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New drugs, new indications in 2015: little progress, and threats to access to quality healthcare for all

Key points

- **Very little real therapeutic progress was made in 2015, while a large number of unsafe or poorly evaluated drugs were authorised.**
- **The exorbitant prices for some drugs endanger universal healthcare, sometimes obliging health professionals to choose riskier options for their patients.**
- **Health professionals, health authorities and drug companies are jointly responsible for guaranteeing access to quality healthcare for all.**

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In 2015, *Prescrire* published 220 independent, systematic drug reviews in its French edition, including 45 new products, 31 new indications for existing products, and 15 new generic drugs.

2015: mostly minor advances

As in previous years, our reviews of new drugs and indications identified some noteworthy therapeutic advances, but progress was generally modest.

Some noteworthy advances. In 2015, we identified 8 drugs that represented a real therapeutic advance for the patients concerned, albeit with certain limitations. We rated these products "A real advance" (3 cases) or "Offers an advantage" (5 cases).

Drug therapy is necessary for some infants who have severe haemangiomas or are at risk of complications. Clinical evaluation of an oral solution of *propranolol*, a beta-blocker, showed that this drug is more effective than placebo, and that its adverse effect profile is generally better than that of long-term oral corticosteroid therapy, provided the infant is carefully monitored both when starting treatment and following dose increments (Prescrire Int n° 162).

In 2015, the fixed-dose combination of *ledipasvir* + *sofosbuvir* was the first-choice antiviral combination for patients with genotype 1 hepatitis C virus infection: it had good virological efficacy and was the best-assessed *interferon*-free treatment. However, as the adverse effects of these two antivirals are not adequately documented, active pharmacovigilance is crucial (Prescrire Int n° 166).

Because it is not hepatotoxic, *cholic acid* is a welcome alternative to *chenodeoxycholic acid* in cerebrotendinous xanthomatosis, a rare but serious disorder of primary bile acid synthesis. *Cholic acid* is probably also effective in two other primary bile acid synthesis disorders (type 4 and cholesterol 7-alpha-hydroxylase deficiencies), warranting further evaluation (Prescrire Int n° 157).

In late 2014, in France, 5% *permethrin* cream, a first-choice treatment for scabies, became available in community pharmacies. It had previously (since 2013) been authorised only for compassionate use in hospitals. This new authorisation and reimbursement by the national health insurance system facilitate patient access to this drug, which is an alternative to oral *ivermectin* (Rev Prescrire n° 384).

In late 2014, *ketoconazole* was authorised in the European Union for the treatment of selected patients with Cushing's syndrome. Its harm-benefit balance is favourable in this setting, provided the patient's hepatic and adrenal status is monitored and the many potential drug interactions are taken into account (Prescrire Int n° 169).

Pasireotide in acromegaly and *rituximab* in severe polyangiitis are two new options for patients in whom other treatments have failed (Prescrire Int n° 161, 168).

Drugs representing minor advances for patients informed of their limitations. In 2015, we rated 15 new drugs or new indications for existing drugs "Possibly helpful", signifying that they represent an additional option, but not a major breakthrough, for selected patients. These drugs are sometimes used as an adjunct to other treatments of choice, or when there are no other acceptable treatment options.

For example, some drugs that proved beneficial in adults were authorised for paediatric use. This was the case for *eculizumab* in paroxysmal nocturnal haemoglobinuria, a rare but life-threatening genetic disease (Prescrire Int n° 160); and *darunavir* combined with *ritonavir* as first-line treatment for HIV-infected children (aged 3 years and older), representing an alternative to the *lopinavir* + *ritonavir* fixed-dose combination (Rev Prescrire n° 381).

