

Towards better patient care: drugs to avoid in 2020



ABSTRACT

- To make it easier to choose quality care, and to prevent disproportionate harm to patients, *Prescrire* has published its annual update of drugs to avoid.
- *Prescrire's* assessments of the harm-benefit balance of drugs in given situations are based on a rigorous procedure involving a systematic and reproducible literature search, results based on patient-relevant outcomes, prioritisation of the supporting data based on the strength of evidence, comparison with standard treatment (if one exists), and taking into account known and potential adverse effects, as well as the uncertainties surrounding them.
- This annual review of drugs to avoid covers all the drugs examined by *Prescrire* between 2010 and 2019 that are authorised in the European Union or in France. We identified 105 drugs (92 of which are marketed in France) that are more harmful than beneficial in all their approved indications.
- In most cases, when drug therapy appears to be the best course of action, other drugs with a better harm-benefit balance are available.
- Even if a patient has a serious condition for which no effective treatment exists, there is no justification for prescribing a drug with no proven efficacy that provokes severe adverse effects. It is sometimes acceptable to test these drugs in clinical trials, but patients must be informed of the uncertainties over their harm-benefit balance as well as the trial's objectives. If this option is not chosen, appropriate support and symptomatic care should be implemented when there are no effective treatments for improving the prognosis or quality of life.

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This is *Prescrire's* eighth consecutive annual review of drugs to avoid, which includes documented cases of drugs that are more dangerous than beneficial (1,2). The aim is to make it easier to choose safe, effective treatments, primarily to avoid exposing patients to unacceptable harms. The drugs listed (sometimes a particular form or dose strength) should be avoided in all the clinical situations for which they are authorised in France or in the European Union.

A reliable, rigorous and independent methodology

What data sources and methodology do we use to assess a drug's harm-benefit balance?

Our list of drugs to avoid concerns drugs and indications on which we published detailed analyses in our French edition over the 10-year period from 2010 through 2019 inclusive. Some drugs and indications were examined for the first time, while others were re-evaluated as new data on efficacy or adverse effects have become available.

One of the main objectives of our publications is 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 in the relevant area, 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).

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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. Similarly, treatment options evolve as new drugs arrive on the market.

Some drugs offer a therapeutic advantage, while others are more dangerous than beneficial and should not be used (3).

Prescrire’s assessments of drugs and indications are all 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. double-blind, randomised controlled trials;
- the drug is compared with a carefully chosen standard treatment, if one exists (not necessarily a drug);
- the results taken into account are based on the clinical endpoints most relevant to the patients concerned. This means that wherever possible we ignore surrogate endpoints such as 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. 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.

When a new drug is approved, many uncertainties remain. Some rare and serious adverse effects may have been overlooked during clinical trials and may only emerge after several years of routine use by a large number of patients (3).

Empirical data and personal experience: risk of major bias. Empirical assessment of a drug’s harm-benefit balance, based on individual experience, can help to guide further research, but it is subject to major bias that strongly reduces the level of evidence of the findings (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 cannot know how many other patients’ conditions worsened when they received the same treatment (3).

The best way to minimise subjective bias caused by non-comparative evaluation of a few patients is to prioritise the results of clinical trials, 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.

But patients in this situation must not be treated as guinea pigs. “Trials” of drugs belong in the sphere of formal, properly-conducted clinical research, not health care. It is useful of course to enrol patients in clinical trials, provided they are informed of the harms and the uncertain nature of the possible benefits. The trial results should be published (whether positive, negative or inconclusive) in order to advance medical knowledge.

However, patients must always 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 the aim of supportive care and symptomatic treatment is not to modify the underlying disease, they are useful elements of patient care.

While there is a great deal of uncertainty surrounding the harm-benefit balance of drugs that are under evaluation in clinical trials, 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, additional information on efficacy is collected once marketing authorisation has been granted (3).

105 authorised drugs that are more dangerous than beneficial

As of late 2019, based on the drugs examined by Prescrire between 2010 and 2019 that are authorised in France or in the European Union, 105 drugs were identified as more dangerous than beneficial in all their authorised indications. 92 of these drugs are marketed in France (a).

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a- Nintedanib is mentioned twice in this review, in lung cancer and idiopathic pulmonary fibrosis, but was counted as one drug to avoid.

