# North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis

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This guideline addresses the appropriate use of non-steroidal anti-inflammatory drugs in the primary care treatment of patients with joint pain believed to be caused by degenerative arthritis. It does not consider therapies other than drug treatment. General practitioners must use their professional knowledge and judgement when applying guideline recommendations to the management of individual patients. They should note the information, contraindications, interactions, and side effects contained in the *British National Formulary*.[1]

This is a summary of the full version of the guideline.[2] In this article, the statements accompanied by categories of evidence (cited as Ia, Ib, IIa, IIb, III, and IV) and recommendations classified according to their strength (A, B, C, or D) are as described previously and are summarised in the box.[3]

## Summary points

- Nearly 1.5 million person years of non-steroidal anti-inflammatory drug treatment, at a cost of £150 million, were prescribed by general practitioners in 1995
- Initial treatment for osteoarthritic pain should be paracetamol, followed by ibuprofen
- Routine prophylaxis for gastrointestinal injury associated with non-steroidal anti-inflammatory drugs is not appropriate in patients with osteoarthritis
- Potential risks of side effects should be discussed with patients before starting or changing treatment
- Paracetamol is the most cost effective drug, followed by ibuprofen
- Topical non-steroidal anti-inflammatory agents cannot be recommended as evidence based treatment

## Methods

The methods used to develop the guideline have been described previously.[3] Briefly, we searched the electronic databases Medline and Embase, using a combination of subject heading and free text terms aimed at locating systematic reviews, meta-analyses, randomised trials, quality of life studies, and economic studies. The search was backed up by the expert knowledge and experience of group members.

### Synthesising and describing published reports

The quality of relevant studies retrieved was assessed, and the information from relevant papers was synthesised using meta-analysis. This provided valid estimates of treatment effects using approaches that provided results in a form that could best inform treatment recommendations.

## Osteoarthritis

### Caseload

Osteoarthritis is one of a continuum of connective tissue disorders. The extent to which these interrelate and share common treatment is uncertain. Assuming a general practice list of 2000 patients, 374 will have a connective tissue disorder (ICD-9 codes 710-739). However, only 63 of the 374 will be formally identified as having osteoarthritis (fig 1).[4]

### Current patterns of drug use

In England, nearly 1.5 million person-years of non-steroidal anti-inflammatory drug treatment were prescribed by general practitioners in the year from April 1995. The cost was nearly £150 million, and ibuprofen and diclofenac constituted 26% and 37% respectively of the total volume. These figures do not include over the counter sales of ibuprofen.

## Evidence from randomised trials

### Pain at rest

Three trials (four comparisons), in which a total of 969 patients were randomised to simple analgesia or a

**Strength of recommendation**

A—Directly based on category I evidence
B—Directly based on category II evidence or extrapolated recommendation from category I evidence
C—Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D—Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

**Categories of evidence**

Ia—Evidence from meta-analysis of randomised controlled trials
Ib—Evidence from at least one randomised controlled trial
IIa—Evidence from at least one controlled study without randomisation
IIb—Evidence from at least one other type of quasiexperimental study
III—Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV—Evidence from expert committee reports or opinions, clinical experience of respected authorities, or both

non-steroidal anti-inflammatory drug, examined pain at rest by using a visual analogue scale.[5–7] The pooled standardised weighted mean difference was 0.35 (95% confidence interval 0.17 to 0.53), indicating that non-steroidal anti-inflammatory drugs were slightly more effective than simple analgesia (fig 2). We found evidence of heterogeneity (Q = 6.69; df = 3; P = 0.08),

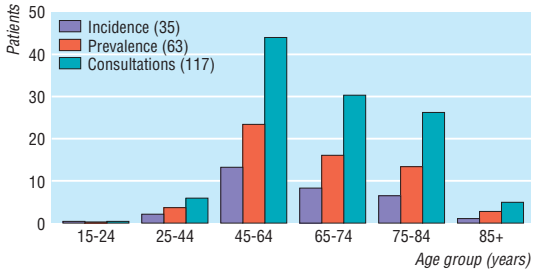


**Fig 1** Yearly caseload of osteoarthritis (ICD 715) in primary care (assuming a list size of 2000 patients)

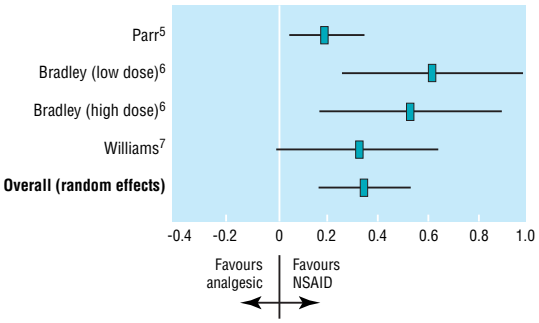


**Fig 2** Resting pain score (standardised weighted mean difference) for non-steroidal anti-inflammatory drugs (NSAID) compared with simple analgesia

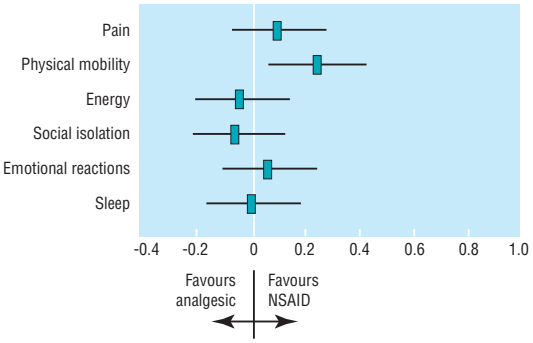


**Fig 3** Diclofenac sodium (non-steroidal anti-inflammatory drug (NSAID)) compared with co-proxamol (analgesic) in relation to Nottingham health profile dimensions (standardised effect sizes)[5]

confirming the appropriateness of the random effects model. However, a fixed effects approach provides a similar estimate of effect, with a standardised weighted mean difference of 0.29 (0.17 to 0.41). Thus, the pain score of the average patient treated with non-steroidal anti-inflammatory drugs is less than that of 64% of patients in the control group.

