Evidence-based prescribing

May 2007
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A publication from the BMA Science & Education Department and the Board of Science

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Acknowledgements

The association is very grateful for the help provided by the BMA committees and many outside experts and organisations. We would particularly like to thank:

Professor David J Webb, Professor of Therapeutics and Clinical Pharmacology, Clinical Pharmacology Unit, Centre for Cardiovascular Science, University of Edinburgh, and Chair of the Scottish Medicines Consortium.

Professor James M Ritter, Professor of Clinical Pharmacology, Department of Clinical Pharmacology, St Thomas’ Hospital, King’s College London.

British Library Cataloguing-in-Publication Data.
A catalogue record for this book is available from the British Library.


Cover photograph: Getty Images Creative

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This report was prepared under the auspices of the Board of Science of the British Medical Association, whose membership for 2006/07 was as follows:

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Approval for publication as a BMA policy report was recommended by BMA Board of Professional Activities on 30 April 2007.

Declaration of interest
Sir Charles George is a non-executive director of the BMJ Publishing Group. There were no other competing interests with any Board member involved in the research and writing of this report. For further information about the editorial secretariat or Board members please contact the Science and Education Department which holds a record of all declarations of interest:
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Introduction

Evidence-based prescribing
Evidence-based medicine can be defined as ‘the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients’.

With the advent of clinical governance, as introduced in the 1998 government white paper A first class service: quality in the new NHS, emphasis is placed on ensuring a high standard of care, and continual improvement in quality of care. It is no longer acceptable for clinical decisions to be made solely based on opinion, but rather practice should be evidence-based. As set out in Good medical practice, the General Medical Council (GMC) requires that doctors provide effective treatments based on the best available evidence. Medical litigation is reflecting this move towards evidence-based practice. In determining whether a doctor has provided the standard of care required by law, increasingly a demonstration of ‘logical analysis’ leading to a reasoned and evidence-based decision is required by the Court.

Aside from patient consultations, the most common intervention of the National Health Service (NHS) is the issuing of prescriptions. In 2005, a total of 720 million prescription items were dispensed in England, an increase of 5 per cent on 2004. This represented a total cost of £7.9bn. Evidence-based prescribing is essential in providing good quality, effective, and safe healthcare to patients. This includes the cost-effective use of medicines, which is particularly important in the current climate of NHS deficits. Complications from inappropriate prescribing, through both the overuse and underuse of drugs, can include adverse reactions, increased hospital admissions, anti-microbial resistance, increased consultations, and wastage of medicines.

It is worth noting that evidence-based prescribing is not necessarily restricted to the prescription of medicines, and can include the prescription of lifestyle interventions such as exercise referral schemes, pedometers and community based exercise programmes. Prescribing is not solely carried out by members of the medical profession. Nurse and pharmacist independent prescribers can now prescribe any licensed medicine for any medical condition within their clinical and professional competence. The content of this report therefore extends to all healthcare professionals who prescribe.

This report discusses the factors that may affect prescribing practice, and how evidence-based prescribing can be achieved. It outlines the limitations of the current evidence base, and highlights the information resources available to healthcare professionals for evidence-based prescribing.

The evaluation of medicines for use within the NHS
New medicines are licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Evaluation Agency (EMEA). Medicines must have a license, termed a ‘marketing authorisation’, to be prescribed or sold in the UK, which is granted if they meet standards of safety, quality and efficacy. The companies involved in the manufacture and distribution of the medicine must have manufacturer and wholesale dealer licenses. A clinical trial authorisation is required before testing on human subjects for new medicines that are still undergoing development.

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1 The Medicines and Healthcare products Regulatory Agency (MHRA) define an adverse drug reaction (ADR) as an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs, suspected to be related to the drug. The reaction may be a known side effect of the drug or it may be new and previously unrecognised. Source: www.mhra.gov.uk (accessed April 2007).
Medicines are given a legal status as part of the marketing authorisation, which controls their sale and supply. The categories are:

- pharmacy (can only be sold or supplied by, or under supervision of, a pharmacist at a registered pharmacy)
- prescription only (can only be sold or supplied with an appropriate practitioner’s prescription by, or under supervision of, a pharmacist at a registered pharmacy)
- general sale list (can be sold from a wider range of premises).

Decisions regarding the use of most medicines are made locally in the NHS (please see the section on resources for effective prescribing), but where there is inequality in the prescription of a drug, or its value is controversial, the decision is referred to the National Institute for Health and Clinical Excellence (NICE) in England and Wales. This is the independent body responsible for national guidance on the following three areas of healthcare:

- health technologies – new and existing medicines, treatments and procedures
- clinical practice – appropriate treatment for specific conditions
- public health – promotion of good health and prevention of ill health.

NICE only examines drugs that are referred to it by the Department of Health (DH) and the Welsh Assembly. NICE manages the early stages of topic selection on behalf of the DH, considering topics that come from a number of sources, including clinical and public health professionals (through a form on its website), the DH and NICE itself. Once the topics have been filtered using criteria set by the DH, the suggestions are reviewed by consideration panels consisting of experts on the topic. The DH then make the final decision on which topics NICE will produce guidance on. The selection criteria for the choice of new topics include:

- burden of disease
- resource impact
- policy importance
- whether there is inappropriate variation in practice across the country
- factors affecting the timeliness or urgency for guidance to be produced.

NICE guidance is based on a review of clinical and economic evidence. NICE has two systems for the appraisal of drugs. The multiple technology appraisal process is used for appraisals of more than one drug, and looks at groups of drugs that are already on the market, in order to compare them to one another. For the rapid assessment of single new drugs, existing drugs with new indications and other treatments, a single technology appraisal process has recently been introduced. The NHS is legally obliged to resource medicines recommended by NICE in England and Wales.