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

These 105 drugs comprise:

- Active substances with adverse effects that, given the clinical situations in which they are used, are disproportionate to the benefits they provide;
- Older drugs that have been superseded by newer 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 that of a placebo, but that carry a risk of particularly severe adverse effects.

The main reasons why these drugs are considered to have an unfavourable harm-benefit balance are explained on a case-by-case basis. 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 "Main changes in the 2020 update", right.



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, 184). 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, yet they all have numerous adverse effects, including cutaneous, haematological and renal disorders (*Prescrire Int* n° 85, 117, 174). When a fibrate is justified, *gemfibrozil* is the only one that has been shown to prevent the cardiovascular 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 severe adverse effects, in

Main changes in the 2020 update

P*rescrire* updates its review of drugs to avoid every year. As a result, some drugs are added to the list, while others are removed pending the outcome of our reassessment of their harm-benefit balance. In other cases, the pharmaceutical company or a health authority decided to withdraw the drugs from the market, or new data show that their harm-benefit balance is no longer clearly unfavourable in all their indications. Here we outline the main differences between the 2019 and 2020 lists of drugs to avoid.

Market withdrawals in France. One drug included in *Prescrire's* 2019 list of drugs to avoid is no longer marketed in France: **mephenesin**, a muscle relaxant. The French Health Products Agency withdrew marketing authorisation for products containing this drug in mid-2019, due to its unfavourable harm-benefit balance. We left it on our list of drugs to avoid, however, since it is still marketed for topical application in Belgium, for example.

Gliflozins: harm-benefit balance unfavourable in type 2 diabetes, but under review in type 1 diabetes. As of 2019, glucose-lowering drugs belonging to the gliflozin class (sodium-glucose co-transporter 2 inhibitors) have an unfavourable harm-benefit balance in type 2 diabetes (*Prescrire Int* n° 211). Those currently marketed in Europe are **canagliflozin** (alone or combined with *metformin*), **dapagliflozin** (alone or combined with *metformin* or *saxagliptin*), **empagliflozin** (alone or combined with *metformin* or *linagliptin*), and **ertugliflozin** (*Rev Prescrire* n° 434). However, we did not include the gliflozins in our 2020 list of drugs to avoid, because *dapagliflozin* has been authorised for use in type 1 diabetes, and our analysis of its harm-benefit balance in this situation is in progress.

Selexipag removed from the list in light of new data. The oral prostacyclin receptor agonist **selexipag**, authorised for pulmonary arterial hypertension, has been dropped from this year's list. It was added to our list of drugs to avoid in 2018, because excess mortality had been observed in the main clinical trial on which its marketing authorisation was based. It was removed in 2019 while *Prescrire* reassessed its harm-benefit balance. Following our review of the latest data, **selexipag** has not been put back on our 2020 list, even though its harm-benefit balance is highly uncertain, and the risk that it hastens the death of certain patients during the first months of treatment has not been ruled out (*Rev Prescrire* n° 433).

Additions to this year's list of drugs to avoid: alpha-amylase, diosmectite and other medicinal clays, Ginkgo biloba, etc. Twelve drugs were added to our 2020 list of drugs to avoid because their adverse effects are disproportionate to their efficacy or the severity of the clinical situation for which they are authorised. They are: **alpha-amylase**, authorised for sore throat; **Ginkgo biloba** for cognitive impairment in elderly patients; **naftidrofuryl** for intermittent claudication associated with peripheral arterial disease; oral **pentosan polysulfate** for bladder pain syndrome; **pentoxyverine** for cough; the nonsteroidal anti-inflammatory drug **tenoxicam**; and **xylometazoline**, a nasopharyngeal decongestant available in several European countries; the medicinal clays **attapulgite** (marketed alone and in multi-ingredient preparations), **diosmectite**, **hydrotalcite**, **montmorillonite beidellitique** alias **monmectite** (marketed alone and in multi-ingredient preparations), and **kaolin** (a component of multi-ingredient preparations) are authorised to treat various intestinal disorders, including diarrhoea, but should be avoided due to lead contamination.