Parr et al[5] found a smaller effect than that estimated in either comparison by Bradley et al,[6] and slightly smaller than that found by Williams et al.[7] This may be because patients in the general practice population in the Parr study were less severely affected than those in other trials, who were recruited from secondary care, or it may reflect different inclusion criteria. Both the Bradley and Williams studies required a definite diagnosis of osteoarthritis, while the Parr study did not. In addition, the Parr study compared diclofenac sodium with co-proxamol, which may be more effective than paracetamol alone. However, the confidence intervals of all comparisons overlap, and we cannot exclude the play of chance.

### Pain on motion

Two trials (three comparisons) provided estimates of pain on motion based on visual analogue scales. Although only one of the comparisons was statistically significant alone, the pooled standardised weighted mean difference based on all 390 patients randomised in this comparison is 0.28 (0.08 to 0.48; Q = 1.27, df = 2; P = 0.53). The pain score of the average patient treated with non-steroidal anti-inflammatory drugs is less than that of 61% of patients in the control group.

### Time to walk 50 feet

Two trials (three comparisons) compared the effects of non-steroidal anti-inflammatory drugs and paracetamol treatment on the time taken to walk 50 feet. Overall, the estimate of effect for this outcome is 0.093 (−0.105 to 0.292), a very small effect that may be explained by chance. In addition, the practical importance of this benefit is uncertain: the mean difference in effect in favour of non-steroidal anti-inflammatory drugs was less than one second in all comparisons.

### Impact on quality of life

One study used the Nottingham health profile to describe different elements of the comparison between

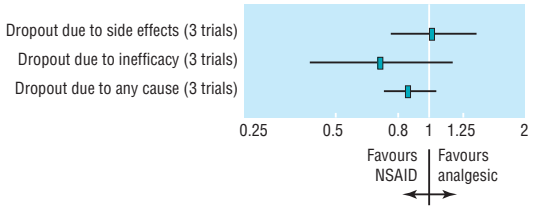


**Fig 4** Treatment withdrawal from included studies: relative risk

diclofenac and co-proxamol on broader health outcomes. The results showed no substantial differences in outcome for simple analgesia compared with non-steroidal anti-inflammatory drugs (fig 3).[5]

### Treatment drop out

Stopping treatment was common in the three trials included in the meta-analyses of efficacy. Overall, there was a small and non-significant reduction in the risk of dropping out for patients allocated to non-steroidal anti-inflammatory drugs rather than simple analgesia (relative risk 0.86, 0.72 to 1.03; $Q=0.48$, $df=3$; $P=0.92$) (fig 4). This translates to an overall reduction in the percentage of patients who drop out of 3.3% (−1.2 to 7.7) over an average of 4.5 months of treatment.

### Efficacy of paracetamol based analgesia

Paracetamol and codeine combined seem to have a slightly greater analgesic effect than paracetamol alone.[8] The combination of paracetamol and dextropropoxyphene also shows small and uncertain benefits over paracetamol alone.[9] However, both combinations are associated with increased side effects (Ib).

## Safety

The relative risk of serious gastrointestinal complications with individual non-steroidal anti-inflammatory drugs was reviewed by Henry et al.[10] They identified 12 controlled epidemiological studies examining 14 drugs from which safety relative to ibuprofen could be derived. The data supported the conclusion of the Committee on Safety in Medicines that ibuprofen is the lowest risk non-steroidal anti-inflammatory drug and azapropazone the highest risk agent. The review also presented evidence that the risk of gastrointestinal injury from non-steroidal anti-inflammatory drugs is greater at higher doses. The magnitude of this increased risk is difficult to estimate since different studies used different definitions of high dose. However, high dose ibuprofen (2.4 mg daily) may be no safer than those non-steroidal anti-inflammatory drugs defined by the Committee on Safety in Medicines as being of intermediate risk—drugs such as diclofenac and naproxen.

**Recommendations: treatment**

- Initial treatment for painful joints attributed to degenerative arthritis should be paracetamol in doses of up to 4 g daily (A)
- If paracetamol fails to relieve symptoms, ibuprofen is the most appropriate alternative and should be substituted at a dose of 1.2 g daily (A)
- If relief of symptoms is still inadequate, paracetamol may be added in doses of up to 4 g daily (D), or the dose of ibuprofen may be increased to 2.4 g daily (D), or both
- If relief of symptoms is still inadequate, alternative drugs such as diclofenac or naproxen (A), or other non-steroidal anti-inflammatory drugs or co-codamol (D) may be considered

### Preventing gastrointestinal injury

*Statement: $H_2$ blockers, misoprostol and proton pump inhibitors reduce the risk of non-steroidal anti-inflammatory drug-induced duodenal ulcers (I)*

*Statement: misoprostol and proton pump inhibitors also reduce the risk of other serious upper gastrointestinal injury (II)*

Both $H_2$ antagonists and misoprostol reduced the risk of duodenal ulcers when given long term but not short term.[11] Omeprazole seems as effective as misoprostol in healing and preventing ulcers induced by non-steroidal anti-inflammatory drugs, and it seems to be better tolerated.[12]

In a recent large double blind trial, primary and secondary care patients with rheumatoid arthritis who were taking non-steroidal anti-inflammatory drugs were randomised to treatment with misoprostol or placebo.[13] The trial assessed the development of serious upper gastrointestinal complications detected by clinical symptoms or findings (rather than scheduled endoscopy) and found a small reduction, of borderline significance, in favour of misoprostol. Twenty five of 4404 patients taking misoprostol and 42 of 4439 patients receiving placebo had a serious upper gastrointestinal complication. The odds ratio for serious gastrointestinal complication was 0.60 (95% confidence interval 0.35 to 1.00 by Gart exact method) in those taking misoprostol over 6 months of follow up. The number needed to treat to prevent one serious gastrointestinal complication in this period is 264 (132 to 5703). In the first month of the study, 5% more patients taking misoprostol withdrew, primarily because of diarrhoea and other side effects.

