Towards better patient care: drugs to avoid in 2017

ABSTRACT

● **To help healthcare professionals and patients choose high-quality treatments that minimise the risk of adverse effects, in early 2017 we updated the list of drugs that *Prescrire* advises health professionals and patients to avoid.**

● ***Prescrire*'s assessments of the harm-benefit balance of new drugs and indications are based on a rigorous procedure that includes a systematic and reproducible literature search, identification of patient-relevant outcomes, prioritisation of the supporting data based on the strength of evidence, comparison with standard treatments, and an analysis of both known and potential adverse effects.**

● **This fifth annual review of drugs to avoid has been extended to cover all drugs examined by *Prescrire* between 2010 and 2016 and authorised in the European Union, whereas previous reviews only considered drugs marketed in France. We identified 91 drugs that are more harmful than beneficial in all the indications for which they have been authorised in France or in the European Union.**

● **In most cases, when drug therapy is really necessary, other drugs with a better harm-benefit balance are available.**

● **Even in serious situations, when no effective treatment exists, there is no justification for prescribing a drug with no proven efficacy that provokes severe adverse effects. It may be acceptable to test these drugs in clinical trials, but patients must be informed of the uncertainty over their harm-benefit balance, and the trial design must be relevant. Tailored supportive care is the best option when there are no available treatments capable of improving prognosis or quality of life, beyond their placebo effect.**

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This is *Prescrire*'s fifth consecutive annual review of "drugs to avoid" (1,2). The drugs listed here are clearly more dangerous than beneficial and should therefore not be used. The aim is to help health professionals choose safe, effective treatments and thereby avoid harming their patients.

A reliable, rigorous and independent methodology

What data sources and methodology do we use to assess the harm-benefit balance of a given drug?

The following review concerns drugs and indications on which we published detailed analyses in our French edition over a seven-year period, from 2010 to 2016. Some drugs and indications were examined for the first time, while others were re-evaluated as new data on efficacy or adverse effects became available.

All our publications are intended to provide health professionals (and thereby their patients) with the clear, independent, reliable and up-to-date information they need, free from conflicts of interest and commercial pressures.

Prescrire is structured in such a way as to guarantee the quality of the information provided to our

subscribers. The Editorial Staff comprise a broad range of health professionals working in various sectors and free from conflicts of interest. We also call on an extensive network of external reviewers (specialists, methodologists, and practitioners representative of our readership), and each article undergoes multiple quality controls and cross-checking at each step of the editorial process (see *About Prescrire* > *How we work* at english.prescrire.org). Our editorial process is a collective one, as symbolised by the "©*Prescrire*" signature.

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Comparison with standard treatments. The harm-benefit balance of a given drug has to be continually re-evaluated as new data on efficacy or adverse effects become available. Likewise, treatment options evolve as new drugs arrive on the market.

Not all drugs are equal: some offer a therapeutic advantage, while others are more harmful than beneficial and should not be used (3).

All *Prescrire*'s assessments of new drugs and indications are based on a systematic and reproducible literature search. The resulting data are then analysed collectively by our editorial staff, using an established procedure:

– Efficacy data are prioritised: most weight is given to studies providing robust supporting evidence, i.e. well-conducted, double-blind, randomised controlled trials;

– The new drug is compared with a carefully chosen standard treatment, if one exists (not necessarily a drug);

– The accent is placed on those clinical endpoints most relevant to the patients concerned. This means that we often ignore surrogate endpoints such as simple laboratory markers that have not been shown to correlate with a favourable clinical outcome (4,5).

Careful analysis of adverse effects. Adverse effects can be more difficult to analyse, as they are often less thoroughly documented than efficacy, and this discrepancy must be taken into account.

The adverse effect profile of each drug is assessed by examining data from clinical trials and animal pharmacotoxicology studies, and any pharmacological affiliation.

The fact that a new drug has been granted marketing authorisation does not signify that its harm-benefit balance has been fully documented. Indeed, rare but serious adverse effects may only emerge after several years of routine use (3).

Empirical data and personal experience: risk of bias. Empirical assessment of a drug's harm-benefit balance based on individual experience can help to guide further research but is subject to major bias and represents only weak evidence (3,4). For example, it can be difficult to attribute a specific outcome to a particular drug, as other factors must be taken into account, including the natural history of the disease, the placebo effect, the effect of another treatment the patient may not have mentioned, or a change in lifestyle or diet. Similarly, a doctor who sees an improvement in certain patients may be unaware that many other patients have been harmed by the same treatment (3).

The best way to overcome this subjective bias due to non-comparative evaluation of a few patients is to prioritise well-conducted clinical studies, particularly double-blind randomised trials versus standard care (3,4).

Serious conditions with no effective treatment: patients should be informed of the consequences of interventions. When faced with a serious condition for which there is no effective treatment, some patients opt to forgo treatment while others are willing to try any drug that might bring them even temporary relief, despite a risk of serious adverse effects.

When the short-term prognosis is poor, some health professionals may propose "last-chance" treatments without fully informing the patient of the harms, either intentionally or unwittingly.

Yet patients in this situation must not be treated as guinea pigs. It is very useful to enrol patients into clinical studies provided they are informed of the harms and the uncertain nature of the possible benefits, and that the results are published in order to advance medical knowledge.

But patients must be made aware that they have the option of refusing to participate in clinical trials or to receive last-chance treatments with an uncertain harm-benefit balance. They must also be reassured that, if they do refuse, they will not be abandoned but will continue to receive the best available care. Even though they are not aimed at modifying the outcome of the underlying disease, supportive care and symptomatic treatment are key elements of patient care.

By their very nature, clinical trials involve a high degree of uncertainty. In contrast, drugs used for routine care must have an acceptable harm-benefit balance. Marketing authorisation should only be granted on the basis of proven efficacy relative to standard care, and an acceptable adverse effect profile: in general, little, if any, extra information on efficacy is collected once marketing authorisation has been granted (3).