Some drugs represent a valid option because their adverse effect profile differs from that of the standard treatment. For example, although *enzalutamide* does not seem to have a better harm-benefit balance than *abiraterone* in metastatic prostate cancer, its different adverse effects (flushing, diarrhoea, neuropsychiatric disorders, seizures, hypertension, neutropenia, falls and fractures) can make it a useful alternative to *abiraterone*, which mainly has mineralocorticoid adverse effects such as oedema, hypertension and hypokalaemia (Rev Prescrire n° 383).

Still too many dangerous new products. In 2015, we considered that 15 new products or indications were more dangerous than useful (rated "Not acceptable"), because they had known or suspected serious adverse effects but uncertain, unproven or only limited efficacy. Thus, several drugs were authorised to treat a variety of malignancies despite an unfavourable harm-benefit balance. They included drugs that inhibit angiogenesis and tumour growth, such as *cabozantinib* in medullary thyroid cancer (Prescrire Int n° 167), *regorafenib* in gastrointestinal stromal tumours after treatment failure (Prescrire Int n° 164), *sorafenib* in differentiated thyroid cancer, and *bevacizumab* in platinum-resistant epithelial ovarian cancer (Prescrire Int n° 168, Rev Prescrire n° 383).

Alogliptin, a fifth gliptin, was authorised in the European Union, even

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though this entire class of glucose lowering drugs should be avoided: these compounds have little impact on blood sugar levels and no proven efficacy, but they have noteworthy adverse effects (Rev Prescrire n° 379).

The higher thromboembolic risk associated with third-generation progestins such as *gestodene* is well established, but a contraceptive patch delivering *gestodene* + *ethinylestradiol* was nonetheless authorised in some EU countries (Prescrire Int n° 167).

Minimal evaluation and premature authorisation

Over the years we have drawn attention to the fact that many drugs are authorised in the European Union despite minimal or inappropriate evaluation. In 2015, we considered that the available data were insufficient to determine the value of six drugs, four of which were indicated in cancer (see note **e** of table below).

The situation is similar in the United States, where researchers report that many marketing authorisations are granted too hastily or on the basis of shaky data. This is particularly the case for drugs indicated in cancer or orphan diseases, and others approved through accelerated procedures (Prescrire Int n° 169).

No blinding, and biased evaluation. Randomised trials versus a standard drug or placebo help to assess the harm-benefit balance of a given drug in a given setting. To reduce the risk of bias and to obtain the most reliable evidence, it is important for these trials to be conducted in a double-blind manner, with neither the patients nor the investigators knowing whether an individual participant is receiving the trial drug or the comparator. Yet some drug evaluation data, including for drugs intended to treat serious diseases, are mainly based on unblinded trials, which influences the reporting of adverse effects during the trial. This was the case for *afatinib* in non-small cell lung cancer, and albumin-bound *paclitaxel* in metastatic pancreatic cancer, for example (Prescrire Int n° 160, Rev Prescrire n° 376).

Another frequent weakness of clinical trial protocols, especially those for cancer drugs, is that patients in the comparator group are switched to the trial drug after disease progression. This amounts to evaluating a protocol rather than the new drug, and usually undermines any differences in robust endpoints such as mortality. Examples include the trial of *regorafenib* for gastrointestinal stromal tumours after treatment failure (Prescrire Int n° 164) and the trial of *sorafenib* in differentiated thyroid cancer (Prescrire Int n° 168).

Trials versus standard treatment: too seldom carried out. Trials versus a standard treatment help to show whether or not a new drug represents an advance in terms of efficacy or adverse effects, which is what matters most to patients and health professionals. Too many drug evaluations are based on a single placebo-controlled trial, even when a standard treatment exists. For example, injectable extended-release (ER) *aripiprazole* was not compared with another injectable ER neuroleptic in schizophrenia (Rev Prescrire n° 378); *macitentan* was not compared with *bosentan*, the standard vasodilator for pulmonary hypertension (and marketed by the same company) (Rev Prescrire n° 381); and *peginterferon beta-1a* was not compared with non-pegylated *interferon beta*, the standard disease-modifying treatment for multiple sclerosis (Rev Prescrire n° 386).

