ABOUT PRESCRIRE

The "just say no…" Charter, 2005

Association Mieux Prescrire (AMP) is the owner and administrator of *la revue Prescrire* and *Prescrire International*. AMP seeks to defend a number of core values such as independence, ethical care, and placing the patient at the centre of the decision-making process and health care systems.

AMP has around 300 members who are increasingly aware that there are many obstacles to these core values. At its December 2004 General Assembly, it was therefore decided that health professionals must sign on this 'Just say no…' Charter every year in order to be granted AMP membership. This obviously applies to Prescrire editors.

The signatories of this charter wish to ensure that health professionals' activities and decisions are dedicated solely to serving patients' best interests.

We are aware that health care, teaching and research activities can be subject to influences that can undermine health professionals' independence and ethics, such as:

– economic and financial influence from pharmaceuticals firms through direct and indirect promotional campaigns aimed at patients and health professionals, through the funding of information resources and initial or permanent training initiatives, and pressure on the public authorities;

– economic, political and financial influence from national or supranational bodies responsible for drafting or applying regulations or for managing preventive, diagnostic and treatment resources;

– the personal interests of the professionals themselves; we are aware that patients too can be influenced by direct or indirect approaches, biased information and funding with a hidden agenda;

– funding of patient groups by the pharmaceuticals industry;

– dissemination of unsubstantiated information, or even pure advertising by drugs manufacturers, via the consumer media, opinion formers etc.;

– the organisation of so-called health awareness campaigns by the industry.

The signatories pledge to work towards quality care and to:

– refuse any direct participation that goes against this aim, especially drugs manufacturers' involvement in health issues;

– refuse benefits in kind, gifts and subsidies from pharmaceuticals firms and other bodies likely to be serving their own interests rather than those of the patients, both individually and on behalf of the professional bodies they serve on;

– be wary of pharmaceuticals firms' promotional activities (advertising, sales reps' visits, "opinion-formers", etc.), so as to distinguish, or at least compare them, with independent source of information;

– choose instead independent sources of information and favour comparative information;

– choose, whenever possible, professional, initial and permanent training that is independent from any kind of subsidy from pharmaceuticals firms or other bodies likely to be serving their own interests rather than those of the patients;

– provide patients with information from reliable, quality sources so as to share decision-making with them on the basis of dependable information.

NEWS OF PRESC

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2004 : Lies and damned lies

Prescrire's Medical Representative Monitoring Network was created 14 years ago and its annual reports have shown a remarkable consistency in the methods employed by medical reps. The tools may change: more reps are now promoting several companies' products; computers are omnipresent; and there is a greater focus on heavy prescribers (1-3). However, the basic trend is the same: benefits are stressed and risks minimized.

A year of pseudo innovation. In 2003 most rep visits reported by the Network focused on old drugs, isomers, metabolites, combinations, range extensions or me-toos (4). The trend continued in 2004, reflecting the lack of true innovation. Most drugs promoted to Network observers were me-toos belonging to already well-represented drug families. They included, for example, almotriptan, dustasteride, manidipine, nebivolol, rosuvastatin, valdecoxib (finally not marketed in France after the prelaunch phase (5)), and zofenopril. Other reps promoted copies with fantasy names such as Divarius° (paroxetine), and range extensions such as Vastarel° 35 mg (trimetazidine).

In total, 50% of reported rep visits focused on new products, but the majority of these new drugs offered no advantages over existing products.

Accompanying information: not reliable. A medical reps Charter signed in late 2004 by the French Pricing Committee and representatives of the pharmaceutical industry states that medical reps must provide prescribers with the French pharmacoeconomic Committee's assessment of the medical benefit of the drugs they promote (6).

Despite this regulatory requirement, the Committee's assessment was only voluntarily provided to physicians in 5% of reported rep visits in 2004. This was a slight improvement over 2003, but still virtually negligible.

The Charter also states that medical reps must not offer gifts of any sort, even when requested by the prescriber. These include office materials and discounts (travel checks, gift vouchers, etc.) (6).

Drastic changes are needed if drug companies are to respect the Charter: all sorts of gifts were offered to Network observers in 2004, ranging from minor office materials to dinner invitations with "specialists" and participation in "phase IV studies" that serve mainly to bolster sales. And

things are unlikely to change much in 2005, judging from the "weekend training sessions" on ezetimib (Ezetrol°, MSD Chibret) that were offered to prescribers in early 2004.

Exaggerated benefits and lack of attention to risks. In 2004, 35% of the indications for drugs that sales reps promoted to Network members were not mentioned in the corresponding SPC. In nearly all of these cases, reps systematically extended the indications, and they simply invented off-licence uses in 9% of cases. The doses they recommended were also higher than those mentioned in the SPC in 15% of cases.

The reps seen by Network members were careful to minimize the risks associated with the products they promoted. For example, they only volunteered complete information concerning contraindications in 8% of cases and partial information in 15% of cases. The respective rates were 9% and 13% for precautions for use, 6% and 15% for interactions, and 13% and 17% for adverse effects. Thus, despite the numerous pharmacovigilance scandals that occurred in 2004, the quality of the information that medical reps provide on the risks associated with the products they promote has hardly improved: the same figures have been found in the last 14 years (7,8).

Cut-throat competition. If the terms of the Charter were respected, relationships between competing firms would be cordial and polite (6).

However, in 2004, as in previous years, Network members found that medical reps were increasingly aggressive towards their competitors. The most intense in-fighting in 2004 focused on the sartans, and on cetirizine, a product whose patent recently expired. A similar feeding frenzy occurred when rofecoxib, a Cox-2 inhibitor, was withdrawn from the market.