In Wales, the All-Wales Medicines Strategy Group (AWMSG) also advises on medicines management. In Scotland, the remit of NICE is covered by the Scottish Medicines Consortium (SMC) and NHS Quality Improvement Scotland (NHS QIS) (including the Scottish Intercollegiate Guidelines Network (SIGN)). NICE multiple technology appraisals apply to Scotland, but with advice on implementation in Scotland from NHS QIS. NICE single technology appraisals do not apply to Scotland, and this role is performed by SMC. NICE has no direct counterpart in Northern Ireland. NICE clinical guidelines and technology appraisals apply, but with advice on implementation in Northern Ireland from the Department of Health, Social Services and Public Safety (DHSSPS).

The award of marketing authorisation already indicates that a licensed drug is clinically effective, and therefore much of the work of NICE and SMC relates to the evidence of cost-effectiveness. When evaluating cost-effectiveness, consideration is given to the effect on NHS patients as a whole, and on the patients who would directly benefit from the medicine. Evidence of the cost-effectiveness of a drug is needed in order to make a balanced decision on its use.
Factors that may lead to non-evidence-based prescribing

There are a number of factors that can affect the prescribing practice of healthcare professionals. Discussed below are some of the main factors that may result in non-evidence-based prescribing, and potential ways in which evidence-based prescribing can be achieved.

Evidence sources
Time constraints, in conjunction with the overwhelming amount of new information continually being produced, make it difficult for healthcare professionals to keep up to date with current developments. It is not always feasible for healthcare professionals to refer to primary sources of information, and in particular, to assess this information critically. The National Prescribing Centre (NPC) therefore suggests that validated, refined information from trusted sources may be most useful for healthcare professionals. The British National Formulary (BNF), NICE guidance, British Medical Journal (BMJ) Clinical Evidence and Cochrane Library reviews are good sources of pre-digested information, as detailed later in this report. Guidance on sourcing the most useful evidence is available from the NPC resource Using evidence to guide practice.

Patient expectations
Patient expectations, and healthcare professionals’ perceptions of them, are influential in the outcome of consultations. A number of studies have shown that some doctors may prescribe unnecessarily when they believe that the patient is expecting a prescription and to maintain a good doctor-patient relationship, the most prominent example of which is the prescription of antibiotics. Healthcare professionals may also consider that a consultation with a patient expecting a prescription will be shorter if that prescription is given, rather than if the patient’s expectations are managed and no prescription is given. Consultation times in the long term, however, may be increased by unnecessary prescribing. The immediate prescription of antibiotics for a sore throat (usually a self-limiting condition), for example, has the effect of increasing reattendance. On being prescribed antibiotics, patients increase their belief that antibiotics are effective, and are therefore more likely to return for future consultations, termed ‘medicalising’.

Patient expectations do not always correlate with healthcare professionals’ perception of them, and it has been suggested that perceived patient pressure has a greater effect on clinical outcome than the preferences of the patients themselves. Indeed, it has been shown that patient satisfaction does not necessarily correspond with receiving prescriptions, and the provision of information and reassurance can sometimes be more important.

There are a number of potential strategies for managing patient expectations. It may be helpful for healthcare professionals to explicitly find out patient expectations in the consultation, thus overcoming any ambiguity or assumption. In the case of antibiotics, explanation of the reasons why they are not being prescribed may be useful in improving patient satisfaction and reducing future consultations. Patient information campaigns on the benefits and disadvantages of antibiotics may also be useful to support evidence-based prescribing. The DH runs an ongoing public education campaign on common misconceptions regarding antibiotics and illnesses featuring ‘Andybiotic’, a cartoon antibiotic character. The campaign was introduced in 1999, and relaunched in March 2006. Healthcare professionals are encouraged to make use of the campaign material, available from the DH website, to inform patients about the use of antibiotics.
Patient concordance
Patient non-adherence\(^1\) in taking prescribed medicines is common. Adherence rates for prescribed medicines are typically about 50 per cent.\(^1\) A Cochrane Review concluded that a number of simple interventions (such as counselling and written information) could help short-term adherence. The methods currently used for improving adherence in long-term medical conditions, however, were found to be mostly complex and not very effective, and the review suggested that further research was required.\(^1\)

A study in 1997 by the Royal Pharmaceutical Society of Great Britain (RPSGB) suggested a model for the relationship between patient and prescriber.\(^3\) The model introduced the term patient ‘concordance’, which advocates a partnership between patients and prescribers with shared decision-making, rather than the traditional terms of patient ‘compliance’ or ‘adherence’, which imply that the patient carries out the prescriber’s instructions. Patients ultimately make the decision as to whether or not to take a medicine that has been prescribed to them. Concordance is an important component of the interaction between patient and prescriber.

Defensive/untargeted prescribing
In some cases, healthcare professionals may overprescribe due to a fear of the clinical outcome if they do not prescribe, or through uncertainty in the diagnosis. A prime example is the prescription of antibiotics for some cases of sore throat. Antibiotics are commonly prescribed, despite evidence that complications for sore throat are rare without prescription, or with delayed prescription, and that essentially the condition is self-limiting.\(^14,20\) One study demonstrated that some general practitioners (GPs) prescribe for sore throats because they are uncertain as to which patients will benefit from the antibiotics, and are concerned about complications.\(^21\) Referral to clinical guidelines and relevant evidence, including the incidence of secondary problems resulting from the complaint can, however, minimise the need for defensive or untargeted prescribing.

Inherent biases
Decision-making in general is subject to several common biases, which may affect the prescribing habits of healthcare professionals, as discussed in a recent review. The predominant biases described are the tendency to:

- assume that similar things must belong to the same category
- make judgements based on what comes to mind easily, or what has recently been encountered
- be over confident in judgements made
- take account of evidence that fits an expectation over other evidence
- see relationships between unrelated events.\(^22\)

There may also be an innate assumption that new and high cost medicines are better than tried and tested medicines. Knowledge of these inherent biases is important in making a rational treatment decision, and advocates a structured and coherent approach to decision-making.