Limited evaluation of adverse effects. More and more new antivirals are being authorised in chronic hepatitis C, despite very poor documentation of their adverse effects. The fixed-dose combination of *ledipasvir* + *sofosbuvir* is one example (Prescrire Int n° 166). Its evaluation contained no new data on the potential cardiac and muscular adverse effects of *sofosbuvir*, a drug that was already on the market. The adverse effects of the ▸▸

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

Prescrire's ratings	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Bravo	1	1	0	0	0	0	0	0	1	0
A real advance	1	2	0	0	1	0	1	0	2	3 (**b**)
Offers an advantage	8	14	6	3	3	3	3	6	5	5 (**c**)
Possibly helpful	31	27	25	14	22	13	14	12	15	15
Nothing new	69	79	57	62	49	53	42	48	35	43
Not acceptable	17	15	23	19	19	16	15	15	19	15 (**d**)
Judgement reserved	8	3	9	6	3	7	7	9	10	6 (**e**)
Total	**135**	**141**	**120**	**104**	**97**	**92**	**82**	**90**	**87**	**87**

a- Readers interested in the results for 1981-2005 can find them in *Rev Prescrire* n° 213 p. 59 and 269 p. 142. This table comprises new products (excepting copies) and new indications, as well as products re-examined with longer follow-up.

b- *Cholic acid* in three types of hereditary primary bile acid synthesis disorder: cerebrotendinous xanthomatosis, type 4 deficiency, and cholesterol 7 alpha hydroxylase deficiency (*Rev Prescrire* n° 386).

– *ledipasvir + sofosbuvir* in chronic hepatitis C due to HCV 1 infection (*Prescrire Int* n° 166).

– *propranolol* oral solution in severe infantile haemangioma (*Prescrire Int* n° 162).

c- *daclatasvir* in chronic hepatitis C due to HCV-3 or HCV-4 infection (*Prescrire Int* n° 166).

– *ketoconazole* in endogenous Cushing's syndrome (*Prescrire Int* n° 169).

– *pasireotide* in acromegaly after treatment failure (*Prescrire Int* n° 168).

– 5% *permethrin* cream in scabies (*Rev Prescrire* n° 384).

– *rituximab* in severe polyangiitis (*Prescrire Int* n° 161).

d- *alogliptin* alone or combined with *metformin* in type 2 diabetes (*Rev Prescrire* n° 379).

– *bevacizumab* in platinum-resistant ovarian epithelial cancer (*Rev Prescrire* n° 383).

– *bupropion + naltrexone* in obesity (*Prescrire Int* n° 164).

– *cabozantinib* in medullary thyroid cancer (*Prescrire Int* n° 167).

– *defibrotide* in hepatic veno–occlusive disease (*Prescrire Int* n° 164).

– *denosumab* in male osteoporosis (*Prescrire Int* n° 168).

– *eltrombopag* in thrombocytopenia associated with hepatitis C (*Prescrire Int* n° 163).

– *ethinyloestradiol + gestodene* patches for female contraception (*Prescrire Int* n° 167).

– *misoprostol* vaginal device for labour induction (*Prescrire Int* n° 166).

– *omalizumab* in spontaneous chronic urticaria (*Prescrire Int* n° 161).

– *ospemifene* in postmenopausal vulvovaginal disorders (*Prescrire Int* n° 168).

– *regorafenib* in gastrointestinal stromal tumours in treatment failure (*Prescrire Int* n° 164).

– *sorafenib* in differentiated thyroid cancer (*Prescrire Int* n° 168).

– *telavancin* in nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus* (*Prescrire Int* n° 165).

– *venlafaxine* in major depressive episodes and recurrence prevention, social phobia, generalised anxiety, and panic disorder (*Prescrire Int* n° 164).

e- *elosulfase alpha* in type 4 mucopolysaccharidosis (*Rev Prescrire* n° 386).