91 authorised drugs more dangerous than beneficial

This review lists drugs that have an unfavourable harm-benefit balance in all their authorised indications, in other words drugs that should be removed from the market on account of their toxicity. Drugs with an unfavourable harm-benefit balance in certain situations but not in others have not been included.

Notable changes in the 2017 update

Only one drug from the list of drugs that *Prescrire* advises health professionals and patients to avoid was withdrawn from the market in 2016: the recombinant urate oxidase *pegloticase.* Its European marketing authorisation, for severe gout, was withdrawn at the request of the pharmaceutical company concerned (*Prescrire Int n° 180*).

Panitumumab, varenicline: *Prescrire* reviewing new data in 2017. The only drugs listed in our 2016 review of drugs to avoid that do not feature in this year's review are *panitumumab* for colorectal cancers and *varenicline* for smoking cessation. This is because we are currently re-evaluating their harm-benefit balance in light of new data published in 2016.

Additions: ambroxol, capsaicin, various antineoplastics. The adverse effects of the mucolytics *ambroxol* and *bromhexine* are better known now that they have been in use for a long time. The hypersensitivity reactions and life-threatening cutaneous disorders they cause make their harm-benefit balance unfavourable. Although these adverse effects are rare, they are unacceptable for drugs that have no efficacy beyond a placebo effect and that are indicated for minor ailments such as cough or sore throat.

The data on *dronedarone* in atrial fibrillation and *capsaicin* in neuropathic pain led us to add these drugs to the list of ones to avoid.

We have also added the vasoconstrictor *phenylephrine*, authorised as a decongestant for nasal use, which we had erroneously omitted from previous lists.

Six of the new products examined by *Prescrire* in 2016 have an unfavourable harm-benefit balance in all their approved indications, and three of them are cancer drugs: *nintedanib* for non-small cell lung cancer and for idiopathic pulmonary fibrosis, *olaparib* for ovarian cancer, *panobinostat* for multiple myeloma, *mepolizumab* for asthma, *ciclosporin* eye drops for dry eye disease, and *idebenone* for Leber's hereditary optic neuropathy.

Additions authorised at European level but not marketed in France. *Prescrire* analyses all drugs that receive authorisation through European or French marketing authorisation procedures. In previous years, we only considered drugs marketed in France when compiling our list of drugs to avoid in order to provide better patient care. This year, for the benefit of readers who do not work or live in France, we have expanded our review to include all the drugs examined by *Prescrire* between 2010 and 2016 and having European marketing authorisation, regardless of their availability in France.

Ten drugs to avoid were added to the list as a result of this approach. All but the first are unavailable in France as of early 2017: *alemtuzumab* for multiple sclerosis, *alogliptin* (alone or combined with *metformin*), *canagliflozin*, *dapagliflozin* and *pioglitazone* for type 2 diabetes, the fixed-dose combinations *bupropion* + *naltrexone* for weight loss, *mannitol* inhalation powder for cystic fibrosis, *mifamurtide* for osteosarcoma, *ranolazine* for angina, and *vernakalant* for atrial fibrillation.

This fifth annual review of drugs to avoid has been extended to cover all the drugs examined by *Prescrire* between 2010 and 2016 that are authorised in the European Union. In previous reviews, we confined our assessment to drugs marketed in France. As of early 2017, we have identified 91 drugs that are more dangerous than beneficial, 82 of which are marketed in France.

They are listed below, based first on the therapeutic area in which they are used and then in alphabetical order of their international nonproprietary names (INNs).

These 91 drugs comprise:
– Active substances with adverse effects that are disproportionate to the benefits they provide in a given situation;
– Older drugs that have been superseded by new drugs with a better harm-benefit balance;
– Recent drugs that have a less favourable harm-benefit balance than existing options;
– Drugs that have no proven efficacy (beyond the placebo effect) but that carry a risk of serious adverse effects.

The main reasons why these drugs are considered to have an unfavourable harm-benefit balance are explained in each case. When available, better options are briefly mentioned, as are situations (serious or non-serious) in which there is no suitable treatment.

The differences between this year's and last year's lists are detailed in the inset above.

Cardiology

• ***Aliskiren***, an antihypertensive renin inhibitor, has not been shown to prevent cardiovascular events. On the contrary, a trial in diabetic patients showed that *aliskiren* was associated with an increase in cardiovascular events and renal failure (*Prescrire Int* n° 106, 129, 166). It is better to choose one of the many established antihypertensive drugs such as a thiazide diuretic or an angiotensin converting enzyme (ACE) inhibitor.

• ***Bezafibrate***, ***ciprofibrate*** and ***fenofibrate*** are cholesterol-lowering drugs with no proven efficacy in the prevention of cardiovascular events (beyond the placebo effect), yet they all have numerous adverse effects, including cutaneous, haematological and renal disorders (*Prescrire Int* n° 85, 117). When a fibrate is justified, *gemfibrozil* is the only one that has been shown to prevent the cardiovas-

cular complications of hypercholesterolaemia, although renal function and serum creatine phosphokinase levels must be closely monitored.

• ***Dronedarone***, an antiarrhythmic chemically related to *amiodarone*, is less effective than *amiodarone* at preventing atrial fibrillation recurrence, yet has at least as many serious adverse effects, in particular hepatic, pulmonary and cardiac disorders (*Prescrire Int* n° 108, 120, 122; *Rev Prescrire* n° 339). *Amiodarone* is a better option.

• ***Ivabradine***, an inhibitor of the cardiac I_f current, can cause visual disturbances, cardiovascular disorders (including myocardial infarction), potentially severe bradycardia and other cardiac arrhythmias. It has no advantages in either angina or heart failure (*Prescrire Int* n° 88, 110, 118, 155, 165). Established treatments shown to be effective in angina include beta-blockers and the calcium channel blockers *amlodipine* and *verapamil*. There are also better options for heart failure: one is to refrain from adding another drug to an optimised treatment regimen; another is to use a beta-blocker with a proven impact on mortality.