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\(^1\) Adherence can be defined as the extent to which a patient’s behaviour coincides with medical or health advice, for example, in taking a prescribed medicine.
Pharmaceutical companies

Pharmaceutical company marketing has been suggested to have an effect on the prescribing habits of GPs. There are statutory measures that control the advertising of medicines, which are enforced by the MHRA. The pharmaceutical industry self-regulates, in the form of codes of conduct administered by trade associations. The Association of the British Pharmaceutical Industry (ABPI) publishes the Code of practice for the pharmaceutical industry.23

A recent report has indicated that GPs who have weekly contact with pharmaceutical company representatives are more likely to prescribe new drugs before evidence-based advice has been released.24 They are also more likely to find consultations resulting only in giving advice dissatisfying, and are more susceptible to pharmaceutical company marketing.24 Incentives from pharmaceutical companies can have a persuasive effect, or induce a feeling of obligation. In Good medical practice, the GMC states that ‘You must not ask for or accept any inducement, gift or hospitality which may affect or be seen to affect the way you prescribe for, treat or refer patients’.3 The 2005 Health Select Committee report The influence of the pharmaceutical industry, fourth report of session 2004-05 suggested that in particular less-experienced and non-specialist doctors can be ill-equipped to cope effectively with promotional material from pharmaceutical companies.5 Healthcare professionals should be aware of the risk of bias in their prescribing practice through the influence of pharmaceutical companies, and apply their own judgement along with the best available evidence, when making prescribing decisions.

Media influence

A more recent influence on prescribing is the effect of media stories regarding the use and efficacy of new drugs. An example of this is trastuzumab (Herceptin) which was licensed in the European Union (EU) by the EMEA in 2002 for use in advanced cases of HER2-positive breast cancer. It was not originally licensed for use in early stage breast cancer, but subsequent clinical trials indicated that it may be beneficial. These results were presented at the American Society of Clinical Oncology annual meeting in 2005, and then published in the New England Journal of Medicine (NEJM),25,26 with an editorial claiming the potential of Herceptin to be ‘revolutionary’.27 Patient demand and media and political pressure grew for the drug to be available for cases of early stage breast cancer. Primary Care Trusts (PCTs) in England were told by the government to consider funding Herceptin prior to its licensing, and the drug began a fast track process through NICE. The Lancet came to a different conclusion to the NEJM, publishing an editorial expressing concerns that the available evidence on the efficacy and safety of Herceptin was insufficient, and cautioning that NICE should be given due time to thoroughly evaluate the drug.28 Three months after licensing, Herceptin was fast tracked through NICE and recommended for use with early stage HER2-positive breast cancer. The SMC also recommended Herceptin for this use on the same day.

Whether NHS funds are best used in providing Herceptin to early stage breast cancer patients is still contentious. Irrespective of this, there was considerable pressure from the media, patient groups, the pharmaceutical company manufacturing the drug, and the government, for this drug to be made available on the NHS.

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1 Herceptin is a medicinal product, for which the active ingredient is trastuzumab.
Problems ensuing from non-evidence-based prescribing

Inappropriate and non-evidence-based prescribing can be detrimental, both to the patient, the healthcare professional, and more widely to the NHS and general population.

First and foremost, inappropriate prescribing can harm the patient. Inappropriate medication can cause adverse reactions, or lack efficacy for the presenting condition. The consequences can be mild to severe, and may result in hospital admission and in some cases fatality. There is little evidence regarding the prevalence of adverse reactions resulting from inappropriate prescribing. Adverse drug reactions in general, however, are common. A study published in 2004 found that 6.5 per cent of hospital admissions in the UK were related to an adverse drug reaction, with a projected annual cost of £466m, and an overall fatality of 0.15 percent. For more information on adverse drug reactions, please see the 2006 BMA publication Reporting adverse drug reactions: a guide for healthcare professionals.

Issuing prescriptions unnecessarily can cause repeat attendance for similar complaints. This practice is therefore detrimental to the healthcare professional, as in the long term, consultation time is increased.

The emergence of antibiotic resistance is a natural occurrence and inevitable with the use of antibiotics. There is extensive, albeit mainly circumstantial, evidence that antibiotics cause drug resistance. The results of a recent randomised controlled trial demonstrate a clear link between antibiotic treatment and the development of antibiotic resistance in the individual treated. Patient non-compliance is also a concern in the development of antibiotic resistance. Where the full course of antibiotics is not completed, there may be an opportunity for microbes to survive the treatment and adapt.

On reducing the use of antibiotics, it is predicted that any decline observed in antibiotic resistance would be slow. Unnecessary prescribing may, however, hasten resistance, posing a serious risk to public health. Antibiotic resistance makes infections more difficult, and more costly, to treat. Organisms that have developed resistance to multiple antibiotics are of particular concern, and have the potential to make some infections untreatable. For more information on healthcare associated infections, please see the 2006 BMA publication Healthcare associated infections – a guide for healthcare professionals.

Over-prescription, ineffective prescription and patient non-compliance can be damaging to the NHS financially through medicine wastage and increased hospital admissions. Prescribing is a major cost to the NHS. Particularly in the current climate of financial deficits within the NHS, cost-effective prescribing is imperative. Part of evidence-based prescribing is using medicines that represent value for money.

Generic prescribing is beneficial in minimising prescribing costs, and therefore in making funds available for innovative treatments. High degrees of generic prescribing are now widely recognised as evidence of good prescribing practice. The exception is when bioavailability problems require the use of branded medicines. The BNF recommends that ‘Where non-proprietary (‘generic’) titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the healthcare service. The only exception is where bioavailability problems are so important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated.’

