New drugs and indications in 2014
Some advances this year, but many drugs are poorly evaluated, too expensive, or more dangerous than useful

Abstract

- Three drugs analysed by Prescrire in 2014 provided a significant therapeutic advance for some patients.
- In 2014, too many drugs are still best avoided, have undergone minimal evaluation, or are excessively expensive.
- Drug regulatory agencies should continue their efforts to improve pharmacovigilance and transparency.

Some tangible progress in 2014

Since the early 2000s, very few new drugs or indications have provided a tangible advance for patients (see the overview of past Prescrire Drug Awards p. 109).

In 2014, Prescrire singled out three new drugs that constitute a significant or major therapeutic advance for some patients.

Three significant advances. Cholic acid (Orphacol®), which received a “Bravo” rating in our analysis, was authorised at the European Union level in late 2013 for certain hereditary defects of bile acid synthesis. The only known curative treatment for these rare disorders, which are usually fatal during childhood, is liver transplantation (Prescrire Int n° 157). In these patients, when initiated early, cholic acid greatly increases life expectancy and eliminates most of their symptoms. Cholic acid was previously available in France as a hospital product and subsequently through a temporary compassionate authorisation (ATU) programme.

Two drugs were rated as “a real advance” in 2014. Intravenous artesunate (Malacef®) is now the standard treatment for severe malaria and is more effective in reducing mortality than injectable quinine. Although few patients require this drug in Europe, it provides a benefit to many patients in regions of the world where malaria is common. In France, artesunate has been available since mid-2011 through an ATU protocol, involving collection of data on the treated patients. As of 3 December 2014, no drug companies had applied for marketing authorisation (MA) for artesunate, which would facilitate access to this drug in the European Union (Prescrire Int n° 154).

The cytotoxic tyrosine kinase inhibitor imatinib (Glivec®) constitutes an advance for some children with Philadelphia chromosome-positive acute lymphoblastic leukaemia, because it prolongs survival considerably (Prescrire Int n° 157).
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Hypoglycaemic drugs to avoid. In 2013, the harm-benefit balance of several new hypoglycaemic drugs or indications was considered unfavourable. This was also the case in 2014. Four of the 19 new drugs or indications rated as "not acceptable" are hypoglycaemic drugs. Insulin degludec, alone or in combination with insulin aspart, has no proven advantages over other long-acting insulins and appears to expose patients to a greater risk of cardiovascular adverse effects (Prescrire Int n° 150). Glitpins such as saxagliptin and vildagliptin have no demonstrated efficacy, yet their serious adverse effects are well established (Prescrire Int n° 152). Canagliflozin, a "me-too" of dapagliflozin, has disproportionate adverse effects, given that its efficacy in preventing the clinical complications of type 2 diabetes has not been demonstrated (Prescrire Int n° 157).

Monoclonal antibodies to avoid. Among the 14 analyses of monoclonal antibodies published in our French edition in 2014, mainly used in rheumatology, oncology or multiple sclerosis, three were rated "not acceptable" due to their unfavourable harm-benefit balance. The adverse effects of monoclonal antibodies are generally serious, because these drugs have effects well beyond their intended target, including immunosuppression, infections, possibly cancers, etc. These adverse effects are unacceptable when the benefit that patients can expect to derive is poorly demonstrated or appears marginal, as is the case with canakinumab in gout attacks (Prescrire Int n° 151), or natalizumab and alemtuzumab in relapsing-remitting multiple sclerosis, for example (Prescrire Int n° 158).

Dangerous routes of administration

A drug’s harm-benefit balance is sometimes unfavourable because its route of administration exposes patients to serious risks. This is the case for the cytotoxic monoclonal antibody trastuzumab, which provokes more frequent serious adverse effects (infections and cardiac disorders) when administered subcutaneously for certain types of breast cancer than when it is administered intravenously (Rev Prescrire n° 374). The same is true for loxapine for oral inhalation, a neuroleptic used in acute agitation, which exposes patients to a high risk of bronchospasm when administered by this route; in addition, it requires the cooperation of agitated patients (see in a coming issue).

