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Towards better patient care: drugs to avoid in 2015

Abstract

● **To help healthcare professionals and patients choose high-quality treatments that minimise the risk of adverse effects, we have updated our list of drugs to avoid in early 2015.**

● ***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 2015 review of medications examined in these pages over a five-year period, from 2010 to 2014, identified 71 drugs that are more harmful than beneficial in all their authorised indications.**

● **Other drugs with a better harm-benefit balance are available in most cases (when drug therapy is really necessary), but sometimes there is no satisfactory medical treatment. However, even in serious situations there is no justification for exposing patients to a risk of severe adverse effects by prescribing a drug with no proven clinical efficacy. Some of these drugs may be worth testing in clinical trials, but patients enrolled in such studies must be aware that the harms and benefits they may experience are uncertain and that the main reason for their participation is to advance medical knowledge. Tailored supportive care is the best option when there are no available treatments capable of improving prognosis or quality of life, beyond the placebo effect.**

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This is *Prescrire's* third consecutive annual review of "drugs to avoid" (1,2). The listed drugs are clearly more dangerous than beneficial and should therefore not be used in any circumstance. The aim is to help healthcare professionals to 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 that we analysed in depth over a five-year period, from 2010 to 2014. 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.

The overriding goal of *Association Mieux Prescrire*, the not-for-profit association that publishes the journals *la revue Prescrire* and *Prescrire International*, is "*to work in total independence to promote quality healthcare, first and foremost in the interest of patients*" (Article 1 of the statutes). All our publications are intended to provide healthcare professionals (and their patients) with the clear, independent, reliable and up-to-date information they need, free of 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 healthcare professionals working in various sectors and free of 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 symbolized by the "*Prescrire*" signature.

Most importantly, *Prescrire* is fiercely independent. Our work is funded solely and entirely by our subscribers. No company, professional organisation, insurance system, government agency or health authority has any financial influence whatsoever over the contents of our publications.

Comparison with standard treatments. The harm-benefit balance of a given drug has to be continually updated 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 an editorial team using an established procedure:

– Efficacy data are prioritised: most weight is given to studies providing ▶▶

▶ solid supporting evidence, i.e. well-conducted, double-blind, randomised controlled trials;
– The new drug is compared with a carefully chosen standard treatment (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 difficult to analyse, as they are often less thoroughly documented than efficacy, and such 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.

Marketing authorisation of a new drug 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 (2).

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 physician 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 a standard treatment (3,4).

Severe 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 healthcare professionals may propose last-chance treatments without properly informing the patient of the harms, either intentionally or unwittingly. Yet patients in this situation must not be treated as guinea pigs but rather enrolled in clinical research protocols after being fully informed of the harms and the uncertain nature of the possible benefits. It is crucial that the results of these trials be published.

Patients must be aware that they are free to refuse to participate in clinical trials of last-chance treatments with poorly known harms and benefits. They must also be reassured that, if they do refuse to participate, they will not be abandoned but 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 a standard treatment, and an acceptable adverse effect profile: in general, little extra information on efficacy is collected once marketing authorisation has been granted (2).

71 drugs more dangerous than beneficial

Between 2010 and 2014, we identified 71 drugs marketed in France that are more dangerous than beneficial. They are listed below, based first on their therapeutic class and then in alphabetical order of their international nonproprietary names (INN).

These 71 drugs comprise:
– Active substances with adverse effects that are disproportionate to the benefits they provide;
– 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.

Some drugs added to the 2014 list. All the drugs listed in our 2014 review are also included this year, with the exception of *omalizumab*, a drug being assessed in urticaria, and *pirfenidone*, the assessment of which in idiopathic pulmonary fibrosis we have updated.

It is noteworthy that none of the dangerous drugs we have identified were withdrawn from the French market in 2014. The following drugs are newly listed in 2015: *natalizumab* in multiple sclerosis (following a reassessment that included new data); *olmesartan*, an antihypertensive drug with more adverse effects than other members of its class; and two new drugs: *pegloticase* in severe attacks of gout and *teriflunomide* in multiple sclerosis.

Diclofenac and *aceclofenac* are not added to the list despite their cardiovascular averse effects that seem more frequent than with other established nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, we are updating our review on cardiovascular adverse effects of NSAIDs.