There is also a need for disinvestment from treatments that have been used for many years, but that are not evidence-based. The Committee on the Review of Medicines was set up in 1975 to advise on the safety, quality and efficacy of medicines on the UK market. The Committee reduced the number of medicines available on the UK market from 39,000 in 1975 to 10,000 in 1990. NICE is now beginning work on a programme of ineffective practice review, to identify treatments that are not clinically or cost-effective for use on the NHS.

Generic prescribing is where drugs are prescribed by their non-proprietary name, rather than by a brand name. Generic medicines are equivalents of brand-named drugs for which the patent has expired, and tend to be less expensive.
Limitations of available evidence

Clinical trials
Clinical trials are important in establishing a sound evidence base for the usage of medicines. A general hierarchy exists for the validity of evidence obtained by different methodologies. Retrospective studies, such as case-control studies, are more susceptible to bias than prospective studies. Prospective, double-blinded randomised controlled trials (RCT) are considered to be the gold standard for reliability. For further information on clinical trials, please see the 2004 BMA Clinical trials internet resource.

There are limitations to clinical trials, however, even when the most reliable methodologies are used. Although they may demonstrate the efficacy of medicines, clinical trials are rarely able to determine their long-term impact. They are generally not conducted over extended periods of time, and therefore do not eliminate the risk of unknown future complications. Clinical trials tend to use a wide range of exclusions and contra-indications to participation, and are conducted on only a limited number of individuals, who are therefore unlikely to be representative of the whole population. Genetic variation within the population, the differing medical histories and existing conditions of patients, and the different drugs and combinations of drugs that they may be taking, can all have an effect on drug response.

Pharmacogenetics is the study of the effect of genetic variation on drug response. It is an emerging field of study, which may have the potential to lead to more targeted therapeutics for individual patients, increasing efficacy and safety. There is evidence to suggest that polymorphisms in the genes encoding drug-metabolising enzymes can alter the activity of the enzymes, and thereby the drug response. Prominent examples are the enzymes N-acetyltransferase (NAT) and those of the cytochrome P450 family, as detailed below.

• N-acetylation by NAT is a pathway of drug metabolism. Genetic variation results in high or low levels of NAT activity, which in turn causes rapid or slow rates of acetylation in individuals. The metabolism of a number of drugs varies as a result of this, as do their action and toxicity, including the anti-tuberculosis drug isoniazid.
• Metabolism by the cytochrome P450 enzymes is the most common route for drug elimination. It has been demonstrated that genetic variation affecting the activity of some members of this family is associated with the response to many widely prescribed drugs. Cytochrome P450 2D6, for example, can affect efficacy and clearance of a large number of drugs, such as nortriptyline, and cytochrome P450 2C19 affects the ability to metabolise omeprazole. A gene chip is available to screen individuals for the common polymorphisms in these two enzymes (Roche AmpliChip CYP450).

Genetic variation in genes encoding drug transporters and drug targets can affect the response to medication. Pharmacogenetics has the potential to aid drug selection and dosage for individuals, and subsequently improve efficacy and reduce adverse drug reactions. Clinical outcome data are, however, signally lacking for nearly all available genetic tests. Ideally such tests would be validated through an RCT demonstrating a better outcome in the group for whom the genetic test was used. The reality of using genomics at the bedside is, at present, still a long way off.

Evidence-based prescribing
Due to the limitations of clinical trials, pharmacovigilance is essential following licensing. The effective reporting of adverse drug reactions accumulates an evidence base that can inform prescribing, improving safety and efficacy. For further information on pharmacovigilance, and the professional responsibility of healthcare professionals in reporting adverse drug reactions, please see the 2006 BMA report *Reporting adverse drug reactions, a guide for healthcare professionals*.

The validity of clinical trial outcomes cannot always be assumed. Concerns have long been raised over bias in some clinical trials sponsored by pharmaceutical companies. A number of opportunities for bias were identified in *The influence of the pharmaceutical industry, fourth report of session 2004-05*, which examined the influence of pharmaceutical companies on the conduct and publication of medical research. Potential ways in which bias may occur in clinical trials are listed below.

- Inappropriate choice of comparator drugs and selection of dosage, or use of placebo control treatment, to show the new drug in the best light.
- Ghost authorship, where the contribution of the sponsoring pharmaceutical company is not acknowledged in the publication. A recent article has demonstrated that there is a high prevalence of ghost authorship in industry-initiated randomised trials.
- Selective publishing, where negative or equivalent results are not published, skewing the published evidence base.
- Retrospective subgroup analysis/post hoc analysis, which increases the likelihood of achieving false positive results. Subgroup analysis is, however, valuable when applied appropriately, ie for hypothesis generation.
- Using multiple outcome measures, which increases the likelihood of achieving false positive results. There is a need for one appropriate primary outcome measure, with pre-specified secondary measures and appropriate statistical analysis.
- Presenting effects in terms of relative, as opposed to absolute risks. Relative efficacy is good for quantifying the effectiveness of a drug, but is not adequate on its own to inform clinical decisions. The absolute risks and benefits (expressed as numbers needed to harm, numbers needed to benefit) are needed, taking prior probability into account.

Concerns over clinical trial regulation and selective publishing are being addressed. From July 2005 the International Committee of Medical Journal Editors (ICMJE) has required that trials be registered at inception to be considered for publication. The World Health Organisation (WHO) is setting up an International Clinical Trials Registry Platform (ICTRP). The aim of this platform is to ensure the registration of all clinical trials, and therefore that the information is publicly available, and to set international standards for the registration of clinical trials and reporting. Healthcare professionals should be aware of the risk of bias or inaccuracy in clinical trial data, and results should not be taken at face value.

