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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.**

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In 2014, *Prescrire* published 249 independent, systematic drug reviews in its French edition, including 43 new products (excluding generics), 26 new indications for existing products, 9 line extensions, 13 new generic drugs and 18 labelling changes.

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). ▶▶

▶ **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 (*Prescrire Int* 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 syringe and is sometimes helpful in children aged 5 years and over (*Rev Prescrire* n° 365).

For adults with chronic hepatitis C, the antiviral *sofosbuvir* appears to be at least as active as viral protease inhibitors such as *boceprevir*, and is somewhat less dangerous. Its use can shorten antiviral therapy by several months. Uncertainties remain over adverse effects and drug interactions, however (*Prescrire Int* n° 156).

Many useless or even dangerous new products and indications. In 2014, 35 of our 87 ratings were "nothing new", and 19 were "not acceptable", given to drugs with an unfavourable harm-benefit balance in some or all of their authorised indications (see table p. 109). In summary, more than half of the new drugs or indications analysed were no better or were actually worse than existing treatment options.

Hypoglycaemic drugs and monoclonal antibodies with more harms than benefits

Too many hypoglycaemic drugs and monoclonal antibodies constitute a step backwards.

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). Gliptins 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 *loxapi-ne* 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 reassessed 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 *aflibercept* in central retinal vein occlusion and *ocriplasmin* in vitreomacular 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, *nalmefene* 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

Prescrire's ratings of new products and indications over the last 10 years (a)

Prescrire's rating	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Bravo	0	1	1	0	0	0	0	0	0	1 (**b**)
A real advance	1	1	2	0	0	1	0	1	0	2 (**c**)
Offers an advantage	4	8	14	6	3	3	3	3	6	5 (**d**)
Possibly helpful	20	31	27	25	14	22	13	14	12	15
Nothing new	38	69	79	57	62	49	53	42	48	35
Not acceptable	19	17	15	23	19	19	16	15	15	19 (**e**)
Judgement reserved	2	8	3	9	6	3	7	7	9	10 (**f**)
Total	**84**	**135**	**141**	**120**	**104**	**97**	**92**	**82**	**90**	**87**

a- *Results for the years 1981 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-assessments "with more follow-up".*

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

c- *The drugs are:*

– artesunate in severe malaria (Prescrire Int n° 154);

– 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);

– sofosbuvir in chronic hepatitis C (Prescrire Int n° 156);

– Japanese encephalitis vaccine for patients 2 months of age and older (Rev Prescrire n° 371);

– meningococcal group B vaccine in the prevention of meningitis and other infections due to meningococcal group B bacteria for patients 2 months of age and older (Prescrire Int n° 152);

– vemurafenib in certain types of metastatic melanoma (Prescrire Int n° 159, p. 88-90).

e- *The drugs are:*

– alemtuzumab in relapsing-remitting multiple sclerosis (Prescrire Int n° 158);

– the combination of beclometasone + formoterol in asthma attacks (Rev Prescrire n° 367);

– canagliflozin in type 2 diabetes (Prescrire Int n° 157);

– canakinumab in gout attacks (Prescrire Int n° 151);

– insulin degludec in type 1 or 2 diabetes (Rev Prescrire n° 364);

– the combination of insulin degludec + insulin aspart in type 1 or 2 diabetes (Prescrire Int n° 150);

– lanthanum oral powder in hyperphosphataemia in renal failure (Rev Prescrire n° 363);

– lapatinib in certain types of metastatic breast cancer (Rev Prescrire n° 371);

– lorcaserin in obesity (Prescrire Int n° 149);

– loxapine oral inhalation powder in acute agitation (Rev Prescrire n° 374);

– natalizumab in relapsing-remitting multiple sclerosis (Prescrire Int n° 158);

– pegloticase in severe gout with tophi (Prescrire Int n° 151);

– rivaroxaban 2.5 mg in the prevention of recurrences after acute coronary syndrome (Prescrire Int n° 153);

– saxagliptin in type 2 diabetes (Prescrire Int n° 152);

– teriflunomide in relapsing-remitting multiple sclerosis (Prescrire Int n° 158);

– trastuzumab for subcutaneous use in certain types of breast cancer (Rev Prescrire n° 374);

– varenicline in smoking cessation, especially after failure of an initial course of varenicline therapy (Prescrire Int n° 152);

– vildagliptin (alone and in combination therapy) in type 2 diabetes (Rev Prescrire n° 365);

– zonisamide in partial seizures in patients aged 6 years and over (Rev Prescrire n° 368).

f- *The drugs are:*

– para-aminosalicylic acid in multidrug-resistant tuberculosis (Prescrire Int n° 153);

– adalimumab in severe Crohn's disease in patients aged 6 years and over (Rev Prescrire n° 364);

– aflibercept in visual impairment due to macular oedema secondary to central retinal vein occlusion (Prescrire Int n° 157);

– baclofen through an RTU temporary (compassionate) authorisation in alcohol cessation (Prescrire Int n° 153);

– bedaquiline in multidrug-resistant tuberculosis (Prescrire Int n° 153);

– bosutinib in chronic myeloid leukaemia (Prescrire Int n° 151);

– ocriplasmin in vitreomacular traction (Rev Prescrire n° 372);

– rufinamide in Lennox-Gastaut syndrome (Rev Prescrire n° 367);

– trastuzumab emtansine in certain types of metastatic breast cancer (Prescrire Int n° 155);

– vismodegib in metastatic or locally advanced basal cell carcinoma (Prescrire Int n° 156).

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 RTU). 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 RTU. 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 patients and society (*Prescrire Int* n° 154).

Other overpriced drugs that we reviewed in 2014 include: *canakinumab*, best avoided in gout attacks, and costing about €12 000 for a single injection (*Prescrire Int* n° 151); and *ivacaftor*, with an uncertain harm-benefit balance in cystic fibrosis, which costs about €19 000 per month (*Rev Prescrire* n° 366).

The need for robust pharmacovigilance, independent of industry

Pharmacovigilance was reorganised in the European Union in 2010, and again in 2012 (*Prescrire Int* n° 155, 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. ▶▶

► 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 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 gastroparesis. 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) *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.