Citalopram and *escitalopram*, which can cause QT prolongation, are not included in our list (Rev Prescrire n° 369). We are planning to review this adverse effect with the various SSRI antidepressants.

Oncology

– *Catumaxomab*, used in malignant ascites, has serious adverse effects (possibly fatal) in more than three-quarters of patients (Prescrire Int n° 109). It is more prudent to drain ascites, at intervals guided by symptoms.
– *Panitumumab* does not prolong survival in metastatic colorectal cancer, yet about 90% of patients experience adverse effects, which include severe skin damage (sometimes resulting in fatal infections), gastrointestinal and ocular disorders, interstitial pneumonia and hypersensitivity reactions (Prescrire Int n° 138). It is unwise to add *panitumumab* to tried-and-tested chemotherapy regimens such as those based on *fluorouracil*, alone or combined with other cytotoxic drugs.
– *Trabectedin* showed no tangible efficacy in comparative trials in ovarian cancer and soft-tissue sarcomas but has very frequent and severe gastrointestinal, haematological, hepatic and muscular adverse effects (Prescrire Int n° 102 and 120; Rev Prescrire n° 360). It is unwise 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 no proven impact on survival in patients with metastatic or

inoperable medullary thyroid cancer. As too many patients were lost to follow-up in placebo-controlled trials, evidence of an increase in progression-free survival is unconvincing. Serious adverse effects (diarrhoea, pneumonia, hypertension) occur in about one-third of patients. There is also a risk of interstitial pneumonia, torsades de pointes and sudden death (Prescrire Int n° 131). Here too it is best to focus on tailored supportive care.
– *Vinflunine* has uncertain efficacy in advanced-stage and metastatic bladder cancer. A clinical trial provided weak evidence of a survival advantage of no more than two months compared to palliative care. There is a high risk of haematological adverse effects (including aplastic anaemia), serious infections, and cardiovascular disorders (torsades de pointes, myocardial infarction, ischaemic heart disease), sometimes resulting in death (Prescrire Int n° 112). When platinum-based chemotherapy is ineffective it is best to focus on tailored supportive care.

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 excess of cardiovascular events and renal failure (Prescrire Int n° 106 and 129). It is more prudent to choose one of the many tried-and-tested antihypertensive drugs such as a diuretic or an angiotensin-converting-enzyme (ACE) inhibitor.
– *Fenofibrate, bezafibrate* and *ciprofibrate* 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 and 117). When a fibrate is considered, *gemfibrozil* is the only one that has been shown to prevent cardiovascular complications of hypercholesterolaemia, although it must be used with care.
– *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 angina or heart failure (Prescrire Int n° 88, 110, 118, 155). Treatments shown to be effective in angina include beta-blockers and the calcium channel blockers *amlodipine* and *verapamil*. There are also far 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 in the prevention of effort angina, can cause severe mucocutaneous ulceration (Prescrire Int n° 81, 95, 110, 132). It is more prudent to use a nitrate to prevent effort angina.
– *Olmesartan*, an angiotensin II antagonist (sartan) that is no more effective than other sartans in arterial hypertension, can cause bowel inflammation with chronic diarrhoea (potentially severe) and weight loss, and, possibly, an increased risk of cardiovascular mortality (Prescrire Int n° 148). It is better to choose another of the many available sartans, such as *losartan* or *valsartan*, which do not appear to have these adverse effects.
– *Trimetazidine*, a drug with uncertain properties, is used in angina despite its only modest symptomatic efficacy (shown mainly in stress tests), yet it can cause parkinsonian syndromes, hallucinations and thrombocytopenia (Prescrire Int n° 84, 100, 106). It is far more prudent to choose better-known treatments for angina, such as certain beta-blockers or the calcium channel blockers *amlodipine* and *verapamil*.

Dermatology - Allergy

– Topical *tacrolimus*, an immunosuppressant used in atopic eczema, increases the risk of skin cancer and lymphoma yet its efficacy is barely different from that of topical corticosteroids (Prescrire Int n° 101, 110, 131, Rev Prescrire n° 367). It is far more prudent to use a topical steroid to treat exacerbations.
– *Mequitazine*, a sedative and antimuscarinic antihistamine used in allergies, has only modest efficacy but carries a higher risk than other antihistamines of cardiac arrhythmias due to QT prolongation in patients with low cytochrome P450 iso-enzyme CYP2D6 activity, and during co-administration of drugs that inhibit this isoenzyme (Rev Prescrire n° 337). It is far more prudent to choose a non-sedative and non-antimuscarinic antihistamine such as *loratadine* or *cetirizine*.
– 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). It is more prudent to use injectable *dexchlorpheniramine*, which does not appear to carry these risks (1).

