

Towards better patient care: drugs to avoid in 2016

Abstract

● To help healthcare professionals and patients choose high-quality treatments that minimize the risk of adverse effects, in early 2016 we updated our list of drugs 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.

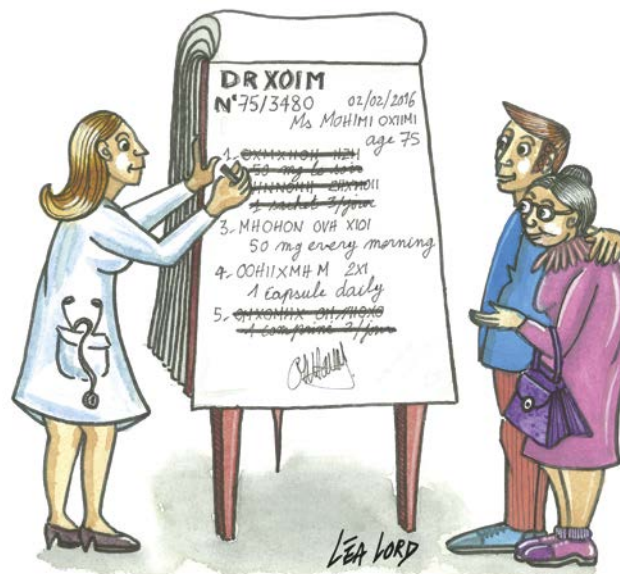
● This 2016 review of medications examined by *Prescrire* over a six-year period, from 2010 to 2015, identified 74 drugs that are more harmful than beneficial in all the indications for which they have been authorised in France.

● 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 the placebo effect.

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This is *Prescrire's* fourth 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 health 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 on which we published detailed analyses in our French edition over a six-year period, from 2010 to 2015. 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 organisation 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 bylaws). All our publications are intended to provide health 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 health 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 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 (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.

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 (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 a standard treatment (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 properly 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 research 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 aware that they are free to refuse 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 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 (3).

74 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.

Between 2010 and 2015, we identified 74 drugs marketed in France that are more dangerous than beneficial. 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 74 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.

The differences between this year's and last year's lists are detailed in the inset on p. 107.

Antibiotics

• **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° 84, 88, 94, 106, 154). Another macrolide such as *spiramycin* is a better option.

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, 129, 166). It is better to choose one of the many tried-and-tested 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 cardiovascular complications of hypercholesterolaemia, although renal function and serum creatine phosphokinase levels must be closely monitored.

- **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, 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 in the prevention of 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 sartin) that is no more effective than other ARBs in hypertension, can cause sprue-like enteropathy 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 ARBs, 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 parkinsonism, hallucinations and thrombocytopenia (*Prescrire Int* n° 84, 100, 106). It is better to choose better-known treatments for angina, such as certain beta-blockers or the calcium-channel blockers *amlodipine* and *verapamil*.

Dermatology - Allergy

- **Mequitazine**, a sedating antihistamine with antimuscarinic properties, used in allergies, has only modest efficacy but carries a higher risk than other antihistamines of cardiac arrhythmias due to QT prolongation in patients who are slow cytochrome isoenzyme P450 CYP2D6 metabolisers, and during

Notable changes in the 2016 update: citalopram, escitalopram, diclofenac added to the list of drugs to avoid

Three of the drugs that have featured in our list of drugs to avoid since the first version, published in 2013, were withdrawn from the French market in 2015 by the pharmaceutical companies concerned: *asenapine* for manic episodes; *iron dextran* for anaemia; and *floctafenine* for moderate pain.

Pirfenidone: not listed in 2016, but many uncertainties. All the drugs listed in our 2015 review are also included this year, with the exception of *pirfenidone*, whose harm-benefit balance in idiopathic pulmonary fibrosis has become more uncertain in light of new clinical data. Its clinical evaluation includes some favourable data but still does not show whether or not *pirfenidone* reduces mortality, even after one year. It is not clear whether the uncertain benefit of this treatment outweighs its harms, which markedly reduce the quality of life of patients whose life expectancy is short, but this does not justify its continued inclusion in our list of drugs to avoid (*Rev Prescrire* n° 384).

Confirmation: thiocolchicoside, venlafaxine, omalizumab. In 2015, we re-examined certain aspects of the harm-benefit balance of several drugs from our list of drugs to avoid. Our re-evaluation of *thiocolchicoside*, a drug with a similar chemical structure to *colchicine*, confirmed its place on the list. *Thiocolchicoside* has a variety of serious hepatic, pancreatic, muscular, haematological and neurological adverse effects, yet has not been shown to be more effective than placebo in muscle pain (*Prescrire Int* n° 168).

