Towards better patient care: drugs to avoid in 2019

ABSTRACT

● To make it easier to choose quality care, and to prevent disproportionate harms 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 that includes 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 treatments, and an analysis of both known and potential adverse effects.

● This annual review of drugs to avoid covers all the drugs examined by *Prescrire* between 2010 and 2018 that are authorised in the European Union or in France. We identified 93 drugs (82 of which are marketed in France) that are more harmful than beneficial in all the approved indications.

● 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 is sometimes acceptable to test these drugs in clinical trials, but patients must be informed of the uncertainty over their harm-benefit balance and of the trial's objectives. Tailored supportive care should be used when there are no effective treatments for improving prognosis or quality of life.

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This is *Prescrire*'s seventh 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?

The following review concerns drugs and indications on which we published detailed analyses in our French edition over a nine-year period, from 2010 to 2018. Some drugs and indications were examined for the first time, while others were re-evaluated as new data on efficacy or adverse effects became available.

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

Prescrire is structured in such a way as to guarantee the quality of the information provided to our subscribers. The Editorial Staff comprise a broad range of health professionals working in various sectors and free from conflicts of interest. We also call on an extensive network of external reviewers (specialists, methodologists, and practitioners rep-

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

All *Prescrire*'s assessments of 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. double-blind, randomised controlled trials;

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

– the accent is placed on results based on 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, 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.

When a new drug is approved many uncertainties remain. Some rare and serious adverse effects may be overlooked during clinical trials and may only emerge after several years of routine use by many patients (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 that strongly reduces the level 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 may be unaware that many other patients have been harmed by the same treatment (3).

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

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

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

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 into clinical trials, provided they are informed of the harms and the uncertain nature of the possible benefits, and that the trial results are published 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 they are not aimed at modifying the outcome of the underlying disease, supportive care and symptomatic treatment are useful elements of patient care.

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

Main changes in the 2019 update

Prescrire 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, or because the pharmaceutical company or a health authority decided to withdraw them from the market, or because new data show that their harm-benefit balance is no longer clearly unfavourable in all their indications.

Market withdrawal. One drug included in *Prescrire*'s 2018 review of drugs to avoid is no longer marketed: *telithromycin*, a macrolide antibiotic, which was withdrawn worldwide in early 2018 by the company (*Prescrire Int* n° 196).

Harm-benefit balance under review. Oral *selexipag*, a prostacyclin receptor agonist authorised for pulmonary arterial hypertension, has been dropped from this year's list while *Prescrire* reassesses its harm-benefit balance in light of new published data.

Removed from the list in light of new data: olaparib, omalizumab, panitumumab and varenicline. Several drugs that previously featured in *Prescrire*'s list of drugs to avoid have been removed from the list, because new data showed that their harm-benefit balance is not clearly unfavourable, or that they are useful options in rare situations.

In patients with relapsed platinum-sensitive ovarian cancer with a BRCA gene mutation, ***olaparib*** prolongs the median time before exposure to another cytotoxic drug by a little over a year, but without prolonging survival. This benefit came at the cost of immediate exposure to *olaparib*'s adverse effects, which are common, and serious in about 10% of patients (*Prescrire Int* n° 200).

Omalizumab, an anti-IgE monoclonal antibody, is an option for patients with severe asthma in the rare cases in which the symptoms remain unbearable despite high doses of corticosteroids, or when the adverse effects of corticosteroid therapy are intolerable. It has serious adverse effects, including anaphylactic reactions, infections, arterial, cardiac and cerebral thromboembolic events, and severe thrombocytopenia (*Prescrire Int* n° 199). ***Mepolizumab*** was also removed from the list of drugs to avoid despite an inadequate assessment and an uncertain role, because it has some efficacy in this setting, a similar mechanism and similar adverse effects.

In patients with metastatic colorectal cancer without a RAS mutation, the anti-EGFR monoclonal antibody ***panitumumab*** is an option. But it exposes about 25% of patients to serious and sometimes fatal adverse effects (*Prescrire Int* n° 198).

According to our review of the data available in 2018 on ***varenicline***, its harm-benefit balance is not clearly unfavourable, although it is less favourable than that of *nicotine* replacement therapy. The adverse effects of *varenicline* are mainly neuropsychiatric disorders in patients with a history of mental illness, as well as serious cardiac disorders. In light of these data, it would appear preferable to make repeated smoking cessation attempts with *nicotine*-containing products rather than resorting to *varenicline* (*Prescrire Int* n° 196).

Additions to this year's review of drugs to avoid: ulipristal 5 mg, mephenesin, oxomemazine. ***Ulipristal*** 5 mg is best avoided by patients with uterine fibroids in light of the serious hepatic adverse effects reported in this clinical situation since its market introduction (*Prescrire Int* n° 198; *Rev Prescrire* n° 418).