Diabetes - Nutrition

– Dipeptidyl peptidase 4 inhibitors (gliptins) have no proven efficacy on complications of diabetes (cardiovascular events, renal failure, neurological disorders, etc.). This is the case of *linagliptin, saxagliptin, sitagliptin* and *vildagliptin*, whether used alone or in combination with *metformin*. These four drugs have an unfavourable adverse effect profile that includes severe hypersensitivity reactions (anaphylaxis, Stevens-Johnson syndrome), infections (urinary tract and upper respiratory tract infections), pancreatitis and bullous pemphigoid Prescrire Int n° 121, 135, 138, Rev Prescrire n° 365, 366, 373). A proven treatment such as *metformin*, *glibenclamide* or *insulin*, or targeting a higher HbA1c, are more reasonable choices.
– *Orlistat* has only modest and transient efficacy in terms of weight loss (about 3.5 kg more than placebo after 12 to 24 months). There is no evidence of long-term efficacy. Gastrointestinal disorders are very frequent, while other adverse effects include hepatic disorders, 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 can be reduced if orlistat provokes severe diarrhoea (Prescrire Int n° 57, 71, 107, 110, Rev Prescrire n° 374). There are currently no drugs capable of inducing permanent weight loss. It is best to focus on dietary changes and physical activity.

Pain - Rheumatology

Analgesics. Many analgesics and anti-inflammatory drugs should be avoided, especially since alternatives with a better harm-benefit balance are available. *Paracetamol* is the first-choice analgesic: it is effective on moderate pain and poses little danger when the maximum recommended dose is not exceeded. Alternatives include some nonsteroidal anti-inflammatory drugs (NSAIDs) such as *ibuprofen* and *naproxen*, when used at the lowest effective dose and for the shortest possible period.
– 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 (Rev Prescrire n° 344, 361, 374).
– *Floctafenine*, a NSAID authorised for use as an analgesic, can cause severe ▶▶

▶ hypersensitivity reactions, including bronchospasm and angioedema, yet is no more effective than other options (Prescrire Int n° 137).
– *Ketoprofen* gel causes more photosensitivity reactions (eczema, bullous rash) than other, equally effective topical NSAIDs (Prescrire Int n° 109 and 137).
– *Piroxicam*, a NSAID, is associated when used systemically with an increased risk of gastrointestinal and cutaneous disorders (including Lyell's syndrome) but is not more effective than safer NSAIDs (Rev Prescrire n° 321).

Osteoporosis. Several drugs authorised for osteoporosis should be 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, and 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 and 130)(**a**).
– *Strontium ranelate* has only modest efficacy in preventing 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 Lyell's syndrome and DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) (Prescrire Int n° 117, 125, 139, 142, 156).

Osteoarthritis. Drugs authorised for long-term treatment of osteoarthritis should be avoided because they have significant adverse effects but no proven efficacy beyond the placebo effect. *Paracetamol* is a more prudent first-choice treatment for pain, provided the recommended dose is not exceeded. Carefully chosen and closely monitored non-steroidal anti-inflammatory drug therapy is sometimes an acceptable option.
– *Diacerein* causes gastrointestinal disorders (including gastrointestinal bleeding and colonic melanosis), angioedema, and hepatitis (Rev Prescrire n° 282; 321).
– *Glucosamine* causes allergic reactions (angioedema, acute interstitial nephritis) and hepatitis (Prescrire Int n° 84, 137).