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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 over other available options in either angina or heart failure (*Prescrire Int* n° 88, 110, 111, 118, 155, 165; *Rev Prescrire* n° 403, 413). Established treatments shown to be effective in angina include beta-blockers or, as an alternative, calcium channel blockers such as *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 preventing effort angina, can cause severe mucocutaneous ulceration (*Prescrire Int* n° 81, 95, 110, 132, 163, 175; *Rev Prescrire* n° 419). 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). Among the many other ARBs available, it is better to choose *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 disorders, neuropsychiatric disorders, palpitations, bradycardia, hypotension, QT prolongation and peripheral oedema (*Prescrire Int* n° 102; *Rev Prescrire* n° 350; *Interactions Médicamenteuses Prescrire*).

- **Trimetazidine**, a drug with uncertain properties, is used in angina despite its modest effect on symptoms (shown mainly in stress tests), yet it can cause parkinsonism, hallucinations and thrombocytopenia (*Prescrire Int* n° 84, 100, 106; *Rev Prescrire* n° 404). It is better to choose better-known treatments for angina: certain beta-blockers, or, as an alternative, calcium-channel blockers such as *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). *Amiodarone* is a more prudent choice 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 particular in patients whose cytochrome P450 isoenzyme CYP2D6 metabolises the drug slowly (and generally, neither the patient nor the doctor would be aware of this), 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.
- Injectable **promethazine**, an antihistamine used to treat severe urticaria, can cause thrombosis, skin necrosis and gangrene following extravasation or accidental injection into an artery (*Prescrire Int* n° 109). 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, 428). Judicious use of a topical corticosteroid to treat flare-ups is a better option in this situation (b).



Diabetes - Nutrition

- Diabetes.** A variety of 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) and many adverse effects. A far more reasonable choice is the well-established treatment *metformin*. If *metformin* is insufficiently effective, other options to consider are: a sulfonylurea such as *glibenclamide*, an insulin, a combination of *metformin* + *exenatide* or *metformin* + *liraglutide*, or, in some cases, slightly raising the HbA1c target.
- The gliptins (dipeptidylpeptidase-4 (DPP-4) inhibitors), i.e. **alogliptin**, **linagliptin**, **saxagliptin**, **sitagliptin** and **vildagliptin**, used alone or in combination with *metformin*, have an unfavourable adverse effect profile that includes serious hypersensitivity reactions (anaphylaxis and cutaneous reactions such as Stevens-Johnson syndrome), infections (of the urinary tract and upper respiratory tract in particular), pancreatitis, bullous pemphigoid, and intestinal obstruction (*Prescrire Int* n° 121, 135, 138, 158, 167, 186; *Rev Prescrire* n° 365, 366, 379, 434).
 - **Pioglitazone** has a long list of adverse effects, including heart failure, bladder cancer and bone fractures (*Prescrire Int* n° 129, 160).

b- Oral or injectable *tacrolimus* is a standard immunosuppressant for transplant recipients, and in this situation its harm-benefit balance is clearly favourable.

Weight loss. As of late 2019, no drugs are capable of inducing lasting weight loss without harm. It is better to focus on dietary changes and physical activity, with psychological support if necessary.

- The weight loss product **bupropion + naltrexone** combines a drug chemically related to amphetamines (*bupropion*) with an opioid receptor antagonist (see also Smoking cessation on p. 51-10) (*Prescrire Int* n° 164).

- **Orlistat** has only a modest and transient effect on weight loss: patients lost about 3.5 kg compared with placebo over 12-24 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). The severe diarrhoea caused by *orlistat* can reduce the efficacy of oral contraceptives (*Prescrire Int* n° 57, 71, 107, 110; *Interactions Médicamenteuses Prescrire*).



Gastroenterology

- **Obeticholic acid**, a bile acid derivative authorised for primary biliary cholangitis, does not improve patients' health status, either used alone or in combination with *ursodeoxycholic acid*. It often worsens the main symptoms of the disease (pruritus and fatigue) and appears to provoke severe and sometimes fatal hepatic adverse effects. Even after other treatments have failed, *obeticholic acid* is a drug to avoid (*Prescrire Int* n° 197).