Re-analysis also confirmed *venlafaxine* as an antidepressant to be avoided. This antidepressant with serotonergic and noradrenergic activity causes more cardiovascular adverse effects, and is more likely to result in death in the event of overdose,

than many other antidepressants over which it has no proven advantages (*Rev Prescrire* n° 386 and *Prescrire Int* n° 170).

Omalizumab, which is authorised for use in asthma and chronic spontaneous urticaria, is no more effective than a corticosteroid. In addition to its immunosuppressant effect, this monoclonal antibody causes hypersensitivity reactions and cardiac disorders (*Prescrire Int* n° 115, 161).

Additions: drugs that are more harmful than similar options. An analysis of the cardiac adverse effects of antidepressants revealed that the "selective" serotonin reuptake inhibitors (SSRIs) *citalopram* and *escitalopram* are no more effective than other SSRIs but cause more cardiac disorders, including dose-dependent prolongation of the QT interval and torsades de pointes (*Rev Prescrire* n° 386).

Analysis of the cardiovascular adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) revealed that *diclofenac* causes more cardiovascular adverse effects, including myocardial infarction, heart failure and cardiovascular deaths than other NSAIDs, such as *ibuprofen* (up to a maximum dose of 1200 mg per day) or *naproxen*, but is no more effective. In the absence of evidence to the contrary, *aceclofenac* was considered to expose patients to similar risks to *diclofenac* due to their chemical affiliation, and should therefore also be avoided (*Prescrire Int* n° 167; *Rev Prescrire* n° 374).

The efficacy of *defibrotide*, an antithrombotic authorised in severe hepatic veno-occlusive disease following haemopoietic stem cell transplantation, is too uncertain when balanced against its serious adverse effects, in particular haemorrhages (*Prescrire Int* n° 164).

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co-administration of drugs that inhibit this isoenzyme (*Rev Prescrire* n° 337). A non-sedating antihistamine without antimuscarinic activity, such as *loratadine* or *cetirizine*, is a better option in this situation.

- **Omalizumab** in chronic spontaneous urticaria (see the Pulmonology - ENT section on p. 111) (*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 (*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

• Gliptins inhibit dipeptidylpeptidase-4 (DPP-4), an enzyme that catabolises the gut hormones (incretins) that stimulate postprandial insulin secretion, but these drugs have no proven efficacy against the 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, bullous pemphigoid and intestinal obstruction (*Prescrire Int* n° 121, 135, 138, 158, 167; *Rev Prescrire* n° 365, 366). A proven treatment such as *metformin*, or *glibenclamide* or *insulin* if *metformin* is insufficiently effective, 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 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 anti-epileptics). 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 better to focus on dietary changes and physical activity.

Gastroenterology

• *Domperidone* and *droperidol*, two neuroleptics, can cause ventricular arrhythmias and sudden death, which are disproportionate to the symptoms and their weak efficacy against nausea and vomiting, and, for *domperidone*, against gastro-oesophageal reflux (*Prescrire Int* n° 129, 144; *Rev Prescrire* n° 365, 371). Other drugs such as antiacids and *omeprazole* have a much better harm-benefit balance in gastro-oesophageal reflux disease. In the rare situations in which treatment with an antiemetic neuroleptic appears justified,

it is better to use *metoclopramide*, very 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, 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.

Neurology

Alzheimer's disease. The drugs available for Alzheimer's disease in early 2016 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.

• *Donepezil*, *galantamine* and *rivastigmine*, three cholinesterase inhibitors, can cause gastrointestinal disorders (including severe vomiting), neuro-psychiatric disorders, cardiac disorders (including bradycardia, malaise and syncope) and cardiac conduction disorders (*Prescrire Int* n° 162, 166; *Rev Prescrire* n° 337, 340, 344, 349).

• *Memantine*, an NMDA glutamate receptor antagonist, can cause neuro-psychiatric disorders such as hallucinations, confusion, dizziness, headache (creating a risk of violent behaviour), seizures, and serious skin disorders (*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 clearly unfavourable. 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 1000 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. 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 drug, can cause life-threatening liver damage (*Rev Prescrire* n° 330). When other treatment options have been exhausted, *entacapone* is a better option.

Oncology - Haematology

• *Catumaxomab*, used in malignant ascites, has serious adverse effects (possibly fatal) 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 approved to treat 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.

- **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 lung disease and hypersensitivity reactions (*Prescrire Int* n° 138). It is unreasonable to add *panitumumab* to tried-and-tested chemotherapy regimens such as those based on *flourouracil*, 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, 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 no proven impact on 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). Here too it is best to focus on tailored supportive care.

- **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 palliative care. 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). When platinum-based chemotherapy is ineffective, it is best to focus on tailored supportive care.