– *idelalisib* in the chronic lymphoid leukaemia and follicular lymphoma (*Rev Prescrire* n° 385).

– *ipilimumab* in metastatic or inoperable melanoma (*Prescrire Int* n° 159).

– *ledipasvir + sofosbuvir* in chronic hepatitis C due to HCV-3 or HCV-4 infection (*Prescrire Int* n° 166).

– *lenalidomide* in some myelodysplastic syndromes (*Prescrire Int* n° 160).

– *ponatinib* in Philadelphia-positive leukemia (*Prescrire Int* n° 161).

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"Orphan" drug status: abuse of incentives

In 2015, we noticed a sharp increase in the number of new drugs or indications authorised with "orphan" drug status, increasing to 17 in 2015 from only 6 in 2014 and 9 in 2013.

Orphan drug status has been recognised in the European Union since 2000. The aim was to encourage the development of drugs for patients with rare diseases (mostly genetic), defined as 5 or fewer cases per 10 000 inhabitants (Rev Prescrire n° 380, 382). There are about 6000 or 7000 known rare diseases worldwide, affecting tens of thousands of people in total.

Regulatory and financial advantages. Companies that develop "orphan" drugs enjoy significant benefits, including an accelerated marketing authorisation (MA) process, an often limited application dossier (conditional authorisation, mainly bibliographic data) and a 10-year market monopoly.

"Orphan" drugs offer companies other financial incentives. Clinical trials are small and therefore generally less costly. Very high prices can be demanded because there is no therapeutic alternative and the patient population is small, greatly limiting health insurers' bargaining power. And marketing costs are lower because only a handful of specialists are likely to prescribe the drug.

Abuse. The past 15 years have seen the emergence of a vigorous "orphan" drug market, but patients have not always benefited. Some "orphan" drugs should even be avoided. Examples in 2015 include: *defibrotide*, a drug with uncertain utility in hepatic veno-occlusive disease (Prescrire Int n° 164); and *cabozantinib and sorafenib* (Prescrire Int n° 167, 168), two tyrosine kinase inhibitors that are more dangerous than beneficial in patients with thyroid cancer.

Some companies focus exclusively on very narrow markets or on niches abandoned by previous players. Thus, a year after the approval of Orphacol® (*cholic acid*) for two rare bile acid deficiencies, an EU marketing application was filed for Kolbam® (*cholic acid*) in three other rare bile acid deficiencies (Rev Prescrire n° 386). *Cholic acid*, which is extensively used as a food emulsifier, costs between 139 and 175 euros for a single 250-mg capsule in France depending on the product, despite the virtual lack of clinical studies.

Some "orphan" drugs are eventually authorised in several indications, expanding market share but not leading to significant price cuts. For example, *lenalidomide* is authorised in some forms of multiple myeloma and myelodysplastic syndromes (Prescrire Int n° 160), while *pasireotide* is authorised in Cushing's syndrome and for acromegaly in treatment failure (Prescrire Int n° 168).

Some rare diseases draw the attention of several drug companies. In 2015, two more vasodilators, *riociguat* and *macitentan*, were authorised for pulmonary hypertension, even though they have no advantages over *bosentan* or *sildenafil* (Prescrire Int n° 165, Rev Prescrire n° 379, 381). Similarly, two anti-CD20 monoclonal antibodies, *obinutuzumab* and *ofatumumab*, were authorised for the treatment of chronic lymphocytic leukaemia, even though they lacked any decisive advantages over *rituximab*, another anti-CD20 monoclonal antibody that has been available for many years (Prescrire Int n° 165).

In summary. The development of drugs with a favourable harm-benefit balance for patients with rare diseases and no other therapeutic options is clearly welcome. However, the overall dynamics of drug research is changing as companies seek to maximise profits by devoting more and more of their resources to "orphan" diseases. Companies know that this strategy allows them to demand exorbitant prices and to exert pressure on the authorities to reduce regulatory requirements. And that is a far cry from research designed to address the healthcare needs of the entire population.