Miscellaneous. Several drugs mainly used in rheumatology should be avoided.
– Muscle relaxants with no proven efficacy: *methocarbamol* has many adverse effects, including gastrointestinal and cutaneous disorders (angioedema), while *thiocolchicoside* causes diarrhoea, stomach pain, photodermatosis and possibly convulsions; it is also genotoxic and teratogenic (Rev Prescrire n° 282; 321; 313, 367). There is no justification for exposing patients with simple muscle pain to these adverse effects. It is more prudent to use an effective analgesic such as *paracetamol*, taken at the appropriate dosage.
– *Pegloticase*, a recombinant uricase used in severe gout, has modest short-term symptomatic efficacy and disproportionate adverse effects, including severe reactions during infusion (despite premedication), anaphylaxis, severe skin infections and, possibly, severe cardiac disorders (Rev Prescrire n° 365). When treatment with the first choice *allopurinol* and the alternative *probenecid*, is inadequate or risky, it is more prudent to manage attacks with symptomatic treatments, pending a better solution.
– *Quinine*, used to treat 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 (Rev Prescrire n° 337; 344). There are no drugs with a favourable harm-benefit balance for patients with cramps. Stretching is sometimes beneficial (Rev Prescrire n° 363).
– Colchimax° (*colchicine* + *opium powder* + *tiemonium*) should be avoided in gout attacks because the action of powdered *opium* and *tiemonium* can mask the onset of diarrhoea, which is an early sign of potentially fatal *colchicine* overdose (Prescrire Int n° 147). It is far more prudent to use a non-steroidal anti-inflammatory drug, or *colchicine* alone.
– The *dexamethasone* + *salicylamide* + *hydroxyethyl salicylate* combination (Rev Prescrire n° 345) and the *prednisolone* + *dipropylene glycol salicylate* combination (Rev Prescrire n° 338), when applied to the skin, expose patients to the adverse effects of corticosteroids and to *salicylate* hypersensitivity reactions. Other drugs such as oral *paracetamol* (at the recommended 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).

Gastroenterology

– *Domperidone* and *droperidol*, two neuroleptics can cause ventricular arrhythmias and sudden death, which are disproportionate to the symptoms and their weak efficacy on nausea and vomiting, and for *domperidone*, on gastroesophagal reflux (Prescrire Int n° 129, 144, Rev Prescrire n° 365, 371). Other drugs such as antacids and *omeprazole* have a much better harm-benefit balance in gastroesophageal reflux disease. When treatment with an anti-emetic neuroleptic is nonetheless justified, it is best to use *metoclopramide*, carefully, at the lowest possible dose and for the shortest possible period.
– *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) and teratogenicity (Prescrire Int n° 116 and 137). 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 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.

Haematology

– *Iron dextran* has no advantages over other injectable iron products and carries a higher risk of hypersensitivity reactions (Rev Prescrire n° 349, Prescrire Int n° 151).

Antibiotics

– *Moxifloxacin* is no more effective than other fluoroquinolone antibiotics but can cause Lyell's syndrome and fulminant hepatitis and has also been linked to

an increased risk of cardiac disorders (Prescrire Int n° 62, 103, Rev Prescrire n° 371). It is far more prudent to choose another fluoroquinolone such as *ciprofloxacin* or *ofloxacin*.
– *Telithromycin* has no advantages over other macrolide antibiotics but carries an increased risk of QT prolongation, hepatitis, visual disturbances and syncope (Prescrire Int n° 84, 88, 94, 106, 154). Another macrolide such as *spiramycin* is a far more prudent option.

Neurology

Alzheimer's disease. Drugs available for Alzheimer's disease in early 2015 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 dependency, yet all carry a risk of life-threatening adverse effects and severe drug interactions (Prescrire Int n° 128 and 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 caring relatives.
– *Donepezil, galantamine* and *rivastigmine*, three cholinesterase inhibitors, can cause gastrointestinal disorders (including severe vomiting), neuropsychiatric disorders, cardiac disorders (including bradycardia, malaise and syncope), and cardiac conduction disorders (Rev Prescrire n° 337; 340; 344; 349; 362, 374).
– *Memantine*, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders such as hallucinations, confusion, dizziness, headache (creating a risk of violent behaviour) and seizures (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 other such treatments is no better and sometimes far worse. This is particularly the case of two immunosuppressants, which have disproportionate adverse effects and should be avoided.
– *Natalizumab*, a monoclonal antibody, can lead to life-threatening opportunistic infections, including progressive multifocal leukoencephalopathy (in about 2 per 1 000 patients), potentially severe hypersensitivity reactions, and liver damage (Rev Prescrire n° 330, 333, 374).
– *Teriflunomide* has potentially life-threatening adverse effects, including liver damage, leukopenia and infections. There is also a risk of peripheral neuropathy (Rev Prescrire n° 373).