Pain - Rheumatology

- **Analgesics.** Many nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, especially since alternatives with a better harm-benefit balance are available. *Paracetamol* is the first-choice analgesic: it is effective for moderate pain and poses little danger when taken at the appropriate dosage. Certain NSAIDs, such as *ibuprofen* and *naproxen*, used at the lowest effective dose and for the shortest possible period, are an alternative.

- 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).

- **Diclofenac** and **acedofenac** cause more cardiovascular adverse effects (including myocardial infarction and heart failure) and 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, is associated with an increased risk of gastrointestinal and cutaneous disorders (including toxic epidermal necrolysis (Lyell's syndrome)) but is not more effective than other 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, 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" (a).

- **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 syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) (*Prescrire Int* n° 117, 125, 139, 142, 156).

Osteoarthritis. Drugs authorised as disease-modifying osteoarthritis drugs should be avoided because they have significant adverse effects but no proven efficacy beyond the placebo effect. A better option in this situation is *paracetamol* as the first-choice treatment for pain, when taken at the appropriate dosage. Carefully chosen and closely monitored nonsteroidal anti-inflammatory drug therapy is sometimes an acceptable option.

- **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 primarily in rheumatology should be avoided.

- Muscle relaxants with no proven efficacy beyond the placebo effect: **methocarbamol** has many adverse effects, including gastrointestinal and cutaneous disorders (angioedema); **thiocolchicoside**, which is related to *colchicine*, causes diarrhoea, stomach pain, photodermatosis and possibly convulsions; it is also genotoxic and teratogenic (*Rev Prescrire* n° 282, 321, 313, 367; *Prescrire Int* 168). There is no justification for exposing patients with simple muscle pain to these adverse effects. An effective analgesic such as *paracetamol* is a better option, when taken at the appropriate dosage.

- **Pegloticase**, a recombinant urate oxidase 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 ▶▶

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a- A 120-mg strength *denosumab* product is notably authorised for bone metastases from solid tumours. In this setting, *denosumab* offers no tangible clinical advantage, but its harms do not clearly outweigh its benefits (*Prescrire Int* n° 130).

▶ with the first-choice drug *allopurinol* and the alternative *probenecid* is inadequate or risky, it is better 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). A nonsteroidal anti-inflammatory drug, or *colchicine* alone, are better options in this situation.

- 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 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).

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 better to choose an antidepressant 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).

- **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 increase the incidence of QT prolongation and torsades de pointes compared with other SSRI antidepressants (*Rev Prescrire* n° 369, 386).

- **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 and *Prescrire Int* n° 170).

- **Tianeptine**, a drug with no proven efficacy, can cause hepatitis, life-threatening skin reactions (including bullous rash), abuse 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. 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 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).

• **Varenicline** can cause depression, suicide, severe skin rash (including Stevens-Johnson syndrome) and cardiac disorders (angina, myocardial infarction, atrial fibrillation) (*Prescrire Int* n° 124, 131; *Rev Prescrire* n° 377).

Pulmonology - ENT

• Oral and nasal vasoconstrictive decongestants (*ephedrine*, *naphazoline*, *oxymetazoline*, *pseudoephedrine* and *tuaminoheptane*) can cause serious and even life-threatening cardiovascular disorders, including hypertensive crisis, stroke and arrhythmias. This is unacceptable for drugs that are indicated for minor, rapidly self-resolving ailments such as the common cold (*Prescrire Int* n° 136).

• **Omalizumab**, an anti-IgE monoclonal antibody approved in severe persistent asthma and chronic spontaneous urticaria, causes disproportionate adverse effects: infections, hypersensitivity reactions and cardiac disorders (*Prescrire Int* n° 115, 161). Corticosteroid therapy at the lowest effective

dose is a better option in both of these situations.

• **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 *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 and even 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.

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 health 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 remain on the market.

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Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2015" *Prescrire Int* 2015; **24** (158): 78-79.

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 Rédaction "Objectifs des traitements: à partager avec les patients" *Rev Prescrire* 2012; **32** (345): 544-546.



Coming soon...

NEW PRODUCTS

- *Dasabuvir* in hepatitis C
- *Dalbavancin* in bacterial infections of the skin
- *Ramucirumab* in gastric cancer

ADVERSE EFFECTS

- *Ondansetron* and pregnancy: possible congenital heart defects
- Drug-induced hair loss
- Bradycardia with *sofosbuvir*

REVIEWS

- *Ranibizumab* or *bevacizumab* in age-related macular degeneration
- *Pivmecillinam* in cystitis

Outlook

- New drugs and indications in 2015
- United States: student action reduces industry influence in medical schools