Four other drugs were added because their adverse effects are disproportionate in all their authorised indications: ***mephenesin***, a "muscle relaxant"; ***oxomemazine***, a sedating antihistamine with antimuscarinic activity and neuroleptic properties, authorised as a cough suppressant; topical ***glyceryl trinitrate***, a nitrate used for anal fissure; and ***obeticholic acid***, a bile acid derivative authorised for primary biliary cholangitis.

Cimetidine should be avoided because it has far more drug interactions than other H2-receptor antagonists. These drug interactions can cause serious adverse effects, yet *cimetidine* has no advantages over other H2-receptor antagonists.

93 authorised drugs that are more dangerous than beneficial

As of early 2019, based on the drugs examined by *Prescrire* between 2010 and 2018, that are authorised in France or in the European Union, 93 drugs were identified that are more dangerous than beneficial in all their authorised indications. 82 of these drugs are marketed in France (**a**).

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

These 93 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;

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

– Drugs that have no proven efficacy (beyond the placebo effect) 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 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 page 3.

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 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 If 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). It is better to choose among the many ARBs, *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).

• ***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). It is better to use *amiodarone* for pharmacological cardioversion.

Dermatology - Allergy

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

• 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; *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 (**b**).

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

Diabetes - Nutrition

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

• The gliptins (dipeptidyl peptidase 4 (DPP-4) inhibitors) ***alogliptin***, ***linagliptin***, ***saxagliptin***, ***sitagliptin*** and ***vildagliptin***, used alone or in combination with *metformin*, have an unfavourable adverse effect profile that includes serious hypersensitivity reactions such as anaphylaxis and Stevens-Johnson syndrome, infections (of the urinary tract and upper respiratory tract), pancreatitis, bullous pemphigoid, and intestinal obstruction (*Prescrire Int* n° 121, 135, 138, 158, 167, 186; *Rev Prescrire* n° 365, 366, 379).

• ***Pioglitazone*** has a long list of adverse effects, including heart failure, bone fractures and bladder cancer (*Prescrire Int* n° 129, 160).

Weight loss. As of early 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 p. 8) (*Prescrire Int* n° 164).

• ***Orlistat*** has only a modest and transient effect on weight loss: patients lost about 3.5 kg more than with placebo over 12-24 months, with no evidence of long-term efficacy. Gastrointestinal disorders are very common, while other adverse effects include liver damage, hyperoxaluria, and bone fractures in adolescents. *Orlistat* alters the gastrointestinal absorption of many nutrients (fat-soluble vitamins A, D, E and K), leading to a risk of deficiency, and also reduces the efficacy of some drugs (thyroid hormones, some antiepileptics). Oral contraceptive efficacy is reduced when *orlistat* provokes severe diarrhoea (*Prescrire Int* n° 57, 71, 107, 110).

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).

• ***Cimetidine***, a histamine H2-antagonist authorised for various gastro-oesophageal disorders, can cause accumulation of and increase in dose-dependent adverse effects of a number of other drugs, as *cimetidine* inhibits many P450 cytochrome isoenzymes. It has an unfavourable harm-benefit balance when compared with other H2-receptor antagonists that do not expose to these drug interactions, such as *ranitidine*.

• 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 such as antacids or *omeprazole* have a favourable harm-benefit balance in gastroesophageal reflux disease. In the rare situations in which treatment with an antiemetic neuroleptic appears justified, it is better to choose *metoclopramide*, which also provokes serious cardiac events but has proven efficacy against nausea and vomiting. It should be used at the lowest possible dose, taking drug interactions into account and monitoring the patient frequently.

• ***Nifuroxazide***, an intestinal "anti-infective" agent with no proven efficacy in diarrhoea, can provoke serious immunological reactions (*Prescrire Int* n° 187). 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, 137, 175). There is no justification for exposing patients with simple constipation to such risks. If dietary measures are ineffective, then bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer than *prucalopride*.

• ***Glyceryl trinitrate*** 0.4% ointment, a nitrate authorised for anal fissure, has no proven efficacy beyond the placebo effect 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 ovarian cancer (*Prescrire Int* n° 83, 11, 137).

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 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 early 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). It is better to focus on reorganising the patient's daily life, keeping him or her active, and providing support and help for caregivers and family members.
• 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; *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 (*Rev Prescrire* n° 359, 398, 422).