• ***Nicorandil***, a vasodilator with solely symptomatic efficacy as a preventive treatment in effort angina, can cause severe mucocutaneous ulceration *(Prescrire Int* n° 81, 95, 110, 132). A nitrate is a better option to prevent angina attacks.

• ***Olmesartan***, an angiotensin II receptor blocker (ARB or sartan) that is no more effective than other ARBs against the complications of hypertension, can cause sprue-like enteropathy leading to chronic diarrhoea (potentially severe) and weight loss, and, possibly, an increased risk of cardiovascular mortality (*Prescrire Int* n° 148, 171). It is better to choose another of the many ARBs available, such as *losartan* or *valsartan*, which do not appear to have these adverse effects

• ***Ranolazine***, an antianginal with a poorly understood mechanism, provokes adverse effects that are disproportionate to its minimal efficacy in reducing the frequency of angina attacks, including: gastrointestinal and neuropsychiatric disorders, palpitations, bradycardia, hypotension, QT prolongation and peripheral oedema (*Prescrire Int* n° 102; *Rev Prescrire* n° 350, 386 suppl. 2-3-7).

• ***Trimetazidine***, a drug with uncertain properties, is used in angina despite its only modest symptomatic effects (shown mainly in stress tests), yet it can cause parkinsonism, hallucinations and thrombocytopenia (*Prescrire Int* n° 84, 100, 106). It is better to choose better-known treatments for angina, such as beta-blockers or the calcium-channel blockers *amlodipine* and *verapamil*.

• ***Vernakalant***, an injectable antiarrhythmic used in atrial fibrillation, has not been shown to reduce mortality or the incidence of thromboembolic or cardiovascular events. Its adverse effects include various arrhythmias (*Prescrire Int* n° 127). It is better to use *amiodarone* for pharmacological cardioversion.

Dermatology - Allergy

• ***Mequitazine***, a sedating antihistamine with antimuscarinic activity, authorised for allergies, has only modest efficacy but carries a higher risk than other antihistamines of cardiac arrhythmias through QT prolongation in patients who are slow CYP2D6 metabolisers (and CYP2D6 metaboliser status is rarely known) or when co-administered with drugs that inhibit CYP2D6 (*Rev Prescrire* n° 337). A "non-sedating" antihistamine without antimuscarinic activity, such as *cetirizine* or *loratadine*, is a better option in this situation.

• ***Omalizumab*** in chronic spontaneous urticaria (also see the Pulmonology - ENT section on page 7) (*Prescrire Int* n° 161).

• Injectable ***promethazine***, an antihistamine used to treat severe urticaria, can cause thrombosis, skin necrosis and gangrene following extravasation or inadvertent injection into an artery (*Rev Prescrire* n° 327). Injectable *dexchlorpheniramine*, which does not appear to carry these risks, is a better option.

• Topical ***tacrolimus***, an immunosuppressant used in atopic eczema, can cause skin cancer and lymphoma, yet its efficacy is barely different from that of topical corticosteroids (**a**) (*Prescrire Int* n° 101, 110, 131; *Rev Prescrire* n° 367). Judicious use of a topical corticosteroid to treat flare-ups is a better option in this situation.

Diabetes - Nutrition

Diabetes. Various glucose-lowering drugs have an unfavourable harm-benefit balance. They reduce blood glucose slightly but have no proven efficacy against the complications of diabetes (cardiovascular events, renal failure, neurological disorders, etc.) yet many adverse effects. Far more reasonable choices are to use a proven treatment such as *metformin*, or a sulfonylurea such as *glibenclamide* or an insulin if *metformin* is insufficiently effective and, in some cases, setting a higher HbA1c target.

• The gliptins (dipeptidyl peptidase 4 (DPP-4) inhibitors) ***alogliptin***, ***linagliptin***, ***saxagliptin***, ***sitagliptin*** and ***vildagliptin***, used alone or in combination with *metformin*, have an unfavourable adverse effect profile that includes serious hypersensitivity reactions such as anaphylaxis and Stevens-Johnson syndrome, infections (urinary tract and upper respiratory tract infections), pancreatitis, bullous pemphigoid and intestinal obstruction (*Prescrire Int* n° 121, 135, 138, 158, 167; *Rev Prescrire* n° 365, 366, 379).

• ***Canagliflozin*** and ***dapagliflozin*** can provoke hypotension, urinary tract and genital infections, renal failure, ketoacidosis, haematocrit elevation (a risk

a- *Oral or injectable tacrolimus is a standard immunosuppressant for transplant recipients, and in this situation its harm-benefit balance is clearly favourable (Rev Prescrire n° 386 suppl. 10-1).*

factor for thromboembolism), and possibly bladder, breast and prostate cancer (*Prescrire Int* n° 147, 157, 169, 175).
• ***Pioglitazone*** has a burdensome adverse effect profile, including heart failure, bone fractures and bladder cancer (*Prescrire Int* n° 129, 160).

Weight loss. As of early 2017, no drugs are capable of inducing lasting weight loss without risk. It is better to focus on dietary changes and physical activity, providing psychological support if necessary.
• The weight loss drug ***bupropion*** + ***naltrexone*** combines a drug chemically related to amphetamines (*bupropion*) with an opioid receptor antagonist (also see the Psychiatry - Addiction section on page 7) (*Prescrire Int* n° 164).
• ***Orlistat*** has only a modest and transient effect on weight loss: patients lost about 3.5 kg more than with placebo over 12 to 24 months, with no evidence of long-term efficacy. Gastrointestinal disorders are very common, while other adverse effects include liver damage, hyperoxaluria, and bone fractures in adolescents. *Orlistat* alters the gastrointestinal absorption of many nutrients (fat-soluble vitamins A, D, E and K), leading to a risk of deficiency, and also reduces the efficacy of some drugs (thyroid hormones, some antiepileptics). Oral contraceptive efficacy is reduced when *orlistat* provokes severe diarrhoea (*Prescrire Int* n° 57, 71, 107, 110; *Rev Prescrire* n° 374).