On the basis of this trial in patients with rheumatoid arthritis,[13] a general policy of prescribing prophylaxis of gastrointestinal injury associated with non-steroidal anti-inflammatory drugs for osteoarthritis patients (generally a less severe patient group) does not seem appropriate. This may not be true for a selected group of high risk patients (for example, those with previous gastrointestinal bleeding) in whom non-steroidal anti-inflammatory drug treatment cannot be modified. However, the method of reporting and small number of serious gastrointestinal events in the large trial of misoprostol prophylaxis[13] preclude examination of benefits of treatment in subgroups.

### Reducing gastrointestinal symptoms

*Statement: $H_2$ antagonists may have a small impact upon severe gastric symptoms in patients taking non-steroidal anti-inflammatory drugs, though it is not clear that benefits generally exceed those from antacids (I)*

There are few available data examining strategies to reduce gastrointestinal symptoms induced by non-

**Recommendations: safety**

- Potential risks of side effects of non-steroidal anti-inflammatory drugs should be discussed with patients before starting or changing treatment (D)
- Patients' requirements for non-steroidal anti-inflammatory drugs should be reviewed regularly (at least six monthly) and the use of these drugs on a limited "as required" basis should be encouraged. At review doctors should consider substituting paracetamol for a non-steroidal anti-inflammatory drug (D)
- If upper gastrointestinal side effects occur with non-steroidal anti-inflammatory drugs, consider the following review steps:
  - Establish the accuracy of the diagnosis of non-steroidal anti-inflammatory drug associated dyspepsia (D)
  - Review and confirm the need for any drug treatment (D)
  - Consider substituting paracetamol for a non-steroidal anti-inflammatory drug (D)
  - If paracetamol provides insufficient analgesic relief, consider substituting co-codamol (D)
  - Consider substituting low dose ibuprofen (1.2 g daily) for co-codamol (D)
  - Consider lowering the dose of the currently used non-steroidal anti-inflammatory drug (B)
- If sufficient analgesia is achieved only with non-steroidal anti-inflammatory drugs and the patient has dyspeptic symptoms, consider using acid suppression as adjunctive therapy (D)
- The guideline development group could not find sufficient evidence to decide whether these patients required endoscopy (D)

steroidal anti-inflammatory drugs. In one randomised trial of patients with osteoarthritis treated with non-steroidal anti-inflammatory drugs, allocation to nizatidine reduced appreciably the use of (much less expensive) antacids, but overall symptoms were similar in the two groups.[14] Similarly, in a randomised trial of patients with either rheumatoid arthritis or osteoarthritis, allocation to ranitidine led to no difference in epigastric pain or in withdrawal from treatment.[15] In a randomised trial of patients with ulcers induced by non-steroidal anti-inflammatory drugs, patients allocated to omeprazole had less abdominal pain than those allocated to misprostol.[16]

## Economic considerations

*Statement: substantial differences are found in the costs of non-steroidal anti-inflammatory drugs, both between drugs and between different preparations (II)*

*Statement: there is no evidence to support the use of more expensive preparations over cheaper ones (II)*

*Statement: no evidence supporting the use of the modified release preparations has been found (IV)*

Paracetamol remains a cost effective alternative to any non-steroidal anti-inflammatory drug. It is cheaper and has less gastrointestinal toxicity, and similar proportions of patients withdraw from treatment.

Ibuprofen seems safer than diclofenac or naproxen[10] and is three to four times cheaper, given the forms in which these drugs are currently prescribed. Ibuprofen is therefore the most cost effective first line non-steroidal anti-inflammatory drug.

The purchase costs of different preparations of the same non-steroidal anti-inflammatory drug vary widely. There is no evidence to support the use of more expensive preparations over cheaper ones or the use of the modified release preparations. Head to head trials comparing different non-steroidal anti-inflammatory drugs are of a poor quality and show many biases.[17 18]

Routine and prophylactic treatment with misoprostol for unselected patients taking non-steroidal anti-inflammatory drugs has not been shown to be cost effective. Case review and sequential selection of treatment, beginning with simple analgesia, will probably minimise the frequency of adverse events in the general patient group.

Preventive strategies should not be confused with treatment of (common) dyspepsia, where prescription or over the counter purchase of antacids may be considered when non-steroidal anti-inflammatory drug treatment cannot be modified.

## Topical preparations

*Statement: the appropriate role of topical non-steroidal anti-inflammatory drugs is unclear (IV)*

Topical non-steroidal anti-inflammatory drugs may have some benefit in patients with osteoarthritis as their use may reduce the risk of unwanted gastrointestinal side effects. Well designed, large scale randomised trials in which topical non-steroidal anti-inflammatory treatment is compared directly with oral non-steroidal anti-inflammatory treatment in patients with osteoarthritis are required to estimate the relative effectiveness and efficiency of these alternative treatments. We were unable to find any such trial. Therefore, the use of topical non-steroidal anti-inflammatory drugs in patients with osteoarthritis cannot be recommended as an evidence based treatment.