**Paediatric prescribing**

Evidence for medicine use in children is limited as children have traditionally been excluded from clinical trials. This is due to the complex ethical issues surrounding clinical trials in children, problems in recruiting sufficient children for participation, and the high cost of the studies compared to the often small size of the potential market. Pharmaceutical companies are not legally obliged to conduct trials in children if the drug is not to be licensed for their use.

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A study on paediatric wards in five European countries, including the UK, showed that almost half of drug prescriptions to children were either unlicensed or off label (prescribed outside the terms of the product license), with the vast majority being off label. In the UK, 30 per cent of prescriptions to children were either unlicensed or off label. The prescriptions may or may not be appropriate, but at present there is little evidence on which to base decisions. The lack of evidence on medicine use in children can have two consequences. Firstly, medicines or dosages being used may be ineffective or even harmful to children. Secondly, there may be adult medicines that are effective and safe in children, but which have not been trialled, and therefore licensed, for paediatric use.

The problem of paediatric prescribing is beginning to be addressed. The DH has launched the Medicines for Children Research Network (MCRN), which is part of the UK Clinical Research Network. The MCRN is a managed research network, funding research into the development and provision of drugs that are safe and effective for children, with a particular focus on clinical trials. The second edition of the British National Formulary for Children (BNFC) was published in July 2006, providing up to date information to healthcare professionals on the use of medicines for the treatment of children. This resource provides information that has been validated against emerging evidence, best-practice guidelines and a network of clinical experts on both licensed and unlicensed drugs for children.

Growing concern in Europe has led to a proposal by the European Commission for a Regulation on medicinal products for paediatric use, which was agreed by the European Parliament in June 2006. The Regulation predominantly aims to ensure that medicines used by children have been subject to high quality, ethical research and clinical trials. New drugs developed will either require a plan of clinical trials in children (for which a six-month patent extension will be given), or a certificate stating that the drug is not suitable for children. Existing drugs that have been appropriately tested for use in children will be given a new licence of ‘paediatric use marketing authorisation’ (PUMA). All of these measures are leading towards a better evidence base for paediatric medicine use, and therefore safer and more effective prescribing practice.

**Prescribing for pregnant women**

Most drugs are unlicensed for use in pregnant women due to the difficulties of involving them in clinical trials. Women of child-bearing age and women who are pregnant have traditionally been under-represented in research trials due to concerns about the possible effects of new drugs or new procedures on the woman’s long-term reproductive health or any existing fetus. This has meant that pregnant women have often been unable to have medicines specifically shown to be effective and safe during pregnancy, although there are some drugs that have a long history of safe use.

Drugs can have a harmful effect on the fetus during pregnancy. The BNF provides a list of drugs to be avoided or used with caution in pregnancy. Underprescribing can also be a problem in pregnant women, as in certain cases the effects of the condition untreated can be more harmful for the fetus than appropriate drug treatment. The level of compliance and required dosage may also vary for pregnant women. The BNF recommends that ‘Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used.’

Although there has been great reluctance to involve pregnant women in research, or women of childbearing age generally in early studies (Phase 1 trials), ethical guidance from bodies such as the Royal College of Physicians (RCP) has long countenanced the possibility of pregnant women taking part in research into pregnancy-related conditions which could not be conducted on other people. RCP
guidance from 1990, for example, emphasised that where pregnant women participate in research into pregnancy-related illness, the research ethics committee which scrutinises the trial protocol should pay particular attention to the likelihood of the research having any effect on the fetus and specify the nature and magnitude of such effects.

Research protocols should be scrutinised by an independent ethics committee whose role is to ensure that the benefits of the research outweigh the potential harms, and that the safety of trial participants is paramount. For any such study, satisfactory reproductive toxicology studies must have been performed before human participants are involved. Eventually, this should produce medical solutions for the conditions experienced by pregnant women. In the meantime, however, evidence-based prescribing for this patient group still poses some problems. Women who are planning pregnancy must also be taken into account with regard to prescribing.

**Prescribing for older people**

Older people have traditionally been under-represented in clinical trials. They may be excluded for a number of reasons, including concerns over their frailty, co-morbidity or use of multiple medicines, potential complications surrounding consent, and mobility and transport problems. This under-representation in clinical trials makes older people vulnerable to inappropriate prescribing.

Men and women aged 60 and over received 57 per cent of prescription items in England in 2005, and on average each older person received 38 prescriptions over the course of that year. Older people are at greater risk of adverse reactions to drugs because of increased sensitivity to their effects, reduced effectiveness of homeostatic mechanisms and an increased risk of idiosyncratic reactions. Liver size and hepatic blood flow decrease with age, resulting in a reduced ability to metabolise drugs, and a reduction in renal clearance causes slower excretion of drugs. Older people are at greater risk of drug interactions, as they are more likely to be taking more than one drug, and also of failure of compliance.

There are initiatives targeting the health of older people. The National Service Framework (NSF) for Older People was published in 2001. It is a 10-year programme setting national standards and service models of care for older people in England, including the use of medicines. An additional report on implementation of aspects relating to medicines was published, and reference is made to the importance of evidence-based prescribing.

The RCP Clinical Effectiveness and Evaluation Unit (CEEU) is also undertaking a programme on the healthcare of older people. One of the aspects of this programme is to develop new algorithms for appropriate prescribing. The CEEU undertook a National Sentinel Clinical Audit of Evidence-based Prescribing for Older People in 1999/2000, to collect and assess the appropriateness of prescriptions to the elderly. The resulting report includes recommendations for improving prescribing practice. An audit tool entitled *Appropriate prescribing of bisphosphonates to prevent glucocorticoid induced osteoporosis – screening in older people* (GIOSCOPE) is available from the publications department of the RCP.