- The medicinal clays **attapulgitte**, **diosmectite**, **hydrotalcite**, **montmorillonite beidellitique** alias **monmectite** and **kaolin** are used alone or in multi-ingredient products to treat various intestinal disorders, including diarrhoea, heartburn and gastroesophageal reflux disease. They should be avoided due to the lead they contain. Lead has neurological, haematological, renal, cardiovascular and reproductive toxicity, and the severity of most of these toxic effects increases with the dose to which patients are exposed (*Prescrire Int* n° 203; *Rev Prescrire* n° 429, 430). In diarrhoea, clays alter stool appearance without reducing fluid loss or the consequent risk of dehydration. In gastroesophageal reflux disease, when pharmacological treatment seems the best course of action, other drugs have a positive harm-benefit balance. The first choice in the absence of complications would be a short course of treatment with a clay-free antacid, used at moderate doses, such as *sodium bicarbonate* + *sodium alginate*.

- **Cimetidine**, a histamine H₂-antagonist authorised for various gastroesophageal disorders, when combined with many other drugs can cause these drugs to accumulate in the body, thereby enhancing their dose-dependent adverse effects, due its inhibitory effect on numerous cytochrome P450 isoen-

zymes. Its harm-benefit balance is unfavourable compared with other H₂-receptor antagonists which do not expose to these drug interactions (*Interactions Médicamenteuses Prescrire*).

- The neuroleptics **domperidone**, **droperidol** and **metopimazine** can provoke arrhythmias and sudden death. These adverse effects are unacceptable given the symptoms they are used to treat (nausea and vomiting, and gastroesophageal reflux in the case of *domperidone*) and their weak efficacy (*Prescrire Int* n° 129, 144, 175, 176, 179; *Rev Prescrire* n° 403, 404, 411). Other drugs have a favourable harm-benefit balance in gastroesophageal reflux disease, such as clay-free antacids or, when symptoms are severe or persistent, *omeprazole* for a few weeks at most. In the rare situations in which treatment with an antiemetic neuroleptic appears justified, *metoclopramide* is a less risky option. It 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.

- **Nifuroxazide**, an intestinal "anti-infective" agent with no proven efficacy in diarrhoea, can provoke rare but serious immune-mediated and haematological effects (*Prescrire Int* n° 187). The treatment of acute diarrhoea is based above all on replacing fluid losses.

- **Prucalopride**, a drug chemically related to neuroleptics, is authorised for chronic constipation but shows only modest efficacy, and only 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, 175). There is no justification for exposing patients with simple constipation to such risks. If dietary measures are ineffective, bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer than *prucalopride*.

- **Glycerol trinitrate** 0.4% ointment, a nitrate authorised for anal fissure, has no proven efficacy beyond that of a placebo in healing chronic anal fissures or alleviating the pain they cause. Headache is a very common adverse effect, and can be severe (*Prescrire Int* n° 94). Treatment of the pain associated with anal fissure is based on an oral analgesic such as *paracetamol* and sometimes topical *lidocaine*.



Gynaecology - Endocrinology

Menopause. Two drugs authorised for postmenopausal hormone replacement therapy have an unfavourable harm-benefit balance and should therefore be avoided. When hormone therapy is chosen despite its adverse effects, the most reasonable option is an oestrogen-progestogen combination, used at the lowest possible dose and for the shortest possible period.

- The fixed-dose combination **conjugated equine oestrogens + bazedoxifene** contains oestrogen and an oestrogen receptor agonist-antagonist, but the risks of thrombosis and hormone-dependent cancers have not been adequately evaluated (*Prescrire Int* n° 184).

- **Tibolone**, a synthetic steroid hormone, has androgenic, oestrogenic and progestogenic properties and carries a risk of cardiovascular disorders, breast cancer and endometrial cancer (*Prescrire Int* n° 83, 111; *Rev Prescrire* n° 427).

Uterine leiomyoma (fibroids). One drug authorised for fibroids should be avoided.

- **Ulipristal** 5 mg, an antagonist and partial agonist of progesterone receptors, authorised for uterine fibroids, can cause serious liver injury, sometimes requiring liver transplantation (c). When treatment is considered desirable to postpone surgery or await menopause, other less risky options are available: insertion of a *levonorgestrel* intrauterine device (IUD) is the first choice despite its limitations; an alternative in some cases is an oral progestogen, but the harm-benefit balance of treatment durations of more than a few months is uncertain (*Prescrire Int* n° 198; *Rev Prescrire* n° 418).