## Research questions

In developing this guideline the group identified important issues that need further research. Well designed, large scale randomised trials that compare alternative treatments directly are required to evaluate the following:

**Recommendations: cost effectiveness**

- Patients with joint pain believed to be caused by degenerative arthritis should be given paracetamol initially, and if this is inadequate ibuprofen is the most cost effective alternative (C)
- Modified release preparations are relatively expensive, and as there is no evidence that they are more effective than standard treatment, they should not be used (D)
- Prophylaxis with misoprostol or proton pump inhibitors should not be used routinely as it is not cost effective in reducing serious gastric events (D)
- In some patients at higher risk of upper gastrointestinal bleeding or perforation, prophylaxis may be cost effective, but further evidence of this is required (D)

**Recommendation: use of topical preparations**

- Topical non-steroidal anti-inflammatory agents cannot be recommended as an evidence based treatment (D)

(1) What is the efficacy and safety of simple and compound analgesics compared with non-steroidal anti-inflammatory drugs?
(2) What are the consequences of advising patients to take non-steroidal anti-inflammatory drugs or paracetamol "as required" compared with continuously?
(3) What is the appropriate role of modified release non-steroidal anti-inflammatory drug preparations?
(4) What is the best treatment for patients taking non-steroidal anti-inflammatory drugs who present with dyspeptic symptoms?
(5) Is prophylaxis with misoprostol or proton pump inhibitor agents cost effective in high risk patients in whom withdrawal of non-steroidal anti-inflammatory drug therapy is not possible?
(6) What is the relative effectiveness and efficiency of topical non-steroidal anti-inflammatory drugs and oral non-steroidal anti-inflammatory drugs in patient with osteoarthritis?
(7) What is the role of the new cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs and nitrosated compounds in the primary care treatment of patients with osteoarthritis?
(8) In patients taking non-steroidal anti-inflammatory drugs, what are the added risks of gastrointestinal injury when they also have *Helicobacter pylori* infection?

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Contributors: ME was responsible for: the design and conduct of the guideline development, running the guideline development group, and the joint writing of the full guideline and the summary paper. NF and JM were responsible for: the data extraction and analysis, presenting this to the guideline development group, and the joint writing of the full guideline and the summary paper. The guideline development group (see appendix) considered the evidence, generated the guideline recommendations, and commented on subsequent drafts of the full version of the guideline.

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Conflict of interest: None.

**Appendix**

The guideline development group comprises the following members in addition to the authors: Professor Howard Bird, Chapel Allerton Hospital, Leeds; Mr Mark Campbell, prescribing manager, Regional Drug and Therapeutics Centre, Newcastle upon Tyne; Dr John Dickson, general practitioner, Northallerton; Dr David Graham, general practitioner, Hexham; Professor Christopher Hawkey, University Hospital, Nottingham; Dr Keith MacDermott, general practitioner, York; Dr Tony McKenna, general practitioner, Cleveland; Dr Maureen Norrie, general practitioner, Stockton on Tees; Dr Colin Pollock, medical director, Wakefield Health Authority; Dr Jeff Rudman, Workington.

The project steering group comprised: Professor Michael Drummond, Centre for Health Economics, University of York; Professor Andrew Haines, Department of Primary Care and Population Studies, University College London Medical School and Royal Free Hospital School of Medicine; Professor Ian Russell, Department of Health Sciences and Clinical Evaluation, University of York; Professor Tom Walley, Department of Pharmacology and Therapeutics, University of Liverpool.

1 *British national formulary*. London: British Medical Association, Royal Pharmaceutical Society of Great Britain, 1996. (No 32.)
2 North of England Evidence Based Guidelines Development Group. *Non-steroidal anti-inflammatory drugs (NSAIDs) versus basic analgesia in the treatment of pain believed to be due to degenerative arthritis*. Newcastle: Centre for Health Services Research, 1997.
3 Eccles M, Freemantle N, Mason JM. North of England Evidence Based Guidelines Development Project: methods of developing guidelines for efficient drug use in primary care. *BMJ* 1998;316:1232-5.
4 McCormick A, Fleming D, Charlton J. *Morbidity statistics in general practice: fourth national study 1991-1992*. London: HMSO, 1995. (Series MB5 No 3.)
5 Parr G, Darekar B, Fletcher A, Bulpitt CJ. Joint pain and quality of life; results of a randomized trial. *Br J Clin Pharmacol* 1989;27:235-42.
6 Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Treatment of knee osteoarthritis: relationship of clinical features of joint inflammation to the response to a nonsteroidal antiinflammatory drug or pure analgesic. *J Rheumatol* 1992;19:1950-4.
7 Williams HJ, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum* 1993;36:1196-206.
8 De Craen AJM, Guilio GD, Lampe-Schoenmaeckers AJEM, Kessels AGH, Kleijnen J. Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996;313:321-5.
9 Wan Po LA, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextroproxyphene to paracetamol. *BMJ* 1998;315:1565-71.
10 Henry D, Lim LL-Y, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;312:1563-6.
11 Koch M, Dezi A, Ferrario F, Capurso L. Prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal mucosal injury: a meta analysis of randomized controlled clinical trials. *Arch Intern Med* 1996;156:2321-32.
12 Hawkey CJ, Swannell AJ, Yeomans ND, Langstrom G, Lofberg, Taure E. Site specific ulcer relapse in non-steroidal anti-inflammatory drug users: improved prognosis with H pylori and with omeprazole compared to misoprostol. *Gut* 1996;39(suppl 1):W5.
13 Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;123:241-9.
14 Levine LR, Cloud ML, Enas NH. Nizatidine prevents peptic ulceration in high risk patients taking nonsteroidal anti-inflammatory drugs. *Arch Intern Med* 1993;153:2249-54.
15 Ehsanullah RSB, Page MC, Tildesley G, Wood RJ. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. *BMJ* 1988;297:1017-21.
16 Hawkey CJ, Swannell AJ, Eriksson S, Walan A, Lofberg I, Taure E, et al. Benefits of omeprazole over misoprostol in healing NSAID-associated ulcers. *Gut* 1996;38(suppl 1):T155.
17 Gøtzsche PC. Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Controlled Clin Trials* 1989;10:31-56.
18 Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, et al. A study of manufacturer-supported trials of nonsteriodal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994;154:157-63.

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*Endpiece*

## Nosology

Nor bring, to see me cease to live,
Some doctor, full of phrase and fame,
To shake his sapient head and give
The ill he cannot cure a name.

