

Avoiding iatrogenic complications

Marketing authorisation is being granted prematurely for an increasing number of new drugs, before their efficacy and particularly, their adverse effects have been properly evaluated (*Rev Prescrire* n°326).

One would expect drug regulatory agencies to be more cautious and responsive following scandals such as the *diethylstilbestrol* (DES) disaster and, more recently, the *benfluorex* (ex-Mediator^o) affair (*Prescrire Int* n°105, 107, 113 and *Prescrire* website).

Market withdrawal: an effective measure, especially when timely.

Drug regulatory agencies often appear reluctant to withdraw drugs with negative risk-benefit balances, allowing sales to continue unabated and needlessly exposing patients to a risk of adverse effects.

The return of topical *ketoprofen* to the market after initial withdrawal at the demand of the French drug agency (Afsaps) illustrates how drug companies' financial interests are often put ahead of patient safety (*Prescrire Int* n°109, 112, 113).

In 2010, only a small proportion of drugs with a negative risk-benefit balance were taken off the market, several years after their dangers were first identified. They included *bufexamac*, a topical non-steroidal antiinflammatory drug, because of potentially serious cutaneous disorders (eczema) (*Rev Prescrire* n°321, 325); *carbocisteine* and *acetylcysteine* (mucolytic agents) in infants, because of respiratory adverse effects (*Rev Prescrire* n°320, 324); *rosiglitazone* (an antidiabetic), because of cardiovascular adverse effects (*Rev Prescrire* n°325, 326); and *sibutramine* (an appetite suppressant), also because of cardiovascular adverse effects (*Prescrire Int* n°107).

Refusal to grant marketing authorisation: another effective means of protecting patients.

Patients were protected from exposure to unnecessary risks of certain drugs last year, after the EU Committee for Medicinal Products for Human Use (CHMP) refused to grant market approval or issued an unfavourable opinion, leading the company to withdraw its application. They included:

- refusal of marketing authorisation for *gemifloxacin*, a particularly risky fluoroquinolone (*Rev Prescrire* n°319);
- refusal of marketing authorisation for *ixabepilone* in breast cancer, because of serious and frequent neuropathies and haematological disorders (*Rev Prescrire* n°315);



Drugs to avoid

The following is a list of certain drugs analysed in *Prescrire* in 2010 that have more potential harms than benefits and that should be avoided pending the decision by the authorities (or the drug companies) to take them off the market.

NSAIDs, antidiabetics, psychotropics, etc. Several nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, especially cox-2 inhibitors:

- topical *ketoprofen* gel because of cutaneous disorders (*Prescrire Int* n°109, 112). The French regulator (Afsaps) decided to withdraw these gels in late 2009, but in mid-2010, CHMP recommended that they be allowed to remain on the market;
- *nimesulide* because of potentially life-threatening liver damage (*Rev Prescrire* n°323);
- *celecoxib* (Celebrex^o in rheumatology, and Onsenal^o in familial adenomatous polyposis) and *etoricoxib* because of an excess of cardiovascular and cutaneous disorders (see www.english.prescrire.org and *Prescrire Int* n°108);
- *parecoxib* because of life-threatening skin reactions (*Prescrire Int* n°109).

And also:

- *meprobamate* because of the high risk of adverse effects with this psychotropic drug, too often misused as a “recreational” drug (see www.english.prescrire.org);
- *nicorandil* because of its unproven efficacy in angina pectoris and the risk of serious ulceration (gastrointestinal, vaginal, etc.) (*Prescrire Int* n°110);
- *quinine* for cramps, because of the risk of potentially life-threatening haematological effects (*Rev Prescrire* n°326);
- *pioglitazone*, an antidiabetic drug with adverse effects that outweigh its efficacy (*Rev Prescrire* n°325 and www.english.prescrire.org);

- *ropinirole* in restless legs syndrome: this dopamine agonist has known adverse effects but no proven efficacy in this setting. In 2010, the French authorities recommended that it no longer be reimbursed (*Rev Prescrire* n°325);
- *telithromycin*, a macrolide carrying a risk of cardiac, hepatic and visual disorders (*Prescrire Int* n°106 and www.english.prescrire.org);
- *trimetazidine*, because of a negative risk-benefit balance in angina pectoris, dizziness, tinnitus and visual disorders, and especially a risk of extrapyramidal syndrome and thrombocytopenia (*Prescrire Int* n°106 and www.english.prescrire.org).

On 21 December 2010, the fixed-dose combination containing *dextropropoxyphene* and *paracetamol* was still on the market, but it is slated for European market withdrawal in 2011 (on 1 March 2011 in France) (*Rev Prescrire* n°323 and www.english.prescrire.org).

Cost of inadequate regulation. In view of these few examples, how can decision-makers and health authorities be trusted, when they allow patients to be exposed to harmful drugs, letting society pick up the tab for hospitalisation, sick leave, and agree to provide reimbursement for vastly over-priced drugs.

For example, the direct cost of prescriptions for glitazones in France was about 50 million euros in 2007, for the national health insurance system alone (*Rev Prescrire* n°317).

There is a cost for inadequate regulation. Decision-makers can start to get a grip on health spending by refusing to provide reimbursement for drugs with a negative risk-benefit balance.

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- refusal of extension of the indications for two psychotropics used in fibromyalgia: *pregabalin* and *milnacipran* (in depression) (*Rev Prescrire* n°320).

Adverse effects: insist on more openness. Because marketing authorisation is increasingly granted prematurely, the adverse effect profiles of many new drugs are not properly documented at the time of market release.

Post-marketing data on adverse effects are therefore crucial and must be made available to the public. The European Medicines Agency (EMA) issued alerts on

the following products (among others) in 2010:

- *becaplermin* because of infections and cancer (*Prescrire Int* n°108);
- *fluoxetine* because of cardiac malformations in newborns exposed in early pregnancy (*Rev Prescrire* n°323);
- *lenalidomide* because of myocardial infarction (*Prescrire Int* n°109);
- *olanzapine* because of sudden death and urinary incontinence (*Prescrire Int* n°109);
- *orlistat* because of interactions, pancreatitis and nephropathies (*Prescrire Int* n°107, 110);
- angiotensin II receptor continued p. 109 ▶▶