In summary, the limitations of available evidence, and in some cases, lack of evidence, can be restrictive in evidence-based prescribing, and the potential for bias should not be overlooked. Sources of evidence-based guidance are detailed later in this report. Reference to the best available evidence should be used with clinical expertise to form part of a rounded decision-making process by the healthcare professional.
Education and training

**Undergraduate training**

The GMC requirements for undergraduate medical training are set out in the 2003 version of *Tomorrow’s doctors*. This states that graduates must know about and understand the principles of ‘the effective and safe use of medicines as a basis for prescribing, including side effects, harmful interactions, antibiotic resistance and genetic indicators of the appropriateness of drugs’. In addition, graduates must have the required clinical skills, which include the ability to ‘work out drug dosage and record the outcome accurately’ and ‘write safe prescriptions for different types of drugs’. It is also required that students must be properly prepared for their first day of foundation year 1 (F1), which includes ‘the ability to prescribe drugs under the supervision of a qualified doctor’.

There are some concerns being raised that the level of undergraduate training may be insufficient to prepare medical students for prescribing following qualification. In 2001, the Audit Commission report *A spoonful of sugar – improving medicines management in hospitals* expressed ‘concerns that the core curricula at medical schools do not provide a thorough knowledge of safe medicines prescribing and administration. Shortcomings in doctors’ knowledge mean that there is a particular risk of medication errors when they first arrive in hospital. Only a small proportion of new doctors believe that their induction dealt adequately with medicines management issues’.

Some medical schools have developed individual prescribing formularies. At the University of Liverpool, undergraduate medical students build up personal formularies in their final year. The University of Edinburgh has an online student formulary containing the core drugs covered in the undergraduate curriculum. Clinical skills training also embraces correct dosage calculation and administration of drugs, which are assessed to some depth by Objective Structured Clinical Examinations (OSCEs). A specific assessment in prescribing skills at the end of undergraduate medical training may be beneficial, to ensure that students focus on this aspect of their training, and so that patients can be reassured that new doctors reach a minimum acceptable standard.

The Clinical Section Committee of the British Pharmacological Society has developed a core curriculum for teaching prescribing in UK medical schools, which includes evidence-based prescribing as core knowledge and understanding. Curricula for other undergraduate courses that cover prescribing, such as a Bachelor of Science (BSc) in Pharmacology and pre-registration nursing, are also available from the British Pharmacological Society. These curricula are a good resource for educators to refer to when compiling prescribing curricula.

**Postgraduate training**

In postgraduate medical education, the curriculum for the foundation programme under Modernising Medical Careers (MMC) includes evidence-based prescribing. The core competencies for foundation years 1 and 2 include:

- ‘implements the available evidence base in most areas of clinical care with appropriate usage of NICE and SIGN guidelines’
- ‘demonstrates critical ability in evaluating the evidence base for aspects of clinical practice’
- ‘uses the BNF, pharmacy and computer-based prescribing decision support to access information about drug treatments including drug interactions’
- ‘routinely notifies drug monitoring agencies of possible significant adverse drug reactions’.

OSCEs assess clinical and communication skills by testing candidates’ responses to a series of simulations.
In terms of specialty training, education in evidence-based prescribing will vary according to the specialty. The Royal College of General Practitioners, for example, has a curriculum statement on evidence-based practice. The framework of competences for level 3 training in paediatrics, published by the Royal College of Paediatrics and Child Health, includes competencies on the rational and cost-effective use of medicines.

Nurses and pharmacists who wish to become independent prescribers will need to complete an accredited education and training programme. The courses run over a period of three to six months, and are a minimum of 26 days, with a further 12 days of learning in practice, which are supervised by a medical practitioner. The general curricula for independent pharmacist and nurse prescribers incorporate training in evidence-based prescribing and clinical governance. The adequacy of this training has not yet been evaluated.

**Continuing professional development**

Education in prescribing practice should continue throughout the careers of healthcare professionals through continuing professional development (CPD). The GMC states that ‘doctors must keep up to date with professional duties in all areas of Good medical practice and other guidance which we publish’. Through CPD, healthcare professionals can keep their knowledge and skills up to date following qualification. The National Prescribing Centre currently offers an online support package on Using evidence to guide practice. The University of Keele also runs a distance learning course on Evidence-based practice and clinical governance.
Conclusions

Evidence-based prescribing is essential for safe and effective healthcare. Healthcare professionals need to be aware of the factors that can lead to non-evidence-based prescribing, and also the limitations of the available evidence and opportunities for bias. Reference to the evidence base can minimise the risk of adverse drug reactions, and improve efficacy, and should therefore play an integral part in prescribing decisions. Pre-digested sources of information, such as those detailed later in this report, are a useful resource.

Antibiotics in particular are often prescribed unnecessarily, which can accelerate the development of antibiotic resistance. Responsibility lies with healthcare professionals to prescribe antibiotics only when necessary, and in a manner tailored to the particular condition. It is encouraging to note that the level of antibiotic prescribing in primary care is decreasing. The 2002 DH report Getting ahead of the curve: a strategy for combating infectious diseases reported a fall of 23 per cent in antibiotic prescribing in primary care in England between 1996 and 2000. Healthcare professionals can also encourage patients to complete the course of antibiotics prescribed, and improve their understanding through the provision of relevant information.

The effectiveness of any drug must be weighed against its cost, as the drug chosen dictates not only the clinical outcome for each patient treated, but also the number of patients able to receive that, or another, treatment. Clinical effectiveness is relative, not absolute, as most drugs work to some extent, but not all are good value for money. The GMC requires that healthcare professionals should be aware of the appropriate guidance on the clinical and cost-effectiveness of medicines. Healthcare professionals should use this guidance with their clinical expertise in making evidence-based prescribing decisions.

h Published by NICE in England and Wales, the AWMSG in Wales, the DHSSPS in Northern Ireland and the SMC and NHS QIS in Scotland.
Resources for effective prescribing

National guidance
In Good practice in prescribing medicines the GMC requires that doctors must be aware of guidance published from the sources detailed below.