Gastroenterology

• ***Domperidone*** and ***droperidol***, two neuroleptics, can provoke ventricular arrhythmias and sudden death. This is an unacceptable risk given the symptoms treated and these drugs' weak efficacy against nausea and vomiting, and in the case of *domperidone*, gastroesophageal reflux (*Prescrire Int* n° 129, 144, 175, 176, 179). Other drugs such as antacids and *omeprazole* have a much better harm-benefit balance in gastroesophageal reflux disease. In the rare situations in which treatment with an antiemetic neuroleptic appears justified, it is better to choose *metoclopramide*, which also provokes serious cardiac events but has proven efficacy against nausea and vomiting. It should be used at the lowest possible dose, taking drug interactions into account and monitoring the patient frequently.
• ***Prucalopride***, a drug chemically related to neuroleptics, is authorised for chronic constipation but shows only modest efficacy, in about one in six patients. Its adverse effect profile is poorly documented, particularly with respect to cardiovascular disorders (palpitations, ischaemic cardiovascular events, possible QT prolongation), depression and suicidal ideation and teratogenicity (*Prescrire Int* n° 116, 137, 175). There is no justification for exposing patients with simple constipation to such risks. If dietary measures are ineffective, then bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer than *prucalopride*.

Gynaecology - Endocrinology

• ***Tibolone***, a synthetic steroid hormone used for postmenopausal hormone replacement therapy, has androgenic, oestrogenic and progestogenic properties and carries a risk of cardiovascular disorders, breast cancer and ovarian cancer *(Prescrire Int* n° 83, 11, 137). When hormone therapy is chosen despite the inherent risks, the most reasonable option is an oestrogen-progestogen combination, used at the lowest possible dose and for the shortest possible period.

Infectious diseases

• ***Moxifloxacin*** is no more effective than other fluoroquinolone antibiotics but can cause toxic epidermal necrolysis and fulminant hepatitis and has also been linked to an increased risk of cardiac disorders (*Prescrire Int* n° 62, 103; *Rev Prescrire* n° 371). Another fluoroquinolone such as *ciprofloxacin* or *ofloxacin* is a better option.
• ***Telithromycin*** has no advantages over other macrolide antibiotics but carries an increased risk of QT interval prolongation, hepatitis, visual disturbances and syncope (*Prescrire Int* n° n° 84, 88, 94, 106, 154). Another macrolide such as *spiramycin* or *azithromycin* is a better option.

Neurology

Alzheimer's disease. The drugs available in early 2017 for Alzheimer's disease have only minimal and transient efficacy. They are also difficult to use because of their disproportionate adverse effects and many interactions with other drugs. None of the available drugs has been shown to slow progression toward dependence, yet all carry a risk of life-threatening adverse effects and severe drug interactions (*Prescrire Int* n° 128, *Rev Prescrire* n° 363, 364). It is better to focus on reorganising the patient's daily life, keeping him or her active, and providing support and help for caregivers and family members.
• ***Donepezil***, ***galantamine*** and ***rivastigmine***, three cholinesterase inhibitors, can cause gastrointestinal disorders (including severe vomiting), neuropsychiatric disorders, cardiac disorders (including bradycardia, collapse and syncope), and cardiac conduction disorders (*Prescrire Int* n° 162, 166; *Rev Prescrire* n° 337, 340, 344, 349, 398).
• ***Memantine***, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders (such as hallucinations, confusion, dizziness and headache) that can lead to violent behaviour, as well as seizures and heart failure (*Rev Prescrire* n° 359, 362, 374).

Multiple sclerosis. The standard "disease-modifying" treatment for multiple sclerosis is *interferon beta*, despite its limitations and many adverse effects. The harm-benefit balance of the other disease-modifying treatments is no better and sometimes clearly unfavourable. This applies in particular to three immunosuppressants that have disproportionate adverse effects and should be avoided.

• ***Alemtuzumab***, an antilymphocyte monoclonal antibody, has no proven efficacy and can provoke many serious and sometimes fatal adverse effects, in particular: infusion-related reactions (including atrial fibrillation and hypotension), infections, frequent autoimmune disorders (including autoimmune thyroid disease, immune thrombocytopenic purpura, cytopenia and renal disease) (*Prescrire Int* n° 158; *Rev Prescrire* n° 384).

• ***Natalizumab***, another monoclonal antibody, can lead to sometimes fatal opportunistic infections, including progressive multifocal leukoencephalopathy, potentially serious hypersensitivity reactions, and liver damage (*Rev Prescrire* n° 330, 398; *Prescrire Int* n° 122, 158, 182).

• ***Teriflunomide*** has serious and potentially fatal adverse effects, including liver damage, leukopenia and infections. There is also a risk of peripheral neuropathy *(Prescrire Int* n° 158).

Miscellaneous. A number of drugs used in migraine and Parkinson's disease should also be avoided.

• ***Flunarizine*** and ***oxetorone***, two neuroleptics used to prevent migraine attacks, have at best only modest efficacy (*flunarizine* prevents about one attack every two months) but can cause extrapyramidal disorders, cardiac disorders and weight gain (*Prescrire Int* n° 137). It is better to choose another drug such as *propranolol*.

• ***Tolcapone***, an antiparkinsonian COMT inhibitor, can cause life-threatening liver damage (*Prescrire Int* n° 82, *Rev Prescrire* n° 330). When other treatment options have been exhausted, *entacapone* is a better option.

Oncology - Haematology

Antineoplastics. Various antineoplastic drugs have a clearly unfavourable harm-benefit balance. They are often authorised for situations in which other treatments are ineffective. When exposure to highly toxic drugs is not justified by proven benefits, it is better to focus on tailored symptomatic treatment and on improving the patient's quality of life.