Infectious diseases

- **Moxifloxacin**, a fluoroquinolone antibiotic that is no more effective than other antibiotics of this class, 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.



Neurology

Alzheimer's disease. The drugs available in late 2019 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, 150; *Rev Prescrire* n° 363). The priorities in the management of Alzheimer's disease are to reorganise the patient's daily life, keep him or her active, and provide support and help for caregivers and family members.

- The cholinesterase inhibitors **donepezil**, **galantamine** and **rivastigmine** can provoke gastrointestinal disorders (including severe vomiting), neuropsychiatric disorders, cardiac disorders (bradycardia, collapse and syncope), and cardiac conduction disorders. *Donepezil* can also cause compulsive sexual behaviour (*Prescrire Int* n° 162, 166, 192, 204; *Rev Prescrire* n° 337, 340, 344, 349, 398, 416).

- **Memantine**, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders (hallucinations, confusion, dizziness and headache) that can lead to violent behaviour, as well as seizures and heart failure (*Prescrire Int* n° 204; *Rev Prescrire* n° 359, 398).

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, and 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 fatal opportunistic infections, including progressive multifocal leukoencephalopathy, potentially serious hypersensitivity reactions, and liver damage (*Prescrire Int* n° 122, 158, 182, 183; *Rev Prescrire* n° 330).

- **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, cognitive impairment, intermittent claudication 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 (*Rev Prescrire* n° 321, 359). *Oxetorone* also causes chronic diarrhoea (*Prescrire Int* n° 193). Other options, such as *propranolol*, are preferable.

- **Ginkgo biloba**, used in cognitive impairment in elderly patients, has no proven efficacy beyond that of a placebo, but can cause haemorrhage, gastrointestinal disorders, skin disorders, seizures and hypersensitivity reactions (*Prescrire Int* n° 205; *Rev Prescrire* n° 365). *G. biloba* is also used in some countries for venous insufficiency, as part of a fixed-

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 c- In postcoital contraception, *ulipristal* is taken as a single dose of 30 mg. Although it has not been shown to cause hepatitis when used in this way, *levonorgestrel* would be a more cautious choice (*Prescrire Int* n° 198). Drug interactions between *ulipristal* and hormonal contraceptives can reduce the efficacy of *ulipristal* or the contraceptive (*Prescrire Int* n° 212).

dose combination with *heptaminol* and *troxerutin*, but has no more efficacy in this indication (*Rev Prescrire* n° 413). There are no drugs with a favourable harm-benefit balance in these situations.

- **Naftidrofuryl**, a “vasodilator” authorised for intermittent claudication associated with peripheral artery disease, increases walking distance by a few dozen metres but can cause headache, oesophagitis, mouth ulceration, skin disorders, kidney stones and potentially severe hepatic disorders (*Prescrire Int* n° 192; *Rev Prescrire* n° 427). A walking exercise programme is an effective and less risky treatment.
- **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

- **Defibrotide**, an antithrombotic authorised for severe hepatic veno-occlusive disease following haemopoietic stem cell transplantation, was no more effective in reducing mortality or inducing complete disease remission than symptomatic treatment in a non-blinded trial, yet provokes sometimes fatal haemorrhages (*Prescrire Int* n° 164). A more prudent option would be to focus on preventive measures and symptomatic treatments.

Antineoplastics. Various antineoplastic drugs have a clearly unfavourable harm-benefit balance. They are often authorised for situations in which other treatments seem ineffective. When exposure to highly toxic drugs is not justified by proven benefits, focusing on appropriate symptomatic care and on preserving the patient's quality of life is a prudent choice.

- **Mifamurtide** is authorised 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 more prudent to propose chemotherapy without *mifamurtide*.
- **Nintedanib**, an anti-angiogenic tyrosine kinase inhibitor authorised in combination with *docetaxel* for certain types of non-small cell lung cancer, has not been shown to prolong survival but can provoke many severe adverse effects due to its inhibitory effect on angiogenesis, including venous thromboembolism, bleeding, hypertension, gastrointestinal perforations and impaired wound healing (*Prescrire Int* n° 173).
- **Panobinostat** has not been shown to prolong survival in refractory or relapsed multiple myeloma. It 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 sar-

comas but has very frequent and severe gastrointestinal, haematological, hepatic and muscular adverse effects (*Prescrire Int* n° 102, 115; *Rev Prescrire* n° 360, 426). 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 symptomatic treatments, to limit the clinical consequences of the disease.