The National Institute for Health and Clinical Excellence (NICE)
NICE (www.nice.org.uk) issues recommendations on the use of medicines that are referred to it by the DH and the Welsh Assembly. These recommendations are based on a review of both clinical and economic evidence, and apply to England and Wales. Please see the introduction of this resource for further detail on the role of NICE.

The All-Wales Medicines Strategy Group
In Wales, healthcare professionals should be aware of guidance from the All-Wales Medicines Strategy Group (www.wales.nhs.uk/awmsg), which advises the Welsh Assembly on medicines management.

Scottish Medicines Consortium and NHS Quality Improvement Scotland (NHS QIS)
In Scotland, healthcare professionals need to be aware of guidance from the Scottish Medicines Consortium (www.scottishmedicines.org.uk) and NHS Quality Improvement Scotland (NHS QIS) (www.nhshealthquality.org) (including the Scottish Intercollegiate Guidelines Network (SIGN)), which carry out the equivalent role of NICE in Scotland.

The Department of Health, Social Services and Public Safety (DHSSPS)
In Northern Ireland, healthcare professionals need to be aware of guidance from the DHSSPS (www.dhsspsni.gov.uk).

The British National Formulary (BNF) and BNF for Children
The BNF (www.bnf.org/bnf) is a joint publication by the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain. Guidance is available for health professionals on prescribing, dispensing and administering medicines. The GMC requires that doctors are familiar with this guidance, in particular regarding the use, side effects and contraindications of medicines they prescribe. The BNF for Children (http://bnfc.org/bnfc) provides guidance specifically for paediatric prescribing, an area in which there is little evidence available and medicines prescribed are often unlicensed or off-label.

The Department of Health
The DH (www.dh.gov.uk) publication Building a safer NHS for patients: improving medication safety explores the causes and frequency of errors in medication, details drugs and clinical settings associated with particular risks, and identifies models of good practice to reduce risk.

Further useful sources of information are:
• BMJ Clinical Evidence
  BMJ Clinical Evidence (www.clinicalevidence.com) is a publication providing systematic reviews on the prevention and treatment of clinical conditions. The reviews are based on available systematic reviews, randomised controlled trial data, and observational studies where appropriate.
• BMJ Masterclasses
  BMJ Masterclasses (www.bmjmasterclasses.com) are held on various clinical areas, and help to keep doctors up to date on the latest research, and put the research into practice.
• Drugs and Therapeutics Bulletin (DTB)
  The DTB (www.dtb.org.uk/idtb) is published by the BMJ Group, and provides evaluations and advice on treatments and disease management.
• **The Cochrane Library**
  The Cochrane Library (www.cochrane.org) provides regularly updated, reliable evidence to inform decision making for healthcare professionals. Included within the Library are the Cochrane reviews, which explore the available evidence regarding the effectiveness and appropriateness of treatments.

• **MeReC**
  MeReC (www.npc.co.uk/merec.htm) produces a number of publications which provide evidence-based information on medicines and prescribing. MeReC publications are produced by the NPC and funded by NICE.

• **The National electronic Library for Medicines (NeLM)**
  The NeLM (www.nelm.nhs.uk) disseminates local and national medicines information from NHS organisations, such as NICE, NPC and DH, and professional bodies such as the BMA, and the Royal Pharmaceutical Society and independent organisations. It aims to provide a comprehensive web based medicines resource promoting safe, effective and efficient medicine use within the NHS. It is a part of the National Library for Health (NLH).

• **The National Prescribing Centre (NPC)**
  The NPC (www.npc.co.uk) is a health service organisation which provides education and development (including workshops, conferences and seminars for healthcare professionals), medicines management services, publications providing evidence-based information on prescribing, and support for non-medical prescribing.

**Local arrangements**
In addition to the national guidance described above, there are local arrangements at primary and secondary care level to encourage more effective prescribing. At primary care level, prescribing support/advisory teams or individuals with varied titles (eg pharmaceutical adviser) support and encourage evidence-based and cost-effective prescribing locally.

Drugs and therapeutics committees, area prescribing committees, or similar advisory bodies, provide prescribing guidance and control in hospitals, and manage the content of the formulary. They tend to be made up of primary and secondary care membership, usually pharmacists and clinicians, but also sometimes lay members. Hospitals and trusts may also have their own internal committees to help support/manage secondary care prescribing.

**Computer aided prescribing**
Various computer aides are being developed to assist healthcare professionals in evidence-based prescribing. PRODIGY guidance, for example, is an NHS resource providing information to enable healthcare professionals to make evidence-based decisions. In addition to being available online and in print, PRODIGY guidance is available through all clinical systems used in primary care that are RFA99 accredited. It is an online system for GPs that provides support for clinical decisions. PRODIGY guidance is gradually being replaced by the new resource Clinical knowledge summaries, which expands on the existing PRODIGY resource.

Several computer programs have been developed to assist in calculating the optimum dosages of potentially toxic drugs. A Cochrane Review on these computer programs concluded that there is evidence to support the use of computer assistance in determining drug dosage. The review found that, for drugs with a narrow therapeutic window, computer assistance meant that fewer patients had toxic levels, therapeutic control was achieved earlier, adverse effects were reduced and hospital stays were shorter. The review concluded, however, that further research was required to fully assess the benefits and risks. The computer systems reviewed were found to have a higher degree of accuracy in tailoring drug doses to individual patients than clinicians, although this result cannot necessarily be extrapolated to different computer systems and clinical situations.
Further sources of information

**Association of the British Pharmaceutical Industry (ABPI)**
www.abpi.org.uk
The ABPI is the trade association for companies in the UK producing prescription medicines.

