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).
New drugs and indications in 2014

Hypoglycaemic drugs and monoclonal antibodies with more harms than benefits

A few other advances, especially for children with infectious diseases. In 2014, 20 new drugs or new indications provided a moderate therapeutic advance: 5 were rated as "offers an advantage" and 15 as "possibly helpful". Almost half of these new drugs or indications are used for the prevention or treatment of infectious diseases in children: vaccines against invasive infections with meningococcal group B bacteria ([Rev Prescrire n° 152]) or pneumococcus ([Rev Prescrire n° 369]), and against Japanese encephalitis ([Rev Prescrire n° 371]); antiretrovirals such as darunavir, etravirine, raltegravir and tenofovir, which provide additional options for the treatment of HIV in children ([Rev Prescrire n° 367, 368 and Prescrire Int n° 152]); and peginterferon alfa-2a, an immune response modifier in chronic hepatitis C, which now comes with a graduated response modifier in chronic hepatitis C, and ([Rev Prescrire n° 367, 368 and Prescrire Int n° 152]); and peginterferon alfa-2a, an immune response modifier in chronic hepatitis C, which now comes with a graduated response modifier in chronic hepatitis C, and

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 glargine, 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]). Glitins 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]).

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 aldibercept in central retinal vein occlusion and occlusaamin in vireomacular 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, nalme-fene has not been compared with standard drugs used to treat alcohol dependence ([Prescrire Int n° 150]). And the dose equivalence 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 recommendation (ATU or ATU). An ATU has thus been granted for para-aminosalicylic acid in multidrug-resistant tuberculosis (Prescrire Int n° 153). The gamma-aminobutyric acid (GABA) analogue baclofen has been used off-label in alcohol dependence for several years. While awaiting the results of two ongoing clinical trials, the off-label use of baclofen is regulated in France through an ATU. This measure is intended in particular to collect information that will help evaluate baclofen in this situation and to monitor its adverse effects (Rev Prescrire n° 374).

In the interests of quality care and patient safety, it is better if ATUs and RTUs remain temporary and are upgraded to marketing authorisations as soon as appropriate.

## 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° 156). 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 re-assessments “with more follow-up”.

### a. Results for the years 1982 to 2004 can be found in Rev Prescrire n° 213 p. 59 and 258 p. 140. This table includes new products (other than generics) and new indications proposed in France, as well as re-evaluations “with more follow-up”.

b. The drug is thioctic acid in type 1 or 2 hereditary defects of primary bile acid synthesis (Prescrire Int n° 157).

c. The drugs are:
   - alemtuzumab in relapsing-remitting multiple sclerosis (Prescrire Int n° 158);
   - imatinib in Philadelphia chromosome-positive acute lymphoblastic leukaemia in children (Prescrire Int n° 157).

d. The drugs are:
   - coated-granule formulation of sodium phenylbutyrate in urea cycle disorders (Prescrire Int n° 157);
   - vismodegib in metastatic or locally advanced basal cell carcinoma (Prescrire Int n° 155);
   - adalimumab in severe Crohn’s disease in patients aged 6 years and over (Rev Prescrire n° 366).

Exorbitant prices for certain drugs

### The need for robust pharmacovigilance, 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.
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). Caripiramine, 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 sudden death. In 2014, because of this risk, oral forms delivering a 20 mg dose were withdrawn in France, without any compelling reason for maintaining the other pharmaceutical forms or lower dose strengths on the market (Rev Prescrire n° 369, 371 and 373).

Metoclopramide, a neuroleptic with serious dose-dependent adverse effects, is no longer authorised for adults in a number of situations in which its benefits were unproven, including gastroesophageal reflux disease, dyspepsia and gastro- paresis. The recommended doses and treatment duration were reduced for situations in which it remains authorised (Rev Prescrire n° 368).

Two “vasodilators”, with disproportionate adverse effects given that they have no clinical value beyond the placebo effect, are no longer authorised in several situations: oral forms of piribedil in cognitive and neurosensory deficits in elderly patients, in intermittent claudication due to peripheral artery occlusive disease, and in ophthalmology (Rev Prescrire n° 365); and naftidrofuryl in Raynaud’s syndrome and in cognitive and neurosensory deficits in elderly patients (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) acceclofenac 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.