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 serious and sometimes fatal adverse effects, in particular: infusion-related reactions (including atrial fibrillation and hypotension), infections, frequent autoimmune disorders (including autoimmune thyroid disease, immune thrombocytopenic purpura, cytopenia and renal disease) (*Prescrire Int* n° 158; *Rev Prescrire* n° 384).
• ***Natalizumab***, another monoclonal antibody, can lead to 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 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). *Oxetorone* also causes chronic diarrhoea (*Prescrire Int* n° 193). It is better to choose another drug such as *propranolol*.
• ***Tolcapone***, an antiparkinsonian COMT inhibitor, can cause life-threatening liver damage (*Prescrire Int* n° 82; *Rev Prescrire* n° 330). When other treatment options have been exhausted, *entacapone* is a better option.

c- In postcoital contraception, ulipristal is taken as a single dose of 30 mg. It has not been shown to cause hepatitis when used in this way, but caution means levonorgestrel should be prefered (Prescrire Int n° 198).

Oncology - Haematology

• ***Defibrotide***, an antithrombotic authorised for severe hepatic veno-occlusive disease following haemopoietic stem cell transplantation, had no more impact on mortality or complete disease remission than symptomatic treatment in 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 are ineffective. When exposure to highly toxic drugs is not justified by proven benefits, it is better to focus on tailored symptomatic treatment and on preserving the patient's quality of life.

• ***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 better to propose chemotherapy without *mifamurtide*.

• ***Nintedanib***, a 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 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 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, torsades de pointes and sudden death (*Prescrire Int* n° 131; *Rev Prescrire* n° 408).

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

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 early 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 antidepressants with an adequately documented adverse effect profile.

• ***Agomelatine*** has no proven efficacy beyond the placebo effect, but can cause hepatitis and pancreatitis, suicide and aggressive outbursts, as well as serious skin disorders including Stevens-Johnson syndrome (*Prescrire Int* n° 136, 137; *Rev Prescrire* n° 397, 419).

• ***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) due to its noradrenergic activity. *Duloxetine* can also cause hepatitis and severe cutaneous hypersensitivity reactions such as Stevens-Johnson syndrome (*Prescrire Int* n° 85, 100, 111, 142; *Rev Prescrire* n° 384).

• ***Citalopram*** and ***escitalopram*** are SSRI antidepressants that expose patients to a higher incidence of

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

QT prolongation and torsades de pointes than other SSRIs and worse outcomes in the event of overdose (*Prescrire Int* n° 170, 174; *Rev Prescrire* n° 369, 396).

• ***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 (*Prescrire Int* n° 131, 170; *Rev Prescrire* n° 338).

• ***Tianeptine***, a drug with no proven efficacy, can cause hepatitis, life-threatening skin reactions (including bullous rash) and addiction (*Prescrire Int* n° 127, 132).

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

• ***Dapoxetine***, a "selective" SRI, is used for 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 option.

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.

Pulmonology - ENT

Cough suppressants. A number of drugs used for cough, a minor ailment, have disproportionate adverse effects. When a drug is considered, 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).

• ***Oxomemazine***, a sedating antihistamine of the phenothiazine class used to relieve cough symptoms, has antimuscarinic activity and neuroleptic properties, and its adverse effects are disproportionate.

• ***Pholcodine***, an opioid used 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.

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*** and ***tuaminoheptane***) 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; *Rev Prescrire* n° 312, 342, 345, 348, 361).

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

• ***Mannitol*** **inhalation powder**, authorised as a mucolytic for patients with cystic fibrosis despite the lack of convincing evidence of efficacy, can cause bronchospasm and haemoptysis (*Prescrire Int* n° 148). It is best to choose other mucolytics such as *dornase alfa* in the absence of a better alternative.

• ***Nintedanib***, a tyrosine kinase inhibitor, has not been shown to prolong survival, prevent the progression of fibrosis or relieve symptoms in patients with idiopathic pulmonary fibrosis. 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). It is better to focus on symptomatic treatment.

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

• ***Roflumilast***, a phosphodiesterase type-4 inhibitor with anti-inflammatory effects, has not been shown to prolong survival 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; *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, 193).

• ***Piroxicam***, when used systemically, carries an increased risk of gastrointestinal and cutaneous disorders (including toxic epidermal necrolysis) but is no more effective than other NSAIDs (*Rev Prescrire* n° 321).

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

• ***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, 137; *Rev Prescrire* n° 380).

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

• 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).

• ***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, photodermatosis 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). *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.

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).*

Regular stretching can be beneficial (*Rev Prescrire* n° 362) (**g**).

• Colchimax° (***colchicine*** + ***opium powder*** + ***tiemonium***) has an unfavourable harm-benefit balance for gout attacks because the action of *opium powder* and *tiemonium* can mask the onset of diarrhoea, which is an early sign of potentially fatal *colchicine* overdose (*Prescrire Int* n° 147). A nonsteroidal anti-inflammatory drug or 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).

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) 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 or continue to be marketed.

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g- *Quinine is sometimes useful in malaria (Rev Prescrire n° 360).*

Selected references from Prescrire's literature search

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