Miscellaneous. Some other 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 more prudent to use another drug such as *propranolol*.
– *Tolcapone*, an antiparkinsonian drug, can cause life-threatening liver damage (Rev Prescrire n° 330). When other treatment options have been exhausted, it is far more prudent to use *entacapone*.

Pulmonology - ENT

– Oral and nasal vasoconstrictive decongestants (*ephedrine, naphazoline, oxymetazoline, pseudoephedrine* and *tuaminoheptane*) can cause serious and even life-threatening cardiovascular disorders, including hypertensive episodes, stroke and arrhythmias. This is unacceptable for drugs that are indicated for mild, rapidly self-resolving ailments such as the common cold (Prescrire Int n° 136).
– *Pholcodine*, an opioid used as an antitussive, can cause sensitisation to neuromuscular blocking agents (Rev Prescrire n° 349). 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 *codeine* or *dextromethorphan*, taking into account their limitations and drawbacks (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, and even angioedema (Rev Prescrire n° 320). When a drug is needed to relieve sore throat, *paracetamol* is a far more prudent choice, provided the maximum recommended dose is respected.

Psychiatry - Addiction

Antidepressants. Several drugs authorised for depression carry a greater risk of severe adverse effects but are no more effective than alternative treatments. In general, antidepressants have only modest efficacy and often take some time to work. It is best to choose a well-established antidepressant with an adequately documented adverse effect profile.
– *Agomelatine* has no proven efficacy but can cause hepatitis and pancreatitis, suicide attempts and physical assaults, as well as serious skin disorders including Stevens-Johnson syndrome (Prescrire Int n° 136 and 137).
– *Duloxetine*, a serotonin and norepinephrine reuptake inhibitor, not only has the adverse effects of selective serotonin reuptake inhibitors (SSRIs) but also carries a risk of cardiac disorders (arterial 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).
– *Milnacipran* and *venlafaxine*, two nontricyclic, 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 (arterial hypertension, tachycardia, arrhythmias) due to their noradrenergic activity. *Venlafaxine* also causes QT prolongation (Rev Prescrire n° 338; 343; 362, 374).
– *Tianeptine*, a drug with no proven efficacy, can cause hepatitis, life-threatening skin reactions (including bullous rash), abuse and addiction (Prescrire Int n° 127 and 132).

Other psychotropic drugs. Some other psychotropic drugs have unacceptable adverse effects:
– *Asenapine*, a drug somewhat less effective than other neuroleptics in manic episodes associated with bipolar disorder, can cause potentially severe hypersensitivity reactions (angioedema, hypotension, tongue swelling) as well as hypoaesthesia, in addition to the usual adverse effects of neuroleptics (Prescrire Int n° 131).
– *Dapoxetine*, an SSRI, 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 and Rev Prescrire n° 355). It is more prudent to focus on psychological and behavioural approaches.
– *Etifoxine*, a drug poorly evaluated in anxiety, can cause hepatitis and severe hypersensitivity reactions (including DRESS, Stevens-Johnson and Lyell's syndromes) (Prescrire Int n° 136). When an anxiolytic drug is needed, it is far more prudent to prescribe a benzodi- ▶▶

a- Another product based on denosumab 120 mg (Xgeva°) is authorised for bone metastases of solid tumours. In this setting denosumab has no tangible advantage but we do not include it in the list of drugs to avoid (Prescrire Int n° 130).

► azepine, for the shortest possible period.

Smoking cessation. Some drugs authorised to assist with smoking cessation are no more effective than *nicotine* and have more adverse effects. When a drug is needed to help with smoking cessation, *nicotine* is the most prudent 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 if used during pregnancy (Prescrire Int n° 131).
– *Varenicline* can cause depression, suicide, serious skin rash (including Stevens-Johnson syndrome) and cardiac disorders (angina, myocardial infarction, atrial fibrillation) (Prescrire Int n° 124 and 131)

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?

It is necessary but not sufficient for healthcare professionals to remove these drugs from their list of useful treatments: 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 and should be removed from the market without further delay.

Selected references.
1- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2014" *Prescrire Int* 2014; **23** (150): 161-165.
2- Prescrire Editorial Staff "Towards better patient care: drugs to avoid" *Rev Prescrire* 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; **223** (154) : 274-277.
5- Prescrire Rédaction "Objectifs des traitements à partager avec les patients" *Rev Prescrire* 2012; **32** (345): 544-546.