Minimal evaluation is still too common

In 2014, Prescrire gave a “judgement reserved” rating to 7 newly authorised drugs or indications, as well as one drug authorised several years ago which we re-assessed with more follow-up. In most of these cases, the established adverse effects were disturbing, and while the clinical evaluation included some positive elements, there were insufficient data to determine the harm-benefit balance. This was the case for: the cancer drugs bosutinib, vismodegib and trastuzumab emtansine (Prescrire Int n° 151, 156 and 154); bedaquiline in multidrug-resistant tuberculosis (Prescrire Int n° 153); and the ophthalmology drugs alfibercept in central retinal vein occlusion and ocularplasin in viremocanal traction (Prescrire Int n° 157).

Marketing authorisations granted too easily. Drug regulatory agencies too often grant marketing authorisations on the basis of minimal evaluation (Rev Prescrire n° 363). For example, nalbemfene has not been compared with standard drugs used to treat alcohol dependence (Prescrire Int n° 150). And the dose equivalency of tapentadol with other opioids has not been determined (Prescrire Int n° 149).

A new European regulation on clinical trials, adopted in 2014, failed to require that pharmaceutical companies demonstrate that their new drug constitutes a therapeutic advance, thereby missing the opportunity to encourage comparative evaluations of new drugs against those already available (see english.prescrire.org).

Some useful cases of regulated off-label use

Marketing authorisations give pharmaceutical companies the right to market their drugs, but there is no guarantee that the drug has undergone robust evaluation or that patients will derive any benefit from treatment. They do, however, define how and in which situations a drug should be used, based on the evaluation of the health authorities, and
provide healthcare professionals and patients with useful information about the drug through its summary of product characteristics (SPC) and patient leaflet.

Sometimes, however, in serious or rare disorders, drugs without national or European marketing authorisations are presumed to be useful and are used off-label. In France, this use can be regulated through a temporary compassionate authorisation or production. It is typical to account the recommendations of the Covigilance Risk Assessment Committee (PRAC), and must justify any decisions made to the pharmacovigilance system. Several improvements were achieved in 2013, including: a group of over one hundred oncologists from around the world spoke out against the high cost of tyrosine kinase inhibitors, such as dasatinib, nilotinib and imatinib (Prescrire Int n° 153). In 2014, Gilead Sciences charged the exorbitant price of about €57 000 in France for 12 weeks of treatment with its product Sovaldi® (sofosbuvir), provided through an ATU compassionate use programme, subsequently lowered to €41 000 when marketing authorisation was granted. This price bears no relation whatsoever to the cost of research and development or production. It is typical of the business model adopted by some pharmaceutical companies, based on financial speculation at the expense of patient safety, it is better if ATUs and pharmaceutical companies a key role in transparency is required of drug regulatory agencies.

### Exorbitant prices for certain drugs

The price of various drugs, in particular cancer drugs, has soared in recent years. In 2013, a group of over one hundred oncologists from around the world spoke out against the high cost of tyrosine kinase inhibitors, such as dasatinib, nilotinib and imatinib (Prescrire Int n° 153). In 2014, Gilead Sciences charged the exorbitant price of about €57 000 in France for 12 weeks of treatment with its product Sovaldi® (sofosbuvir), provided through an ATU compassionate use programme, subsequently lowered to €41 000 when marketing authorisation was granted. This price bears no relation whatsoever to the cost of research and development or production. It is typical of the business model adopted by some pharmaceutical companies, based on financial speculation at the expense of patient safety, Pharmaco-vigilance, independent of industry

Pharmacovigilance was reorganised in the European Union in 2010, and again in 2012 (Prescrire Int n° 153, 157).

**Some progress, but drug companies still play a key role in pharmacovigilance.** Several improvements were made to the pharmacovigilance system. For example, European patients now have the option of reporting adverse drug reactions directly to health authorities. The committees that grant marketing authorisations must now take into account the recommendations of the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), and must justify any decisions that differ from the PRAC’s recommendations. The information made available to the public about the harms of drugs has been improved, and greater transparency is required of drug regulatory agencies. However, this reorganisation has given pharmaceutical companies a key role in the collection and interpretation of adverse drug reaction reports, despite the obvious conflicts of interest that would lead them to downplay the adverse effects of their own products.
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It is therefore important that healthcare professionals and patients report adverse drug reactions to their local pharmacovigilance system (regional, national or federal centres), to ensure that safety signals are analysed by an independent organisation (Prescrire Int n° 155, 157).