- **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, torsade de pointes and sudden death (*Prescrire Int* n° 131; *Rev Prescrire* n° 408).
- **Vinflunine** has uncertain efficacy in advanced or metastatic bladder cancer. A clinical trial provided weak evidence that *vinflunine* prolongs 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 (torsade de pointes, myocardial infarction, ischaemic heart disease), sometimes resulting in death (*Prescrire Int* n° 112; *Rev Prescrire* n° 360).



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 have no proven efficacy (*Prescrire Int* n° 181). It is better to use artificial tears for example for symptomatic relief, several types of which are available (d).
- **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 late 2019, there are no treatments with a favourable harm-benefit balance for this rare disease.



Psychiatry - Addiction

Drugs for depression. Several drugs authorised for depression carry a greater risk of severe adverse effects than other antidepressants, without offering greater efficacy. Antidepressants have only modest efficacy and often take some time to work. It is better to choose one of the longer-established

d- Oral or injectable ciclosporin is a standard immunosuppressant for transplant recipients, and in this situation its harm-benefit balance is clearly favourable.

antidepressants with an adequately documented adverse effect profile.

- **Agomelatine** has no proven efficacy beyond that of a placebo, but can cause hepatitis and pancreatitis, suicide and aggressive outbursts, rhabdomyolysis, and serious skin disorders including Stevens-Johnson syndrome (*Prescrire Int* n° 104, 136; *Rev Prescrire* n° 397, 419, 432).
- **Citalopram** and **escitalopram** are so-called selective serotonin reuptake inhibitor antidepressants (SSRIs) that expose patients to a higher incidence of QT prolongation and torsade de pointes than other SSRIs and worse outcomes in the event of overdose (*Prescrire Int* n° 170, 174; *Rev Prescrire* n° 369).
- **Duloxetine**, **milnacipran** and **venlafaxine** are serotonin and norepinephrine reuptake inhibitors that, as well as provoking the adverse effects of SSRI antidepressants, carry a risk of cardiac disorders due to their noradrenergic activity, including hypertension, tachycardia, arrhythmias, and QT prolongation. In addition, **venlafaxine** overdoses are associated with a high risk of cardiac arrest (*Prescrire Int* n° 131, 170, 206; *Rev Prescrire* n° 338; *Interactions Médicamenteuses Prescrire*). **Duloxetine** can also cause hepatitis and severe cutaneous adverse reactions such as Stevens-Johnson syndrome (*Prescrire Int* n° 85, 100, 111, 142; *Rev Prescrire* n° 384).
- **Tianeptine**, a drug with no proven efficacy beyond that of a placebo, can cause hepatitis, life-threatening skin reactions (including bullous rash) and addiction (*Prescrire Int* n° 127, 132; *Rev Prescrire* n° 349).

Other psychotropic drugs. Some other psychotropic drugs have unacceptable adverse effects:

- **Dapoxetine**, a so-called selective serotonin reuptake inhibitor antidepressant (SSRI), is used for sexual dissatisfaction related to premature ejaculation. 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, or application of the anaesthetic combination **lidocaine + prilocaine** on the glans penis are better options in this situation (*Prescrire Int* n° 197).
- **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, a benzodiazepine, used for the shortest possible period, is a better choice.



Pulmonology - ENT

Cough suppressants. A number of drugs used to relieve cough, a sometimes bothersome but minor ailment, have disproportionate adverse effects. When drug therapy for cough seems justified, the opioid **dextromethorphan** is an option, despite its limitations (*Rev Prescrire* n° 358, 391).

- **Ambroxol** and **bromhexine**, mucolytics authorised for cough and sore throat, have no proven efficacy beyond a placebo effect, yet they carry a risk of anaphylactic reactions and sometimes fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (*Prescrire Int* n° 159, 184, 192).
- **Oxememazine** is a sedating antihistamine of the phenothiazine class with antimuscarinic activity and neuroleptic properties. Its adverse effects are disproportionate for a drug used to relieve cough symptoms (*Rev Prescrire* n° 334, 386; *Interactions Médicamenteuses Prescrire*).
- **Pentoxyverine**, a centrally-acting cough suppressant, can cause cardiac disorders including QT prolongation, and serious allergic reactions (*Prescrire Int* n° 208).
- **Pholcodine**, an opioid authorised as an antitussive, can cause sensitisation to neuromuscular blocking agents used in general anaesthesia (*Prescrire Int* n° 184; *Rev Prescrire* n° 349). This serious adverse effect is not known to occur with other opioids.