Matthew Arnold, "A Wish"

Submitted by Ann Dally, Wellcome Institute for the History of Medicine

*Getting research findings into practice*

# Implementing research findings in developing countries

Paul Garner, Rajendra Kale, Rumona Dickson, Tony Dans, Rodrigo Salinas

Developing countries have limited resources, so it is particularly important to invest in health care that works. The growing number of relevant systematic reviews can assist policymakers, clinicians, and consumers in making informed decisions. Developing countries have led the way in generating approaches to ensure professional standards of behaviour through interventions such as producing guidelines and introducing essential drug programmes, and by producing reliable research summaries to help ensure that policies are based on good evidence.

## Summary points

- Financial resources are limited in developing countries so it is vital that the health care provided is effective
- The number of systematic reviews relevant to developing countries is increasing
- Disseminating the findings of systematic reviews to policymakers, health professionals, and consumers is an essential prerequisite to changing practices
- Practice guidelines and international programmes that provide essential drugs are well established and provide a powerful route for reinforcing evidence based practice
- Large obstacles impede the implementation of evidence based practices, such as the unethical promotion of drugs; these problems need to be addressed by regulation
- Action is required at all levels of healthcare systems, from consumers through to health professionals, ministries of health, and international organisations

## Introduction

Yakamul, an illiterate villager in Papua New Guinea, was sitting by a fire listening to a health professional from the West tell her to take chloroquine throughout her pregnancy. She responded: "I ting merisin bilong ol wait man bai bagarapim mi [I think this Western medicine could harm me]." She had never attended a workshop in critical appraisal but she realised that medicine could do her more harm than good. Her response reminds health professionals to ask fundamental questions about the care we provide and of our responsibility to examine evidence using scientific methods. Eventually we tested Yakamul's hypothesis about chloroquine treatment during pregnancy.[1]

Removing erroneous opinions from healthcare policy and practice is part of getting research findings into decision making. Practitioners work in good faith, but if they implement practices or policies that are ineffective they waste resources and may harm people. Nowhere is this consideration more important than in developing countries, in which many practitioners struggle to provide care on less than £7 per person each year.[2] These countries do not have money to waste on a single treatment that is not effective. Equally important is the time and money that patients expend on their health care. If as health professionals we are providing care that is ineffective, then we are responsible for exacerbating patients' deprivation and poverty.

Unfortunately, applying research findings to clinical decisions is not a simple process. Indeed, it is impossible if primary research asks questions that are irrelevant to the study participants. Tropical medicine has a long history of descriptive studies that benefit researchers but have no direct implications for participants. For example, a bibliography of research up to 1977 in Papua New Guinea identifies 135 publications that describe Melanesian blood groups but only 25 concerned with treating malaria.[3] Recently, researchers have begun doing interventional studies that might help participants. Some complex interventions have been tested in randomised controlled trials, such as the effect of improved services to treat sexually transmitted diseases on the incidence of HIV.[4]

Even when research asks questions that might provide useful information, health professionals still confront an increasing pile of medical literature. An up to date systematic review of randomised controlled trials could have helped the health professional respond to Yakamul's question. Systematic reviews offer a critical link in getting research into practice. Clinicians, managers, and patients can draw on them whether they live in Burkina Faso or the Cayman Islands.[5] Reviews and interventions are internationally relevant, but implementation should be done nationally and locally, influenced by the resources available and circumstances. It is naive to believe that systematic reviews alone will change practice in the West or in developing countries.

This article examines the constraints on good practice in developing countries and identifies opportunities that will help the implementation of research findings by health professionals, policymakers, and patients. We aim to reflect our opinions and experiences and to generate discussion; we do not aim to be comprehensive.

## Constraints on good practice

In theory, well organised government funded health systems in developing countries provide good value for money. In many countries, healthcare systems are inefficient, lack reliable funding, and employ large

**This is the last in a series of eight articles analysing the gap between research and practice**

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numbers of health workers for whom there are no incentives to provide effective care. Research led practice seems to be irrelevant when systems are in disarray. However, it is precisely these services that governments and international donors such as the United Kingdom's health and population aid programme are attempting to improve through targeted activities; the donors' logic seems to be that if you cannot make the system work, focus on delivering a single intervention that may save lives. For example, vitamin A supplementation is an intervention that a good systematic review shows is effective in decreasing the risk of illness and death in young children.[6] As new ideas and research findings emerge, donors and policymakers add more "magic bullets" to the healthcare package. Over time this process leads to the development of a comprehensive package that the system was unable to deliver in the past. Nevertheless, there is little evidence that some established magic bullets work. For example, evidence that monitoring children's growth prevents malnutrition and infant death is weak, yet every day health staff and mothers spend thousands of hours at health clinics weighing children.[7] Standard guidelines for antenatal care in many countries recommend up to 14 visits per pregnancy, although a recent trial of fewer visits showed no adverse effects on pregnancy outcome.[8] When healthcare interventions are being implemented the whole healthcare system should be considered, and activities for which evidence of impact is weak should be discarded and new evidence based activities should be added when appropriate.

An even bigger constraint on implementing effective healthcare practices is politics. The per capita allocations for health care by governments in developing countries may be modest, but the totals are large. Therefore, there will always be people with vested interests keen to influence the distribution of funds. Capital investment in new facilities and high technology equipment appeals to politicians and those who vote them in, even when these investments may be the least cost effective. Corruption creates incentives that militate against sensible decision making. These problems are universal, but evidence of effectiveness could provide some support for health professionals who are attempting to contradict claims that high technology will cure all.