• ***Mifamurtide*** is authorised as add-on therapy in combination with other chemotherapy for osteosarcoma but has not been shown to prolong survival and can provoke serious hypersensitivity reactions, pleural and pericardial effusions, neurological adverse effects and hearing loss (*Prescrire Int* n° 115; *Rev Prescrire* n° 341). It is better to propose chemotherapy without *mifamurtide*.

• ***Nintedanib***, a tyrosine kinase inhibitor authorised as add-on therapy in combination with *docetaxel* for certain types of non-small cell lung cancer, has not been shown to prolong survival but can provoke many serious adverse effects related to its inhibitory effects on angiogenesis, including: venous thromboembolism, bleeding, hypertension, gastrointestinal perforations and impaired wound healing (*Rev Prescrire* n° 389).

• ***Olaparib*** has not been shown to prolong survival when used as maintenance treatment for advanced ovarian cancer in women in remission. It has serious adverse effects: haemopoietic disorders, myelodysplastic syndrome, acute myeloid leukaemia (*Prescrire Int* n° 178).

• ***Panobinostat*** has not been shown to prolong survival in refractory or relapsed multiple myeloma, and provokes many, often serious, adverse effects that affect many vital functions, hastening the death of many patients (*Prescrire Int* n° 176).

• ***Trabectedin*** showed no tangible efficacy in comparative trials in ovarian cancer or soft-tissue sarcomas but has very frequent and severe gastrointestinal, haematological, hepatic and muscular adverse effects (*Prescrire Int* n° 102, 120; *Rev Prescrire* n° 360). It is unreasonable to add *trabectedin* to platinum-based chemotherapy for ovarian cancer. When chemotherapy is ineffective in patients with soft-tissue sarcomas, it is best to focus on appropriate supportive care.

• ***Vandetanib*** has not been shown to prolong survival in patients with metastatic or inoperable medullary thyroid cancer. Too many patients were lost to follow-up in placebo-controlled trials to show an increase in progression-free survival. Serious adverse effects (diarrhoea, pneumonia, hypertension) occur in about one-third of patients. There is also a risk of interstitial lung disease, torsades de pointes and sudden death *(Prescrire Int* n° 131).

• ***Vinflunine*** has uncertain efficacy in advanced and metastatic bladder cancer. A clinical trial provided weak evidence that *vinflunine* increases median survival by two months at best compared with symptomatic treatment. There is a high risk of haematological adverse effects (including aplastic anaemia), and a risk of serious infections and cardiovascular disorders (torsades de pointes, myocardial infarction, ischaemic heart disease), sometimes resulting in death (*Prescrire Int* n° 112; *Rev Prescrire* n° 360).

Cancer or cancer therapy complications. Some drugs are authorised for the treatment of cancer complications, such as the peritoneal complication malignant ascites, or for complications of cancer therapy.

• ***Catumaxomab***, for malignant ascites, provokes serious and possibly fatal adverse effects in more than three-quarters of patients (*Prescrire Int* n° 109). Paracentesis is a better option, repeated as necessary to control symptoms.

• ***Defibrotide***, an antithrombotic authorised for severe hepatic veno-occlusive disease following haemopoietic stem cell transplantation, had no

more impact on mortality or complete disease remission than symptomatic treatment in an unblinded trial, but provokes sometimes fatal haemorrhages (*Prescrire Int* n° 164). It is better to focus on preventive measures and symptomatic treatments.

Ophthalmology

• ***Ciclosporin*** eye drops, authorised for the treatment of dry eye disease with severe keratitis, frequently provoke eye pain and irritation, have immunosuppressive effects and may cause ocular or periocular cancer, yet had no proven efficacy when compared with the same eye drops without *ciclosporin* (**b**) (Prescrire Int n° 181). It is better to use artificial tears for example for symptomatic relief, several types of which are available.
• ***Idebenone*** was no more effective than placebo in a trial in Leber's hereditary optic neuropathy, and carries a risk of adverse effects including hepatic disorders (*Prescrire Int* n° 179). As of 2017, there are no drugs with a favourable harm-benefit balance for patients with this rare disease.

Psychiatry - Addiction

Antidepressants. Several drugs authorised for depression carry a greater risk of severe adverse effects than other antidepressants without offering greater efficacy. In general, antidepressants have only modest efficacy and often take some time to work. It is better to choose one of the longer established antidepressants with an adequately documented adverse effect profile.
• ***Agomelatine*** has no proven efficacy beyond the placebo effect, but can cause hepatitis and pancreatitis, suicide and aggression, as well as serious skin disorders including Stevens-Johnson syndrome (*Prescrire Int* n° 136, 137; *Rev Prescrire* n° 397).
• ***Duloxetine***, a serotonin and norepinephrine reuptake inhibitor, not only has the adverse effects of the so-called "selective" serotonin reuptake inhibitors (SSRIs) but also carries a risk of cardiac disorders (hypertension, tachycardia, arrhythmias, etc.) due to its noradrenergic activity. *Duloxetine* can also cause hepatitis and severe cutaneous hypersensitivity reactions such as Stevens-Johnson syndrome (*Prescrire Int* n° 85, 100, 111, 142; *Rev Prescrire* n° 384).
• ***Citalopram*** and ***escitalopram*** are SSRI antidepressants that expose patients to a higher incidence of QT prolongation and torsades de pointes than other SSRIs and worse outcomes in the event of overdose (*Rev Prescrire* n° 369, 396; *Prescrire Int* n° 170, 174).
• ***Milnacipran*** and ***venlafaxine***, two non-tricyclic, non-SSRI, non-monoamine oxidase inhibitor (MAOI) antidepressants, have both serotonergic and noradrenergic activity. Not only do they have the adverse effects of SSRI antidepressants, they also cause cardiac disorders (hypertension, tachycardia, arrhythmias, QT prolongation) due to their noradrenergic activity. In addition, *venlafaxine* overdoses are associated with a high risk of cardiac arrest (*Rev Prescrire* n° 338, 343, 386; *Prescrire Int* n° 170).
• ***Tianeptine***, a drug with no proven efficacy, can cause hepatitis, life-threatening skin reactions (including bullous rash) and addiction (*Prescrire Int* n° 127, 132).

