EDITORIAL

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Drugs: incomplete and inconsistent "official" information

In 2002 an international team studied the consistency of therapeutic information available to health care professionals and patients in 26 countries around the world (a)(1).

They selected three well-known and widely prescribed drugs (nifedipine, fluoxetine and ciprofloxacin) used to treat important health disorders (in terms of morbidity and mortality) and marketed relatively recently in the countries concerned.

The study focused on officially approved information (summary of product characteristics (SPC) annexed to the marketing authorisation, or similar reports), or, in countries where no officially approved information was available, on information provided by the manufacturers to prescribers and patients (1).

The information thus collected was then compared with that published in the British National Formulary (BNF), an independent international reference in use worldwide (b)(1,2). The analysis focused on four issues: indications; adult dose regimen; contraindications and warnings; and common adverse effects affecting at least 1% of patients as well as severe reactions (according to criteria published by the World Health Organisation) (c,d)(1).

The degree of agreement between the information collected and that included in the BNF was calculated for each issue, each drug, and each country (e)(1).

Major differences between the information provided and the BNF. **All the indications included in the BNF were mentioned in the information on nifedipine collected in 11 of the 26 countries, while this was the case for fluoxetine in only 3 countries (Canada, Estonia and the United Kingdom), and for ciprofloxacin in 2 countries (Colombia and the United Kingdom) (1).**

Differences in dose regimens for ciprofloxacin, nifedipine and fluoxetine in comparison to those stated in the BNF were found in respectively 3, 7 and 9 countries.

The major adverse effects of ciprofloxacin and fluoxetine mentioned in the BNF were not found in their entirety in any of the 26 countries. Only in Spain were all the major adverse effects of nifedipine mentioned, while none were mentioned in the information collected in Colombia (1).

In all 26 countries, the information available for all three drugs omitted certain contraindications and warnings mentioned in the BNF.

The information provided by the French regulatory agency was incomplete for all three drugs; the degree of agreement with the BNF was 1 (out of a possible 4) for ciprofloxacin and fluoxetine, and zero for nifedipine (1).

Whose interests do regulatory agencies really serve? **The authors of this study expressed their surprise at the low level of agreement between the information provided in these 26 countries and that included in the BNF. They criticised national regulatory authorities for accepting at face value the information provided by drug companies, instead of examining the many references that are now readily accessible.**

The information provided in marketing authorisation files is incomplete. The information included in SPCs is correct but incomplete; the fact that the SPC does not include specific information does not necessarily mean that the information does not exist.

This study confirms that health professionals must use reliable sources of information such as the BNF and other independent publications, and that regulatory agencies must fulfil their public health responsibilities.

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Management of conflict of interest: the example of the Cochrane Collaboration

The Cochrane Collaboration has developed strict rules to protect its systematic reviews from conflicts of interest.

Created in 1993 and now established in nearly 90 countries, the non-profit Cochrane Collaboration has acquired an international reputation for the Cochrane Database of Systematic Reviews, a collection of regularly updated reviews of the efficacy of a growing number of medical therapies and interventions for disease prevention. The Cochrane review methodology is strict and explicit (1-3).

The Cochrane Database of Systematic Reviews is the main documentary resource in the Cochrane Library. It is published four times a year, both on CD-ROM and online (**a**). In the last few years the Cochrane Collaboration has acquired the active support of health authorities in a number of countries (in South and Central America, Australia, Spain, Ireland, Iceland, Finland, Norway and the United Kingdom). Health care professionals and the public in these countries have benefited from free (publicly funded) access to the online Cochrane Library.

Strict and explicit methods

Thousands of contributors (editors, authors and peer reviewers) participate, on an unpaid basis, in the production of systematic reviews for the Cochrane Collaboration.

In general, teams of unpaid authors propose subjects ("titles") for review articles to one of the 50 thematic editorial teams ("collaborative review groups") covering nearly all fields of medicine.

The interventions, target populations and outcomes assessed during systematic reviews are first agreed upon with the editorial team. Once the title has been defined and accepted, the authors write a detailed protocol describing how the data will be analysed. The protocol must be published in the Cochrane Library before the analytical work begins.