IAN BARRACLOUGH

Outside government, there are further perverse incentives that promote bad practice. Private practitioners sometimes prescribe regimens that are different and more expensive than those that are standard in the guidelines issued by the World Health Organisation.[9] Knowledge is part of the problem; practitioners often depend on drug representatives for information. Commercial companies have much to gain from promoting drugs, whether or not they work. Because of inadequate regulation, promotional activities often extend beyond ethical limits set by many Western societies. At times they may come disguised as continuing medical education. The situation is aggravated by the lack of effective policy regarding marketing approval for drugs. In Pakistan, for example, the lack of any effective legislation means that authorities register about five new pharmaceutical products every day.[10]

Ultimately it is the medical profession that is the main constraint on change. One reason is that in many developing countries, ownership of equipment or hospital facilities by doctors is allowed, or even encouraged, by medical societies and training institutions. This creates conflicts of interest, which may explain the overuse of many diagnostic tests.[11] Furthermore, clinicians and public health professionals in many developing countries are trained in programmes that incorporate traditional models of Western medical education. They base their medical knowledge on foreign (mainly European and US) medical literature, the opinions of foreign visitors, and the opinions of drug company representatives who are promoting new products. In developing countries, medical practitioners respect doctors who know about pathology. Clinicians in many developing countries believe that this scientific understanding is essential to designing rational treatment. Doctors also value the freedom to practise medicine as they deem best. Advocates of change need to be aware that some strategies designed to implement research findings will be perceived as a threat to this freedom.

## Initiatives to develop evidence based care

Researchers, policymakers, and clinicians have already done much to engender a science led culture in developing countries. The Rockefeller Foundation in the United States has supported training in critical appraisal for over 15 years, producing clinicians committed to practising evidence based medicine in their own countries.[12] Practitioners in developing countries are familiar with evidence based practice policies such as those for pneumonia in children,[13] and practice guidelines have been used in Papua New Guinea since 1966.[14] The availability of methodological tools for improving the validity of guidelines has increased dramatically; in the Philippines methodological issues in guideline development were identified, and an approach was developed that could be used by other developing countries.[15] Furthermore, the WHO's essential drugs programme has taken a strong lead internationally in advocating rational prescribing. Together with the International Network for the Rational Use of Drugs it has disseminated research about effectiveness. The network has also encouraged

the development of management interventions to promote good prescribing practice.[16 17]

In 1997, some national governments began taking action to introduce research led practice in their countries. In Chile, the Ministry of Health has established with support from the European Union an office to promote the implementation of research findings. In Palestine, doctors are working with the health minister to establish a national committee on clinical effectiveness. In Thailand, the Ministry of Health and the National Health Services Research Institute are setting up an office to guide a national quality assurance programme (A Supachutikul, personal communication). In South Africa, the Medical Research Council has committed support to the production of systematic reviews and evidence based practice (J Volmink, personal communication). In Zimbabwe and South Africa, researchers are working with their governments to test ways of getting research into policy and practice.[18] In the Philippines, the Department of Health has funded projects to develop evidence based guidelines for its cardiovascular disease prevention programme.[19]

International donors and organisations involved with health in the United Nations have influenced the content and direction of health services in developing countries. They have funded one-off systematic reviews such as the comprehensive review of vitamin A supplementation. Now there is more sustained interest by governments and ministries of health in the production of reliable systematic reviews that are relevant to health care in developing countries. The WHO has also conducted important systematic reviews into topics such as the use of rice based oral rehydration fluid[20]; some of these reviews are being kept up to date in *The Cochrane Library*, such as the review on the effectiveness and safety of amodiaquine hydrochloride in treating malaria.[21] The effective health care in developing countries project, supported by the United Kingdom's health and population aid programme, aims to produce and maintain over 30 systematic reviews in the next four years as part of the Cochrane Collaboration; researchers and clinicians in India, Chile, South Africa, and Zimbabwe are participating in the process.

The World Bank has constructed an essential package of effective healthcare interventions. Many assumptions were made about the effectiveness of treatments, and systematic reviews were not used in compiling the package, as there were very few available then.[22] Now, however, there is the opportunity to refine the contents of the package on the basis of reliable evidence available from systematic reviews.

In the next few years there will be opportunities to draw on more reliable evidence of effectiveness. Methods to apply cost-utility analyses to systematic reviews are already being developed for this process (T Jefferson, personal communication). International donors are also promoting reform of the healthcare sector, especially in the areas of institutional change in governmental health policies. Implementation of reforms is affecting a number of developing countries. Although reforms are different in each country,[23] change provides the opportunity for introducing evidence based approaches.

Evidence of effectiveness is also of interest to those who use healthcare services. In Pakistan the Network of

**Sources of information about evidence based practice**

| Type | Name | Details | Contact Information |
|---|---|---|---|
| Electronic journal | The Reproductive Health Library | Systematic reviews with commentaries | World Health Organisation, 1211 Geneva 27, Switzerland, or khannaj@who.ch |
| Websites | Australasian Cochrane Centre | Reviews of abstracts | som.flinders.ed.au/fusa/cochrane |
| | The Cochrane Library | Web subscription | Synapse.info@medlib.com, or www.medlib.com/ |
| | Effectiveness Update | Summaries of systematic reviews that are relevant to practice in developing countries. Adapted from Cochrane reviews | www.liv.ac.uk/lstm/ind98/edu/html |
| | Ovid | Service includes full text of 200 journals, The Cochrane Library, Best Evidence database, Medline, and HealthStar | www.ovid.com.dotm |
| Paper journals | Evidence-Based Medicine | Summarises results of trials and systematic reviews | BMJ Publishing Group, BMA House, Tavistock Square, London WC1H 9TD, or bmjsubs@dial.pipex.com |
| | Evidence-Based Nursing | Summarises results of trials and systematic reviews | BMJ Publishing Group, BMA House, Tavistock Square, London WC1H 9TD, or bmjsubs@dial.pipex.com |
| Summaries of potential sources | The School of Health and Related Research (ScHARR) Guide to Evidence Based Practice | Bibliography of sources of information | ScHARR Information Resources, Regent Court, Sheffield S1 4DA, or www.shef.ac.uk/uni/academic/r-Z/scharr/ir/netting.html, or through The Cochrane Library |

Associations for the Rational Use of Medication has launched a consumer oriented journal, *Sehat aur sarfeen*, to help develop community pressure against poor pharmaceutical and prescribing practices. In India, the inclusion of medical services under the Consumer Protection Act has increased the accountability of doctors and made patients, especially those in urban areas, more aware of their rights as consumers.