Other psychotropic drugs. Some other psychotropic drugs have unacceptable adverse effects:
• ***Dapoxetine***, a "selective" SRI, is used for premature ejaculation with sexual dissatisfaction. Its adverse effects are disproportionate to its very modest efficacy and include aggressive outbursts, serotonin syndrome, and syncope (*Prescrire Int* n° 105; *Rev Prescrire* n° 355). A psychological and behavioural approach is a better option in this situation.
• ***Etifoxine***, a drug poorly evaluated in anxiety, can cause hepatitis and severe hypersensitivity reactions (including DRESS syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis) (*Prescrire Int* n° 136; *Rev Prescrire* n° 376). When an anxiolytic drug is justified, it is better to choose a benzodiazepine, for the shortest possible period.

Smoking cessation. One drug authorised as a smoking cessation aid is no more effective than *nicotine* and has more adverse effects. When a drug is needed to help with smoking cessation, *nicotine* is a better choice.
• ***Bupropion***, an amphetamine, can cause neuropsychiatric disorders (including aggressiveness, depression and suicidal ideation), potentially severe allergic reactions (including angioedema and Stevens-Johnson syndrome), addiction, and congenital heart defects in children exposed to the drug in utero (*Prescrire Int* n° 131; *Rev Prescrire* n° 377).

Pulmonology - ENT

• Decongestants for oral or nasal use (***ephedrine***, ***naphazoline***, ***oxymetazoline***, ***phenylephrine***, ***pseudoephedrine*** and ***tuaminoheptane***) are sympathomimetic vasoconstrictors. They can cause serious and even life-threatening cardiovascular disorders, including hypertensive crisis, stroke and arrhythmias, as well as ischaemic colitis. These adverse effects are unacceptable for drugs indicated for minor, rapidly self-resolving ailments such as the common cold (*Prescrire Int* n° 136, 172, 178; 183; *Rev Prescrire* n° 312, 342, 345, 348, 361)

b- *Oral or injectable ciclosporin is a standard immunosuppressant for transplant recipients, and in this situation its harm-benefit balance is clearly favourable (Rev Prescrire n° 386 suppl. 10-1).*

• ***Ambroxol*** and ***bromhexine*** are mucolytics with no proven efficacy beyond a placebo effect, yet they carry a risk of anaphylactic reactions and severe, sometimes fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (*Rev Prescrire* n° 400). These adverse effects are unacceptable for drugs used to relieve sore throat or cough.
• ***Pholcodine***, an opioid used as an antitussive, can cause sensitisation to neuromuscular blocking agents used in general anaesthesia (*Rev Prescrire* n° 349, 400). This serious adverse effect is not known to occur with other opioids. Cough is a minor ailment that does not warrant taking such risks. When drug therapy is required for cough, it is better to choose *dextromethorphan*, despite its limitations (*Rev Prescrire* n° 358).
• ***Tixocortol*** (sometimes combined with *chlorhexidine*), a corticosteroid authorised for sore throat, can cause allergic reactions such as facial mucocutaneous oedema, glossitis or angioedema (*Rev Prescrire* n° 320). When a drug is needed to relieve sore throat, *paracetamol* is a better option, when taken at the appropriate dosage.
• ***Omalizumab***, an anti-IgE monoclonal antibody approved for severe persistent asthma and chronic spontaneous urticaria, and the anti-interleukin-5 monoclonal antibody ***mepolizumab,*** approved for severe asthma, provoke disproportionate adverse effects: infections, hypersensitivity reactions and cardiac disorders in the case of *omalizumab* (*Prescrire Int* n° 115, 161; 179). Corticosteroid therapy at the lowest effective dose is a better option in both of these situations.
• ***Mannitol*** inhalation powder, authorised as a mucolytic for patients with cystic fibrosis despite the lack of convincing evidence of efficacy, can cause bronchospasm and haemoptysis (*Prescrire Int* n° 148). It is best to choose other mucolytics such as *dornase alfa* in the absence of a better alternative.
• ***Nintedanib***, a tyrosine kinase inhibitor, has not been shown to prolong survival, prevent the progression of fibrosis or relieve symptoms in patients with idiopathic pulmonary fibrosis, whereas it causes hepatic disorders and many serious adverse effects due to its inhibitory effect on angiogenesis, including: venous thromboembolism, bleeding, hypertension, gastrointestinal perforations and impaired wound healing (*Prescrire Int* n° 173). It is better to focus on symptomatic treatment.

Rheumatology - Pain

Certain nonsteroidal anti-inflammatory drugs. Although nonsteroidal anti-inflammatory drugs (NSAIDs) share a similar adverse effect profile, some expose patients to less risk. When *paracetamol* proves inadequate, *ibuprofen* and *naproxen*, used at the lowest effective dose and for the shortest possible period, are the least risky options.
• Cox-2 inhibitors (coxibs) such as ***celecoxib***, ***etoricoxib*** and ***parecoxib*** have been linked to an excess of cardiovascular events (including myocardial infarction and thrombosis) and skin reactions by comparison with other equally effective NSAIDs (*Prescrire Int* n° 167; *Rev Prescrire* n° 344, 361, 374).
• Oral ***aceclofenac*** and oral ***diclofenac*** cause more cardiovascular adverse effects (including myocardial infarction and heart failure) and more cardiovascular deaths than other equally effective NSAIDs (*Prescrire Int* n° 167; *Rev Prescrire* n° 362, 374).
• ***Ketoprofen*** gel causes more photosensitivity reactions (eczema, bullous rash) than other equally effective topical NSAIDs (*Prescrire Int* n° 109, 137).
• ***Piroxicam***, when used systemically, carries an increased risk of gastrointestinal and cutaneous disorders (including toxic epidermal necrolysis) but is no more effective than other NSAIDs (*Rev Prescrire* n° 321).