Sore throat. When a drug appears necessary to relieve sore throat, in conjunction with non-drug measures such as sipping water or sucking on hard candy, the best option is **paracetamol**, taken at the appropriate dosage.

- **Alpha-amylase**, an enzyme with no proven efficacy against sore throat beyond that of a placebo, can cause severe cutaneous or allergic disorders, including urticaria, pruritus, angioedema, maculopapular rash and erythema (*Rev Prescrire* n° 426).
- **Tixocortol mouth spray** (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) (e).

Miscellaneous. A variety of other drugs used in pulmonary or ENT disorders are best avoided.

- Decongestants for oral or nasal use (**ephedrine**, **naphazoline**, **oxymetazoline**, **phenylephrine**, **pseudoephedrine**, **tuaminoheptane** and **xylometazoline**) are sympathomimetic vasoconstrictors. They can cause serious and even life-threatening cardiovascular disorders (hypertensive crisis, stroke, and arrhythmias, including atrial fibrillation), as well as ischaemic colitis. These adverse effects are unacceptable for drugs indicated for minor, rapidly self-resolving symptoms such as those associated with the common cold (*Prescrire Int* n° 136, 172, 178, 183, 208; *Rev Prescrire* n° 312, 342, 345, 348, 361, 424).

e-**Tixocortol** is also authorised as a nasal suspension, notably for allergic rhinitis, a situation in which the harm-benefit balance of a corticosteroid is not unfavourable.

- **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**, an anti-angiogenic tyrosine kinase inhibitor, has not been shown to prolong survival, prevent the progression of fibrosis or relieve symptoms in patients with idiopathic pulmonary fibrosis. It causes hepatic disorders and many serious adverse effects related to its inhibitory effect on angiogenesis, including venous thromboembolism, bleeding, hypertension, gastrointestinal perforations and impaired wound healing (*Prescrire Int* n° 173). In this context, the priority is to focus on symptomatic care.
- **Roflumilast**, a phosphodiesterase type-4 inhibitor with anti-inflammatory effects, has not been shown to reduce mortality or improve the quality of life of patients with severe chronic obstructive pulmonary disease (COPD), but can provoke gastrointestinal adverse effects, weight loss, mental disorders (including depression and suicide), and possibly cancers (*Prescrire Int* n° 134, 176). Despite its limitations, the treatment of these patients is based above all on inhaled bronchodilators, sometimes with an inhaled corticosteroid, and possibly oxygen therapy.



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 than others. 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 compared with other equally effective NSAIDs (*Prescrire Int* n° 167; *Rev Prescrire* n° 344, 361, 374, 409).
- **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, 210; *Rev Prescrire* n° 362, 374).
- **Ketoprofen gel** causes more photosensitivity reactions (eczema, bullous rash) than other equally effective topical NSAIDs (*Prescrire Int* n° 109, 193).
- **Piroxicam** and **tenoxicam**, when used **systemically**, expose patients to an increased risk of gastrointestinal and cutaneous disorders (including Stevens-Johnson syndrome and toxic epidermal necrolysis) but are no more effective than other NSAIDs (*Prescrire Int* n° 212, *Rev Prescrire* n° 321).

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 that of a placebo. As of late 2019, there are no drugs known to have efficacy against joint degeneration and a favourable harm-benefit balance.

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

“Muscle relaxants”. Various drugs used as muscle relaxants have no proven efficacy beyond that of a placebo but expose patients to the risk of sometimes severe adverse effects. An effective analgesic is a better option, with *paracetamol* as the first choice, taken at the appropriate dosage, or *ibuprofen* or *naproxen* as alternatives.