## Future directions

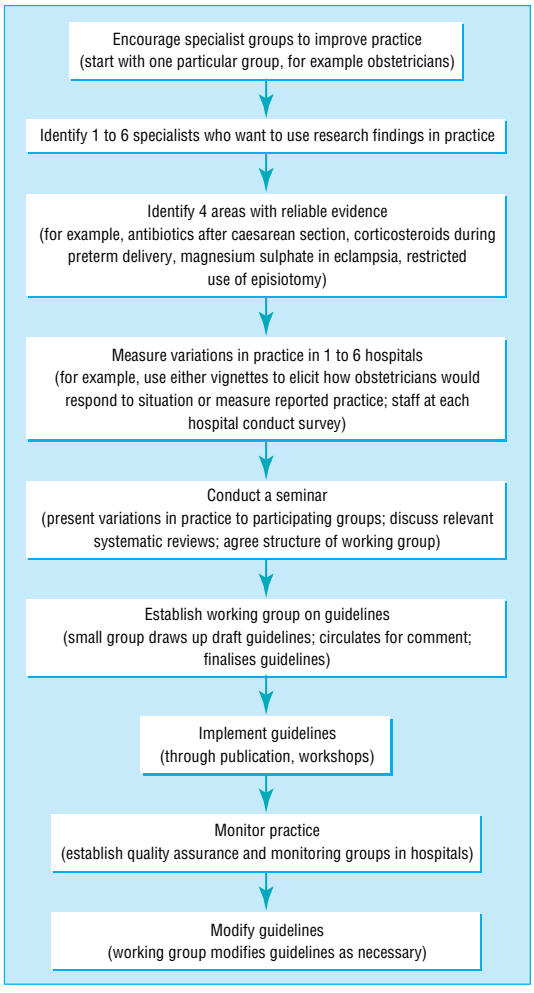
Given the current momentum, how can we promote the use of research findings in practice? We started this article by indicating that systematic reviews were necessary prerequisites to aid clinicians in making sense of evidence buried in a mass of conflicting opinion. Another prerequisite is to ensure that people in developing countries have access to up to date information (box). (Other sources of information can be found in an earlier article in this series by Glanville et al.[24]) It is important to disseminate research findings to a variety of audiences, including other health professionals, lay readers, and journalists. Many mechanisms for implementing good practice are already available in developing countries. In some, guidelines and standardised treatment manuals are better developed than in the West.[14] Other guidelines are likely to become more evidence based over time. Reviews of specific interventions to change professional practice, such as those by Bero et al[25] and those presented by Ross-Degnan et al (international conference on improving use of medicines, Chiang Mai, Thailand, April 1997), will help to ensure that change occurs, but dissemination efforts in developing countries need further evaluation.

Mechanisms for dissemination need to be integrated into healthcare policy and management; this can be done by using a multilevel approach. For example, in June 1995 a large trial showed that magnesium sulphate was the most effective treatment for eclampsia. At that time one third of the world's obstetric practices were using other, less effective therapies.[26] The first level of integration begins internationally, with the WHO ensuring that magnesium sulphate is included on the list of essential drugs. At the national level, ministries of health should include the drug in their purchasing arrangements and ensure that medical curriculums and clinical guidelines are consistent with best treatment practices. At the local level, midwives and doctors need to be aware of the drug's value in treating eclampsia. Additionally, quality assurance programmes and informal clinical monitoring should include the treatment of eclampsia in their audit cycles.

There are a variety of new initiatives to encourage practitioners and policymakers to assess and implement research evidence. Some clinicians examine variations in practice between themselves, for example in Thailand (A Supachutikul, personal communication), and a framework to assist clinicians in applying research evidence to their practice was developed in Chile at the Santiago seminar for getting research into policy (November 1995) (figure). In the Philippines, an ongoing study is looking at the use of standardised clinical encounters in evaluating practice variation. Another mechanism being investigated through the *Reproductive Health Library* is to ask health professionals how they would use the results from a particular systematic review in their practice of reproductive health; if successful, this intervention could be used in other clinical specialties.

In addition to addressing the need for the dissemination of information, policymakers must also address the barriers to wider acceptance of evidence based guidelines. In particular, policies on the ethical promotion of drugs, as well as policies governing continuing medical education and ownership of medical equipment need to be developed.

It is members of the public—irrespective of income or location—who make the ultimate decision whether to avail themselves of our care or advice. Paradoxically, people living in developing countries are sometimes the most critical of the care offered by health professionals. Yakamul was from a tribe that was poor: life was full of risks and time was always short. The villagers were not afraid to be selective about taking only the components that they valued from either traditional or Western health systems.[27] As health professionals, we should remember that it is members of the public who need information about effectiveness. In communicating this information we should be honest, humble, and explicit when the evidence is equivocal.




