appendix 1: Factors that may increase the number and the proportion of significant results favouring a new drug

1. Design bias
2. Selection of patients dissatisfied with control drug
3. Choice of dose
4. Selection of indices
5. Selective reporting among many variables
6. Ineffective blinding
7. Choice of statistical methods or no statistics at all
8. Handling of withdrawals
9. Handling of missing data and other uncertainties
10. Change in measurement scale before analysis
11. Choice of adjustment depending on result
12. Uneven distribution of prognostic factors
13. Wrong sampling unit for effect and side effects
14. Wrong interpretation of within group analyses
15. Repeated testing on several groups or over time
16. Subgroup analysis
17. Selective reporting of $0.05<p<0.10$
18. Omission of significant results favouring the control
19. Wrong calculation
20. One sided tests
21. Fraud
22. Publication bias

Source: Gøtzsche 1989 p.49.