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▸ combination were comparatively evaluated in only 155 patients, even though an estimated 170 million patients worldwide have chronic hepatitis C. The European Medicines Agency (EMA) was particularly lax, taking these minimal data at face value and inferring that this antiviral combination had barely more adverse effects than placebo! (1)

Postmarketing discovery of serious harms. Marketing authorisation, even when based on very fragile clinical data, is rarely challenged once the drug is on the market. Yet knowledge about adverse effects accumulates during routine use. If an initially uncertain harm-benefit balance turns out to be clearly unfavourable, the drug should be withdrawn from the market. Unfortunately, regulators and governments rarely rise to the challenge.

For example, in 2015, cases of severe hyponatraemia were attributed to *aliskiren*, a renin-inhibiting antihypertensive drug that has no proven impact on the complications of hypertension but was linked to cardiovascular events and cases of renal failure in a placebo-controlled trial (Prescrire Int n° 166).

Some glucose lowering drugs with unproven efficacy on the complications of diabetes have been found to have serious, disproportionate adverse effects, including: intestinal obstruction and disabling joint pain with gliptins; and ketoacidosis (especially in patients with type 2 diabetes) with gliflozins (Prescrire Int n° 167, Rev Prescrire n° 386).

Because adverse effects are often poorly documented when marketing authorisation is initially granted, and because health authorities are overly lenient towards drug companies, it is up to patients and health professionals to report all possible adverse effects to their national pharmacovigilance networks in order to identify and prevent serious harms. It is also important to ensure, through collective action, that drugs with an unfavourable harm-benefit balance are not used.

Exorbitant prices endanger access to healthcare and patient safety

Following the example of *sofosbuvir*, prices for new anti-HCV antivirals marketed in the European Union in 2015 continued to soar. For example, in France, a 12- to 24-week course of treatment costs 50 000 to 100 000 euros with the *ledipasvir* + *sofosbuvir* combination, and about 67 000 to 134 000 euros with the *daclatasvir* + *sofosbuvir* combination (Prescrire Int n° 166).

The prices of drugs authorised for rare diseases are also disproportionate (see inset above). For example, *defibrotide* costs about 72 000 euros (excluding tax) for a 21-day course of treatment for hepatic veno-occlusive disease in a patient weighing 70 kg (Prescrire Int n° 164).

The monthly cost of *cholic acid* therapy for patients with certain bile acid deficiencies is about 20 000 euros for an adult weighing 60 kg (Prescrire Int n° 157).

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By agreeing to pay such high prices for new drugs, governments are playing into industry's hands, even though they have the power to halt this pernicious trend.

The commercial strategies of some drug companies compel national health authorities to resort to riskier alternatives. For example, intravitreal *bevacizumab* is significantly cheaper than *ranibizumab* for age-related macular degeneration but has more adverse effects (Prescrire Int n° 163, 171) [see also this issue pp 132-133].

EMA: failure to learn from past scandals places patients at risk

On receiving an application for EU marketing authorisation through the centralised procedure, the EMA's Committee for Human Medicinal Products, on which all EU member states are represented, issues an opinion based mainly on analyses conducted by two national regulatory agencies on behalf of all EU member states. This opinion, following a vote by all member states, is forwarded to the European Commission, which then grants or rejects marketing authorisation, a decision that is binding on all member states. Dissenting opinions must be mentioned in the European public assessment report (EPAR).

Appetite-suppressant drug combinations: danger. In 2015, a fixed-dose combination of *bupropion + naltrexone* was authorised in the EU after receiving a favourable opinion from the EMA (Prescrire Int n° 164). This combination, containing an amphetamine-like substance and an opioid receptor antagonist, only helps obese and overweight patients to lose a few kilos but exposes them to very significant dangers. The French and Irish regulatory agencies issued negative opinions on this combination, but the EU decision to grant marketing authorisation is binding on these member states too. This example shows how little the EMA has learnt from past health disasters, such as the decision by a few European countries to authorise *benfluorex*. Yet, in 2013, the EMA's opinion was against authorising two other weight-loss drugs: *lorcaserin* and the *phentermine + topiramate* combination (Prescrire Int n° 149, 136).