Osteoporosis. Several drugs authorised for osteoporosis are best avoided because their efficacy is at best modest and they have potentially serious adverse effects. When non-drug measures plus calcium and vitamin D supplementation prove inadequate, *alendronic acid* or an alternative, *raloxifene*, have a better harm-benefit balance than other options, despite the significant limitations of both drugs.
• ***Denosumab*** 60 mg in osteoporosis has very modest efficacy in the prevention of osteoporotic fractures and no efficacy for "bone loss" during prostate cancer, but carries a disproportionate risk of adverse effects, including back pain, musculoskeletal pain, and serious infections (including endocarditis) due to the immunosuppressive effects of this monoclonal antibody (*Prescrire Int* n° 117, 130, 168). There is no known satisfactory drug treatment for "bone loss" (**c**).
• ***Strontium ranelate*** has only modest efficacy in the prevention of recurrent vertebral fractures. Yet its adverse effects include neuropsychiatric disorders, cardiovascular disorders (including venous thrombosis and pulmonary embolism, myocardial infarction and cardiovascular death), and hypersensitivity reactions including toxic epidermal necrolysis and DRESS (drug reaction with eosinophilia and systemic symptoms) (*Prescrire Int* n° 117, 125, 139, 142, 156).

Osteoarthritis. Drugs authorised for their supposed effect on the process that results in osteoarthritis should be avoided because they have significant adverse effects but no proven efficacy beyond the placebo effect. There are no drugs with efficacy against joint degeneration and a favourable harm-benefit balance.

c- *A 120-mg strength denosumab product is authorised for use in patients with bone metastases from solid tumours. In this situation, denosumab offers no tangible advantages, but its harms do not clearly outweigh its benefits (Prescrire Int n° 130).*

Drugs that should not be used: swifter action required to protect patients

This fifth edition of our annual review "Towards better patient care: drugs to avoid" provides an opportunity to examine the decisions taken in France by regulators and pharmaceutical companies to protect patients from these drugs.

Various measures available. Regulators can decide to withdraw or suspend a drug's marketing authorisation, remove it from the list of drugs that qualify for reimbursement by the national health insurance system, or reduce the percentage of its cost that is reimbursed. Pharmaceutical companies can decide to stop marketing a product.

Various combinations of these measures have been applied between 2013 and 2016, each to only a handful of drugs, some of which are discussed below.

Marketing authorisations suspended or withdrawn for about 10 drugs, and some half-measures. *Prescrire*'s five annual reviews during this period have identified about a hundred drugs to avoid, but only about ten have been withdrawn from the market through suspension or withdrawal of the marketing authorisations for products containing them. The French Health Products Agency (ANSM) has taken such action far more frequently than the European Medicines Agency.

A number of long-marketed drugs had their marketing authorisations suspended in 2013: products containing *meprobamate* (*Prescrire Int* n° 148) and 5 ergot derivatives (*Rev Prescrire* n° 364).

The marketing authorisation for *indoramin* was withdrawn in 2013, after 28 years on the market (*Rev Prescrire* n° 356) (1). The marketing authorisation for *floctafenine* was revoked in 2015, after 40 years on the market (*Rev Prescrire* n° 321, 384) (1,2).

Marketing authorisation for *domperidone* 20 mg was withdrawn in 2014, after years of procedures (*Prescrire Int* n° 175). But the 10-mg strength, authorised in France since 1980, remains on the market (1).

A few market withdrawals by pharmaceutical companies. A *theodrenaline* + *cafedrine* combination and *nimesulide* were withdrawn from the market in 2013 (*Prescrire Int* n° 147, *Rev Prescrire* n° 364). In 2014, a *quinine*-containing suppository for cramps was also withdrawn (*Rev Prescrire* n° 377). Their French marketing authorisations therefore became null and void (1).

Quinine Vitamine C Grand° (*Rev Prescrire* n° 400) has not been marketed since 2014, but its French marketing authorisation, granted in 1997, remains valid, and other oral *quinine*-containing products for cramps are still available.

In 2016, the European marketing authorisation for *pegloticase*, granted in 2013, was withdrawn when the company stopped marketing it (*Prescrire Int n° 180*).

Iron dextran ceased to be marketed in France in 2015 (*Rev Prescrire* n° 349; *Prescrire Int* n° 151). Its European marketing authorisation, granted in 2007, remains valid (1). The same is true of *asenapine*, a neuroleptic authorised in 2010 (*Rev Prescrire* n° 388) (1).

Delisting: a slow process, sometimes challenged, sometimes partial. If a drug's marketing authorisation is upheld, particularly at European level, a stopgap measure is to reduce the number of patients exposed to it through delisting, i.e. removal from the list of products that qualify for reimbursement by the French health insurance system. A number of *trimetazidine*-containing products, including copies, are still available in early 2017 despite being delisted in 2012, suggesting that significant quantities are still sold (*Rev Prescrire* n° 342). *Strontium ranelate* remains available in early 2017 despite being delisted in 2015 (*Rev Prescrire* n° 377).

Some delisting decisions have been challenged in court by the pharmaceutical companies, as was the case for *ketoprofen* gel (*Prescrire Int* n° 109, 112; *Rev Prescrire* n° 317), *diacerein*, *glucosamine* and *olmesartan* (*Rev Prescrire* n° 395, 380). The French health minister has asked for a "treatment protocol" to be drawn up before considering delisting the 4 drugs for Alzheimer's disease (*Rev Prescrire* n° 398) (3).