**All-Wales Medicines Strategy Group (AWMSG)**
www.wales.nhs.uk/awmsg
The AWMSG advises the Welsh Assembly on strategic medicines management and prescribing.

**British Medical Association (BMA)**
www.bma.org.uk
The BMA general practitioners committee (GPC) has a clinical and prescribing subcommittee which advises the BMA on matters relating to drugs and prescribing. The BMA has also set up a cross-branch of practice committee prescribing forum to ensure coherent responses to government on prescription-related areas.

**BMJ Clinical Evidence**
www.clinicalevidence.com
BMJ Clinical Evidence is a publication providing systematic reviews on the prevention and treatment of clinical conditions. The reviews are based on available systematic reviews, randomised controlled trial data, and observational studies where appropriate.

**BMJ Masterclasses**
www.bmjmasterclasses.com
BMJ Masterclasses are held on various clinical areas, and help to keep doctors up to date on the latest research, and put the research into practice.

**British National Formulary (BNF)**
www.bnf.org/bnf
The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society of Great Britain, providing up to date information to healthcare professionals regarding the use of medicines.

**British National Formulary for Children (BNFC)**
http://bnfc.org/bnfc
The BNFC is a joint publication of the British Medical Association, the Royal Pharmaceutical Society of Great Britain, the Royal College of Paediatrics and Child Health, and the Neonatal and Paediatric Pharmacists Group. It provides up to date information to healthcare professionals regarding the use of medicines for treating children.

**Cochrane Library**
www.cochrane.org
The Cochrane Library provides regularly updated, reliable evidence to inform decision making for healthcare professionals. Included within the Library are the Cochrane reviews, which explore the available evidence regarding the effectiveness and appropriateness of treatments.

**Department of Health (DH)**
www.dh.gov.uk
The DH provides information on prescribing and medicines management, and government policy.
Department of Health, Social Services and Public Safety (DHSSPS)
www.dhsspsni.gov.uk
The DHSSPS provides information on prescribing and medicines management in Northern Ireland.

Drugs and Therapeutics Bulletin (DTB)
www.dtb.org.uk/dtb
The DTB is published by the BMJ Group, and provides evaluations and advice on treatments and disease management.

European Medicines Evaluation Agency (EMEA)
www.emea.europa.eu
The EMEA is a decentralised body of the European Union. It is responsible for the evaluation and supervision of medicines.

General Medical Council (GMC)
www.gmc-uk.org
The GMC provides generic guidance on prescribing, highlighting factors that professionals should take into account.

Medicines and Healthcare products Regulatory Agency (MHRA)
www.mhra.gov.uk
The MHRA is a government agency, which regulates medicines and medical devices.

MeReC
www.npc.co.uk/merec.htm
MeReC produces a number of publications which provide evidence-based information on medicines and prescribing. MeReC publications are produced by the NPC and funded by NICE.

National electronic Library for Health (NLH)
www.library.nhs.uk
The NLH is an electronic health library for NHS staff. Through the NeLM, it disseminates local and national medicines information from NHS organisations, such as NICE, NPC and DH, and professional bodies such as the BMA, and the Royal Pharmaceutical Society and independent organisations.

NHS Quality Improvement Scotland (NHS QIS)
www.nhshealthquality.org
NHS QIS is a special health board providing guidance to NHS Scotland on effective clinical practice, including on the clinical and cost-effectiveness of medicines.

National Institute for Health and Clinical Excellence (NICE)
www.nice.org.uk
NICE is the independent body responsible for national guidance on new and existing medicines in England and Wales.

National Prescribing Centre (NPC)
www.npc.co.uk
The NPC is a health service organisation which provides education and development (including workshops, conferences and seminars for healthcare professionals), medicines management services, publications providing evidence-based information on prescribing, and support for non-medical prescribing.
Royal Pharmaceutical Society of Great Britain (RPSGB)
www.rpsgb.org.uk
The RPSGB is the regulatory and professional body for pharmacists in England, Wales and Scotland.

Scottish Medicines Consortium (SMC)
www.scottishmedicines.org.uk
The SMC advises NHS boards in Scotland on the use of new and existing medicines.
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The Foundation Programme Committee of the Academy of Medical Royal Colleges (2005) Curriculum for the foundation years in postgraduate education and training. London: The Foundation Programme Committee of the Academy of Medical Royal Colleges.
83 www.npc.co.uk (accessed April 2007).
84 www.keele.ac.uk (accessed April 2007).
Department of Science and Education publications

- Breaking the cycle of children’s exposure to tobacco smoke (2007)
- Gambling addiction and its treatment within the NHS: a guide for healthcare professionals (2007)
- Selection for specialty training (2006)
- Doctors as teachers (2006)
- Becoming a doctor 2007 (web resource – updated annually)
- Interprofessional Education (2006)
- The expert patients programme – a discussion paper (2005)
- Sexual orientation in the workplace (2005)
- Medical specialties: the way forward (2005)
- Population and genetic screening (2005)
- Vaccine development – web resource (2005)
- Mobile phones and health – an update (2005)
- Binge drinking (2005)
- Emergency planning arrangements for the NHS in the UK – a collection of responses from the Board of Science (2005)
- Hepatitis B vaccination in childhood (2005)
- Over the counter medication (2005)
- Preventing childhood obesity (2005)
- Biotechnology, weapons and humanity II (2004)
- Refuse management and health (2004)
- Medical education A to Z 2004 (web resource)
- Developing the doctor – manager leadership role (2004)
- Smoking and reproductive life: the impact on smoking, reproductive and child health (2004)

Copies of these and other reports can be obtained from:
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