Simple changes to the SPC rather than market withdrawal. When a drug that is already on the market is found to expose patients to serious harms, or when a drug is withdrawn or due to be withdrawn by a member state's regulatory agency for safety reasons, EU rules stipulate that the drug in question must be re-evaluated by the EMA on behalf of all member states. Unfortunately, this re-evaluation often leads to decisions that seem intended to protect the pharmaceutical industry rather than patients. Instead of taking more radical measures, EU regulators simply add contraindications, precautions or warnings to the summary of product characteristics (SPC).

We examined several such decisions in 2015. In particular, we noticed that *diacerein* was not withdrawn from the European markets even though 9 member states, including France, considered that its adverse effects outweighed its (unproven) efficacy (Prescrire Int n° 159).

Despite the risk of serious cutaneous reactions and anaphylaxis linked to *ambroxol* and *bromhexine*, two mucolytics with no proven efficacy, the EU regulators simply added a warning to the SPC and patient leaflet, a decision criticised by 11 member states (2) (Prescrire Int n° 159).

Withdrawing reimbursement for drugs that are more dangerous than useful: fewer patients at risk

When a drug with an unfavourable harm-benefit balance is approved or maintained on the European market, withdrawal of reimbursement by the national health insurance system is a welcome stopgap measure that limits the number of patients exposed to its harmful effects.

In France, the Transparency Committee (also known as Pharmacoeconomic Committee) of the National Authority for Health (HAS) is responsible for assessing and re-assessing drugs' medical benefit, with a view to reimbursement by the health insurance system or approval for use in healthcare facilities. When re-assessment leads to downgrading of a drug's medical benefit, its reimbursement is reduced accordingly. When medical benefit is rated "inadequate", the drug in question should no longer be reimbursed and should be removed from the list of medicines approved for use in healthcare facilities. Inclusion on the list of OTC drugs or a price reduction can also influence the prescription or sale of a given drug.

Reimbursement was withdrawn for the following products in France in 2015:

– Gels containing *ketoprofen*, a nonsteroidal anti-inflammatory drug that carries a particularly high risk of photosensitisation (Rev Prescrire n° 377);
– *Strontium ranelate*, a drug with adverse effects disproportionate to its modest efficacy in osteoporosis (Prescrire Int n° 156);
– Slow-acting "anti-osteoarthritis" drugs based on *chondroitin, diacerein, glucosamine*, or *avocado* and *soybean* unsaponifiables: no more effective than placebo but with potentially serious adverse effects (Prescrire Int n° 159).

Collective action

The marketing authorisation process is too often a sham, limited to minimal administrative requirements. Patients are understandably inclined to believe that "new" equates with therapeutic progress, but frequently do not realise the harms to which they are exposed.

For example, more and more HCV antivirals are being approved without proper comparative trials designed to identify optimal combinations in terms of efficacy and adverse effects. And it is unacceptable for manufacturers to align their prices on *sofosbuvir*, endangering public health insurance systems.

The European Medicines Agency is clearly more concerned with pharmaceutical industry profits than with patient well-being when it issues favourable marketing opinions for drugs with poorly documented efficacy and unknown adverse effects.

On the positive side, the French and some other national regulatory agencies have taken decisions intended to protect patients' interests, for example by refusing to reimburse risky drugs, or by cancelling reimbursement if they are not withdrawn from the market.

In summary, real therapeutic advances are rare in the global pharmaceuticals market, where "innovation" all too often simply means bigger profits.

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Selected references from Prescrire's literature search.

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