- Oral **mephenesin** provokes drowsiness, nausea, vomiting, hypersensitivity reactions (including rash and anaphylactic shock), abuse and addiction; *mephenesin* ointment provokes severe skin disorders, including erythema multiforme and acute generalised exanthematous pustulosis (*Prescrire Int* n° 125, 138; *Rev Prescrire* n° 414, 430).
- **Methocarbamol** has many adverse effects, including gastrointestinal and cutaneous disorders (including angioedema) (*Rev Prescrire* n° 282, 338).
- **Thiocolchicoside**, which is related to *colchicine*, causes diarrhoea, stomach pain, photodermatitis and possibly convulsions, as well as being genotoxic and teratogenic (*Prescrire Int* n° 168; *Rev Prescrire* n° 282, 313, 321, 367, 400, 412).

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; *Rev Prescrire* n° 425). *Capsaicin* remains an unreasonable choice even when systemic pain medications or local ones such as *lidocaine* medicated plasters fail to provide adequate relief.
- **Denosumab 60 mg** 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, muscle and bone pain, multiple fractures after discontinuation of the drug, osteonecrosis, immune dysfunction, and serious infections (including endocarditis) due to the immunosuppressive effects of this monoclonal antibody (*Prescrire Int* n° 117, 130, 168, 198). In osteoporosis, when non-drug measures plus calcium and vitamin D supplementation prove inadequate, *alendronic acid*, or *raloxifene* as an alternative, have a better harm-benefit balance than other options, despite

the significant limitations of both drugs. There is no known satisfactory drug treatment for "bone loss" (f).

- **Quinine**, authorised 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 (*Prescrire Int* n° 188; *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) (g).

- Colchimax° (**colchicine + opium powder + tiemonium**) has an unfavourable harm-benefit balance, notably in gout attacks and acute pericarditis, 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; *Rev Prescrire* n° 431). A non-steroidal anti-inflammatory drug or a corticosteroid as an alternative are better options for gout attacks.

- Topical **prednisolone + dipropylene glycol salicylate** exposes patients to the adverse effects of corticosteroids and to the risk of *salicylate* hypersensitivity reactions (*Rev Prescrire* n° 338). Other drugs such as oral *paracetamol* (at the appropriate dosage) and topical *ibuprofen* have a favourable harm-benefit balance in patients with painful sprains or tendinopathy, in conjunction with non-drug measures (rest, ice, splints, etc.).



Smoking cessation

- **Bupropion**, an amphetamine authorised for smoking cessation, is no more effective than *nicotine* but 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). When a drug is needed to help with smoking cessation, *nicotine* is a better choice.



Urology

- Oral **pentosan polysulfate**, a heparin derivative authorised for bladder pain syndrome (interstitial cystitis), has uncertain efficacy in relieving the symptoms of this condition and serious adverse effects, including immune-mediated thrombocytopenia with a consequent risk of arterial thrombosis and pigmentary maculopathy (*Prescrire Int* n° 204; *Rev Prescrire* n° 433) (h). In the absence of a better alternative, it is more prudent to offer these patients analgesic medication and non-drug measures with a low risk of adverse effects, such as applying heat or cold to the bladder or perineum, and avoiding foods or activities that exacerbate symptoms.

Putting patients first

Our analyses show that the harm-benefit balance of the drugs listed here is unfavourable in all their authorised indications (unless otherwise mentioned in a footnote). Yet some have been marketed for many years and are commonly used. From the patient's viewpoint, what possible justification is there for exposing them to drugs that have more adverse effects than other members of the same pharmacological class or other similarly effective drugs? And how can one justify exposing them to drugs with severe adverse effects but no proven efficacy beyond that of a placebo or 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.

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f- A 120-mg strength *denosumab* product is authorised for use in patients with bone metastases from solid tumours. In this situation, *denosumab* is just one of several options, but its harms do not clearly outweigh its benefits (*Prescrire Int* n° 130).

g- *Quinine* is sometimes useful in malaria (*Prescrire Int* n° 145).

h- *Pentosan polysulfate* is also authorised in France for topical use as a local adjunctive treatment for minor trauma. It has no proven efficacy in this situation beyond that of a placebo, and little is known about its systemic adverse effect profile.

Selected references from Prescrire's literature search

- 1- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2019" *Prescrire Int* 2019; **28** (203): 108-1-108-10.
- 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?" *Prescrire Int* 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.