Sometimes a drug is delisted for certain authorised indications, while other authorised indications are reimbursed at a reduced rate. For example, topical *tacrolimus* was granted European marketing authorisation in 2002, then in 2014 its reimbursement by the French health insurance system was revoked for children and reduced for adults (*Rev Prescrire* n° 245, 367).

Sometimes reimbursement is reduced to 15% of the product's cost, which was the case in 2016 for *agomelatine*, authorised since 2009 (*Rev Prescrire* n° 397).

Mifamurtide and *vernakalant* obtained European marketing authorisations years ago but are not on sale in France, perhaps due to the unfavourable opinion issued by the committee responsible for recommending whether new drugs should be funded by the national health insurance system (see inset p. 108-3).

In summary: do not wait for companies or regulators to act. The actions taken from 2013 to 2016 by regulators and pharmaceutical companies to rid the market of drugs that are more dangerous than beneficial have been slow and piecemeal, especially at European level.

It is in patients' and health professionals' interests to take matters into their own hands by avoiding these drugs now.

1- ANSM "Répertoire des spécialités pharmaceutiques". http://agence-prd.ansm.sante.fr/php/ecodex/ accessed 6 January 2017.
2- HAS - Commission de la transparence "Avis-Idarac" 15 November 2006.
3- Agence France Presse "Médicaments anti-Alzheimer: Touraine écarte le "déremboursement"" 26 October 2016. www.leparisien.fr accessed 6 January 2017: 3 pages.

• ***Diacerein*** causes gastrointestinal disorders (including gastrointestinal bleeding and melanosis coli), angioedema and hepatitis (*Rev Prescrire* n° 282, 321; *Prescrire Int* n° 159).
• ***Glucosamine*** causes allergic reactions (angioedema, acute interstitial nephritis) and hepatitis (*Prescrire Int* n° 84, 137; *Rev Prescrire* n° 380).

Miscellaneous. A number of other drugs used for specific types of pain or in rheumatology are best avoided.
• ***Capsaicin***, a red chilli pepper extract authorised in patch form for neuropathic pain, is barely more effective than placebo but can provoke irritation, severe pain and burns (*Prescrire Int* n° 108, 180). *Capsaicin* remains an unreasonable choice even when systemic pain medications or local ones such as *lidocaine* medicated plasters fail to provide adequate relief.
• Muscle relaxants with no proven efficacy beyond the placebo effect: ***methocarbamol*** has many adverse effects, including gastrointestinal and cutaneous disorders (angioedema), while ***thiocolchicoside***, which is related to *colchicine*, causes diarrhoea, stomach pain, photodermatosis and possibly convulsions; it is also genotoxic and teratogenic (*Prescrire Int* n° 168, *Rev Prescrire* n° 282, 321, 313, 367, 400). There is no justification for exposing patients to these adverse effects for such little efficacy. An effective analgesic such as *paracetamol* is a better option, when taken at the appropriate dosage.
• ***Quinine*** for cramps can have life-threatening adverse effects including anaphylactic reactions, haematological disorders (including thrombocytopenia, haemolytic anaemia, agranulocytosis, and pancytopenia) and cardiac arrhythmias. These adverse effects are disproportionate in view of its poor efficacy (**d**) (*Rev Prescrire* n° 337, 344). There are no drugs with a favourable harm-benefit balance for patients with cramps. Regular stretching can be beneficial (*Rev Prescrire* n° 362).
• Colchimax® (***colchicine*** + ***opium powder*** + ***tiemonium***) should be avoided in gout attacks because the action of *opium powder* and *tiemonium* can mask the onset of diarrhoea, which is an early sign of potentially fatal *colchicine* overdose (*Prescrire Int* n° 147). A nonsteroidal anti-inflammatory drug or *colchicine* alone are better options for gout attacks.

The ***dexamethasone*** + ***salicylamide*** + ***hydroxyethyl salicylate*** combination (*Rev Prescrire* n° 345) and the ***prednisolone*** + ***dipropylene glycol salicylate*** combination (*Rev Prescrire* n° 338), for cutaneous application, expose patients to the adverse effects of corticosteroids and to *salicylate* hypersensitivity reactions. Other drugs such as oral *paracetamol* (at the appropriate dosage) and topical *ibuprofen* have a better harm-benefit balance in patients with painful sprains or tendinopathy, in conjunction with non-drug measures (rest, ice, splints).

Putting patients first

Our analyses show that the harm-benefit balance of the drugs listed here is unfavourable in all their authorised indications. Yet some have been marketed for many years and are commonly used. How can one justify exposing patients to drugs that have more adverse effects than other members of the same pharmacological class or other similarly effective drugs? And what justification is there for exposing patients to drugs with severe adverse effects but no proven impact (beyond the placebo effect) on patient-relevant clinical outcomes?

It is necessary but not sufficient for healthcare professionals to remove these drugs from their list of useful treatments: regulators and health authorities must also take concrete steps to protect patients and promote the use of treatments that have an acceptable harm-benefit balance.

The drugs listed above are more dangerous than beneficial. There is no valid reason for them to retain their marketing authorisations or continue to be marketed.

▶ Translated from *Rev Prescrire* **February 2017**
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d- *Quinine is a recommended treatment for malaria (Rev Prescrire n° 360).*

Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2016" *Prescrire Int* 2016; **25** (170): 105-111.
2- Prescrire Editorial Staff "Towards better patient care: drugs to avoid" *Prescrire Int* 2013; **22** (137): 108-111.
3- Prescrire Rédaction "Des médicaments à écarter pour mieux soigner: pourquoi?" *Rev Prescrire* 2013; **33** (360): 792-795.
4- Prescrire Editorial Staff "Determining the harm-benefit balance of an intervention: for each patient" *Prescrire Int* 2014; **23** (154): 274-277.
5- Prescrire Editorial Staff "Treatment goals: discuss them with the patient" *Prescrire Int* 2012; **21** (132): 276-278.