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2- Le Masson S "La visite médicale s'externalise de plus en plus" *Pharmaceutiques* 2004; (120): 63.
3- Jarrige C "La nouvelle panoplie de la promotion" *Pharmaceutiques* 2005; (123): 41-45.
4- Prescrire Rédaction "Visite médicale: surtout un engin de guerre entre firmes" *Rev Prescrire* 2004; **24** (247): 104.
5- Prescrire Rédaction "Les prétentions de la firme Pfizer" *Rev Prescrire* 2004; **24** (251): 432.
6- "Charte de la visite médicale" 22 December 2004. Website http://www.leem.org
7- Prescrire Editorial Staff "Report by Prescrire reps monitoring on sales representatives" *Prescrire Int* 1999; **8** (41): 86-89.
8- Prescrire Editorial Staff "Prescrire's sales reps monitoring network" *Prescrire Int* 2004; **13** (71): 116.

PRESCRIRE VIEWPOINT

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Still too many analgesic mixtures

In the early 1980s many preparations sold over the counter in France contained up to eight active substances with various effects, such as nonsteroidal antiinflammatory drugs, caffeine, opiates, barbiturates and antihistamines.

"Anti-mixture" measures in 1982. Work by the French health authorities led to welcome but partial changes in composition, such as the withdrawal of amidopyrine (a pyrazole analgesic); prescription drug status for noramidopyrine (risk of agranulocytosis) and phenacetin (an antipyretic analgesic carrying a risk of nephropathy, haemolytic anemia and methemoglobinemia); and a total dose limit of 8 grams for boxes of paracetamol (to reduce the risk of liver damage after overdose) (1-4).

Further improvements in the 1990s. The composition of some analgesic-based preparations has since been further simplified, such as the gradual disappearance of phenacetin (5); barbiturates (6,7); butalbital (8); quinine derivatives (9); and clearance of bromide from one product (10,11,12). Note that that these changes often consisted of replacing one substance with another, considered less harmful (paracetamol replacing phenacetin, for example).

The French medicines agency era: bad analgesic mixtures still on the market. Analgesic combinations containing three or even four active substances are still on the French market, usually with authorisations decades old. It is well known that these combinations have a negative risk-benefit balance, notably because of additive adverse effects, drug interactions, and risks associated with concurrent intake of another preparation containing the same substances.

Several obsolete substances are still available, such as belladonna powder combined with codeine, caffeine and paracetamol, and opium powder combined with paracetamol and caffeine. Caffeine is ubiquitous, despite the lack of proven analgesic effects and the known risks of excitatory and anxiogenic effects (13). Examples are products containing caffeine combined with aspirin and paracetamol; aspirin and meadow queen (Filipendula maria); paracetamol and codeine; paracetamol and dextropropoxyphene; aspirin and codeine; and a "homeopathic" product containing tinctures of belladonna and other substances combined with standard doses of aspirin and caffeine.

These mixtures have numerous disadvantages, including a risk of additive adverse effects and interactions; different regulatory statuses; risks of interactions with dietary components (especially alcohol and caffeine); various trade names bearing little relevance to the nature of the components; and uninformative packaging (international non proprietary names mentioned in small print on the side of the box but not on the blisters); and incoherent patient information leaflets (**a**).

The French medicines agency seems simply to ignore these facts, doing nothing to withdraw these mixtures from the market.

European measures to be applied in France. European Directive 2004/27/EC stipulates that fixed-dose combinations containing up to three active substances must mention all three international non proprietary names on the outer and inner packaging (14). And, hopefully, the new obligation that information leaflets be tested on panels of potential users will further underline the incoherence of such mixtures.

a- Such combinations can lead to inconsistent patient information leaflets. For example, the Precautions section of the Prontalgine° leaflet specifies that "this drug can cause insomnia and must not be taken at the end of day", while the section on Driving and Machine Use draws attention to the risk of drowsiness.

1- Ministère de la Santé - Direction de la Pharmacie et du Médicament "Synthèse des décisions prises sur les antalgiques" January 1982: 3 pages.
2- Prescrire Rédaction "Modifications de formules" *Rev Prescrire* 1982; **2** (12): 7-8.
3- Prescrire Rédaction "Quelques notes sur… Les changements de formules antalgiques" *Rev Prescrire* 1982; **2** (13): 3.
4- Prescrire Rédaction "Modifications de formules" *Rev Prescrire* 1982; **2** (14): 4.
5- Prescrire Rédaction "Changement de composition: Sédaspir°" *Rev Prescrire* 1989; **9** (85): 200.
6- Prescrire Rédaction "Changement de composition: Céquinyl°" *Rev Prescrire* 1993; **13** (132): 454.
7- Prescrire Rédaction "Changement de composition: Prontalgine°" *Rev Prescrire* 1993; **13** (130): 327.
8- Prescrire Rédaction "Changement de composition: Optalidon°" *Rev Prescrire* 1991; **11** (103): 16.
9- Prescrire Rédaction "Changement de composition: Céquinyl°" *Rev Prescrire* 1999; **19** (197): 515.
10- Prescrire Rédaction "Changement de composition: Prontalgine°" *Rev Prescrire* 1998; **18** (188): 672.
11- Prescrire Rédaction "Changement de composition: Céphyl°" *Rev Prescrire* 1999; **19** (193): 198.
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14- Prescrire Editorial Staff "Medicines In Europe: the most important changes in the new legislation" available free at http://www.prescrire.org/aLaUne/dossierEuropeSynthese2En.php