The editorial teams maintain the responsibility and the right to approve publication, in the Cochrane Library, of protocols and systematic review articles (and updates) covered by their field of interest (**b**).

Funding sources and conflict of interest: clearly stated for each review

The work of the steering group and coordinating office of the Cochrane Collaboration is funded by subscriptions to the Cochrane Library.

Conflict of interest. Authors, who sometimes work free of charge, generally receive financial support from a variety of sources (mainly universities and government agencies). Funding sources and authors' potential conflicts of interest are always listed at the end of each Cochrane review article.

A section of the Cochrane Handbook for Systematic Reviews of Interventions (an official reference manual intended for authors of Cochrane reviews) deals with conflict-of-interest statements (4). It specifies that "*Cochrane Reviews should be free of any real or perceived bias introduced by the receipt of any benefit in cash or kind, any hospitality, or any subsidy derived from any source that may have or be perceived to have an interest in the outcome of the review. It is a matter of Cochrane Collaboration policy that direct funding from a single source with a vested interest in the results of the review is not acceptable*" (4).

Two review articles jointly funded by a pharmaceutical company rekindled a debate on conflict of interest within the Cochrane Collaboration. In 2001, two reviews, ►►

a- The Cochrane Collaboration also produces a register of comparative trials (the Cochrane Controlled Trials Register), a register of publications which report on methodological issues about controlled trials (Cochrane Methodology Register), and a bank of systematic reviews of methodological studies (Cochrane Database of Methodology Reviews). The Cochrane Library contains all the articles of the Cochrane Collaboration as well as those of three other banks of review articles produced by the NHS Centre for Reviews and Dissemination, a British public organisation (ref 1). Commercial distribution of the Cochrane Library, on CD-ROM and online, is handled by the Anglo-American publisher John Wiley & Sons (http://www.thecochranelibrary.com).

b- A list of the Collaborative Review Groups, their websites, protocol titles and review articles can be found on the Cochrane Collaboration website http://www.cochrane.org/contact/entities.htm#CRGLIST (consulted on 2 March 2005).

a- The study was conducted by members of the International Society of Drug Bulletins (ISDB), including Prescrire, in collaboration with Quality Assurance and Safety of medicines (QSM) of the World Health Organisation (WHO). The analysis focused on information collected by health care professionals participating in the study in 26 countries: in the Americas (Argentina, Brazil, Canada, Colombia, U.S., Mexico, Peru and Venezuela); Europe (Croatia, Spain, Estonia, France, Italy, Poland, United Kingdom and Switzerland); Africa (Egypt, Kenya, Mozambique and Tunisia); Asia (India, Pakistan, Philippines, Syria and Thailand); and Australia (ref 1).

b- BNF literature sources include the Martindale database, a global reference in drug therapy (ref 3).

c- Data that were not published in the BNF were not included in the analysis.

d- "Official" information, available at the time of marketing authorisation (e.g. the summary of product characteristics), was obtained for fluoxetine and nifedipine in 18 countries, and for ciprofloxacin in 14 countries (ref 1).

e- The BNF was used to establish a list of items for each of the four types of information (37 items for ciprofloxacin, 48 for fluoxetine, 22 for nifedipine). The authors compared the number of items on this list with those mentioned in the information collected in each country. These figures served to calculate a "degree of agreement" of information, expressed as scores of 1, 0 or -1, for the indications, precautions and adverse effects. For the dose regimen, the authors awarded a score of 1 when the dose corresponded to that mentioned in the BNF, and 0 when the dose was different. The sum of the scores obtained for the four types of information and for a given drug could therefore range from +4 to -3 (ref 1).

1- Reggi V et al. "Prescribing information in 26 countries: a comparative study" *Eur J Clin Pharmacol* 2003; **59** (4): 263-270.
2- British Medical Association and Royal Pharmaceutical Society of Great Britain "British National Formulary (UK)".
3- The Royal Pharmaceutical Society of Great Britain "Martindale The complete drug reference" 34th ed. The Pharmaceutical Press, London 2005: 2 756 pages.

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