Too few market withdrawals of dangerous drugs. Health authorities withdrew a few dangerous drugs from the French market in 2014.

Tablets and suppositories containing salbutamol, a short-acting beta-2 agonist used without evidence of efficacy in obstetrics, were withdrawn due to serious cardiovascular harms to both the mother and the unborn child (Rev Prescrire n° 366).

Carpipramine, an old neuroleptic with no demonstrated efficacy in schizophrenia and anxiety, was withdrawn on account of the serious dose-dependent heart rhythm disorders it provokes (Rev Prescrire n° 373).

Yet many drugs with an unfavourable harm-benefit balance remain on the market and are prescribed too liberally (see our list of drugs to avoid at english.prescrire.org).

Restrictions on use: sometimes justified, but too often only half-measures. One of the tasks of drug regulatory agencies is to define how and in which situations drugs can be used. Some dangerous adverse effects can be limited through special precautions such as restricting the drug’s indications, withdrawing high dose strengths or lowering the approved dosages. But restrictions on use are also a means for drug regulatory agencies to protect themselves while leaving drugs on the market that should be withdrawn because of their unfavourable harm-benefit balance.

Domperidone, a neuroleptic used as an antiemetic, exposes patients to the risk of torsades de pointes, were reduced for patients aged 75 years or older in some situations (Rev Prescrire n° 367).

The maximum intravenous doses of the antiemetic ondansetron, which can cause dose-dependent prolongation of the QT interval, especially in elderly patients, with a risk of fatal torsades de pointes, were reduced for patients aged 75 years or older in some situations (Rev Prescrire n° 364).

The nonsteroidal anti-inflammatory drug (NSAID) aceclofenac exposes patients to a greater risk of cardiovascular events than similar medications, especially at high doses and with prolonged use. It is now contraindicated in patients with cardiovascular disorders, and the recommended dose is limited to the lowest effective dose for the shortest possible duration (Rev Prescrire n° 374).

Health authority transparency: efforts should be continued

In accordance with new pharmacovigilance regulations that came into force two years ago, the European Medicines Agency (EMA) now publishes various types of pharmacovigilance information: the agendas and minutes of PRAC meetings; excerpts from the centralised European pharmacovigilance database, through a limited interface called ADRReports; a little more information about “risk management plans”, as a public summary of the risk management plan for each new drug; and regular updates by the PRAC of the list of drugs “under additional monitoring” (Prescrire Int n° 155).

On the other hand, the EMA’s policy on access to clinical data, released in late 2014, falls far short of the announcements made by EMA directors. As of late 2016, it will be possible to access some clinical trial reports, but only to view online and not to download. And pharmaceutical companies will be able to request the redaction of “any information contained in the clinical reports (…) where disclosure may undermine the legitimate economic interest of the applicant/MAH” (Prescrire Int n° 157).

Patients’ interests must come first

In 2014, Prescrire singled out three drugs that provided significant therapeutic advances.

Health authorities have made some efforts to improve pharmacovigilance and transparency, but they need to do more.

Pharmaceutical companies continue to play key roles in which conflicts of interest exist. They still have a central role in generating the data that underpin their marketing authorisations, and in collecting and analysing adverse effect reports. They demand increasingly exorbitant prices for new drugs, which bear no relation to the cost of production and research, thus endangering access to healthcare and the sustainability of universal healthcare systems.

If we are to put patients’ interests first, the focus of clinical research must shift towards unmet needs, and health authorities must serve the public rather than acting as service providers for the pharmaceutical industry. The mobilisation of healthcare professionals, patients and citizens, in France and in Europe, is more necessary than ever to create the political will to resist illness-based financial speculation by drug companies.