Framework for getting research findings into practice devised at the Santiago seminar for getting research findings into policy (November 1995)

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1 Gulmezoglu AM, Garner P. Malaria in pregnancy in endemic areas. In: Garner P, Gelband H, Olliaro P, Salinas R, Volmink J, Wilkinson D, eds. Infectious diseases module, Cochrane Database of Systematic Reviews [updated 4 March 1997].*The Cochrane Library*. Cochrane Collaboration; Issue 2. Oxford: Update Software, 1998.
2 National Audit Office, Overseas Development Administration. *Health and population overseas aid: report by the Comptroller and Auditor General*. London: HMSO, 1995. (CH 782.)
3 Hornabrook RW, Skeldon GHF. *A bibliography of medicine and human biology of Papua New Guinea*. Goroka: Papua New Guinea Institute of Medical Research, 1977. (Monograph series No 5.)
4 Grosskurth H, Mosh F, Todd J, Mwijarimbi E, Klokke A, Senkorok, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;346:530-6.
5 Garner P, Kiani A, Salinas R, Zaat J. Effective health care. *Lancet* 1996;347:113.
6 Beaton GH, Martorell R, Aronson KJ, Edmonston B, McCabe G, Ross AC, et al. *Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries*. Toronto: University of Toronto, 1993. (Administrative Committee on Coordination/ Subcommittee on Nutrition discussion paper No 13.)
7 Ross DA, Garner P. Growth monitoring. *Lancet* 1993;342:750.
8 Munjanja SP, Lindmark G, Nyström. Randomised controlled trial of reduced-visits programme in Harare, Zimbabwe. *Lancet* 1996;348:364-9.
9 Uplekar MW, Rangan S. Private doctors and tuberculosis control in India. *Tuber Lung Dis* 1993;74:332-7.
10 Bhutta TI, Mirza Z, Kiani A. 5.5 new drugs per day! *The Newsletter* 1995;4:3.
11 Garner P, Kiani A, Supachutikul A. Diagnostics in developing countries. *BMJ* 1997;315:760-1.
12 Halstead SB, Tugwell P, Bennett K. The international clinical epidemiology network (INCLEN): a progress report. *J Clin Epidemiol* 1991;44: 579-89.
13 Shann F, Hart K, Thomas D. Acute lower respiratory tract infections in children: possible criteria for selection of patients for antibiotic therapy and hospital admission. *Bull WHO* 1984;62:749-53.
14 Biddulph J. Standard regimens—a personal account of Papua New Guinea experience. *Trop Doct* 1989;19:126-30.
15 Multisectoral Task Force on guidelines for the detection and management of hypercholesterolemia. Hypercholesterolemia guidelines development cycle. *Philippines J Cardiol* 1996;24:147-50.
16 World Health Organisation. *Interim report of the biennium, 1996-1997: action programme on essential drugs*. Geneva: WHO, 1997.
17 Ross-Degnan D, Laing R, Quick J, Ali H, Ofordi-Adjei D, Salako L, et al. A strategy for promoting improved pharmaceutical use: the international network for the rational use of drugs. *Soc Sci Med* 1992;35:1329-41.
18 Effectiveness Network (European Union). *A statement of intent by three projects in the international co-operation with developing countries programme (framework 4)*. Brussels: European Union Directorate General, 1996.
19 Multisectoral Task Force on the detection and management of hypertension. Philippine guidelines on the detection and management of hypertension. *Philippines J Intern Med* 1997;35:67-85.
20 Gore SM, Fontaine O, Pierce NF. Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. *BMJ* 1992;304:287-91.
21 Olliaro P, Nevill C, Ringwald P, Mussano P, Garner P, Brasseur P. Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet* 1996;348:1196-1201.
22 World Bank. *World development report 1993: investing in health*. Washington: Oxford University Press, 1993.
23 Martinez J, Sandiford P, Garner P. International transfers of NHS reforms. *Lancet* 1994;344:956.
24 Glanville J, Haines M, Auston I. Finding information on clinical effectiveness. *BMJ* 1998;317:200-3.
25 Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA on behalf of the Cochrane Effective Practice and Organisation of Care Review Group. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. *BMJ* 1998;317:465-8.
26 Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. *Lancet* 1995;345:1455-63.
27 Welsch RL. The experience of illness among the Ningerum of Papua New Guinea [dissertation]. Washington: University of Washington, 1982. (Available through University Microfilms International, No 3592.)

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## *When I use a word . . .*
## The venereal game

We all know that a group of lions is called a pride, of geese a gaggle, and of cows a herd. The game of inventing words to describe assemblages of animals or human beings is over 500 years old. The earliest collections of such terms are to be found in *The Egerton Manuscript* (1450) and, more definitively, *The Boke of St Albans* (1486), a collection written by Dame Juliana Berners. The modern source books for this information are *An Exaltation of Larks* by James Lipton (Penguin, 1977 and 1993), the subtitle of one edition of which I have used for the title of this piece, and *A Crash of Rhinoceroses* by Rex Collings (Bellew, 1992).

The game is venereal because it was originally invented as an exclusive jargon by huntsmen (Latin venari, to hunt). There is a long section in chapter 11 of Conan Doyle's novel *Sir Nigel* (1906), in which Sir John Buttesthorn, the Knight of Dupplin, lectures the young Nigel on various aspects of the hunt, including the "private names" of the "collections of beasts of the forest and. . .gatherings of birds of the air."

Lipton classified the terms into six categories and Philip Howard, in an article in *The Times* (17 November 1987) expanded these to eight:

- Medieval comments (an abomination of monks)
- Onomatopoeia (a murmuration of swallows)
- Characteristics (a skulk of foxes)
- Habitat (a warren of rabbits)
- Appearance (a bouquet of pheasants)
- Comment (a murder of crows)
- Error (a school of fish, for a shoal)
- Jokes, usually puns (an anthology of pros, a faction of reporters)

To these he added a ninth group, of collectives made by adding -y or -age (froggery, brigandage).

Here are some medical collectives:

- A hive of allergologists
- A bag of anaesthetists
- A corps of anatomists
- A colony of bacteriologists
- A rash of dermatologists
- A plague of epidemiologists
- A movement of gastroenterologists
- A smear of gynaecologists
- A lump of oncologists
- A brace of orthodontists
- A host of parasitologists
- A body of pathologists
- A pile of proctologists
- A complex of psychoanalysts
- A joint of rheumatologists
- A congress of sexologists

And what about clinical pharmacologists? A concentration ? Too non-specific. An overdose? Surely not. How about an interaction? Yes I like that.

Jeff Aronson, *clinical pharmacologist, Oxford*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to.