



## Towards better patient care: drugs to avoid in 2024

- To make it easier to choose high-quality care, and to prevent disproportionate harm to patients, Prescrie has published its annual update of drugs to avoid.
- Prescrie's assessment of a drug's harm-benefit balance in a given situation is underpinned by a rigorous procedure based on: a systematic and reproducible literature search; data on patient-relevant outcomes; prioritisation of the highest-level evidence; comparison with standard treatment, if one exists; and appraisal of the drug's known, foreseeable and suspected adverse effects.
- Our 2024 review of drugs to avoid covers all the drugs examined by Prescrie between 2010 and 2023 that are authorised in the European Union or in France. It consists of 105 drugs that are more harmful than beneficial in all their approved indications.
- In most situations, when drug therapy appears to be the best course of action, other drugs with a better harm-benefit balance are available. And in some situations, the most prudent option is to forgo drug therapy.
- Even when seriously ill patients have exhausted all other treatment options, there is no justification for exposing them to drugs with serious adverse effects that have not been shown to improve clinical outcomes. It is sometimes acceptable to test such drugs in clinical trials, provided that patients are made fully aware of the uncertainties surrounding the drug's harm-benefit balance, as well as the trial's objectives, through discussions tailored to the patient's level of understanding. When such patients choose not to take part in a clinical trial, appropriate support and symptomatic care are called for, to help them cope with the absence of any effective drug-based options that could improve their prognosis or quality of life.

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**T**his is Prescrire's twelfth consecutive annual review of drugs to avoid (1,2). It identifies drugs that are more dangerous than beneficial, along with supporting references. The aim is to make it easier to choose high-quality treatments, and to avoid harming patients or exposing them to disproportionate risks. The drugs listed (sometimes only 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 2024 review of drugs to avoid is based on the drugs and indications analysed in our French edition between 2010 and 2023. Some 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 or corporate pressure.

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, with no 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](#)). Our editorial process is a collective one, as symbolised by the “©Prescrire” by-line.

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**Comparison with standard treatments.** A drug's harm-benefit balance and the choice of treatment options must be continually re-evaluated as new data on efficacy or adverse effects and new treatments become available.

Some drugs are useful in certain situations, offering advantages over other available treatment options, while other drugs are more dangerous than beneficial and should never be used (3).

Prescrire's assessments of drugs and indications are based on a systematic and reproducible literature search, and collective analysis of the resulting data by our Editorial Staff, using an established procedure:

- efficacy data are prioritised so that most weight is given to studies providing robust supporting evidence, i.e. double-blind, randomised controlled trials;
- the drug is compared with the standard treatment (not necessarily a drug) when one exists, after careful determination of the best comparator;
- the results analysed are those based on the clinical endpoints most relevant to the patients concerned, rather than surrogate endpoints, such as laboratory markers, that have not been shown to correlate with improvements in patients' quality of life (4,5).

**Careful analysis of adverse effects.** A drug's adverse effects can be more difficult to analyse, as they are often less thoroughly documented than its efficacy. This discrepancy must be taken into account when determining the drug's harm-benefit balance.

The adverse effect profile of each drug is assessed by examining various safety signals that emerged during clinical trials and animal pharmacotoxicology studies, and by considering its pharmacological affiliation.

When a new drug is approved, many uncertainties remain. Some rare but serious adverse effects may have been overlooked during clinical trials, and may only emerge after several years of routine use by a greater 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 diet or lifestyle. Similarly, a doctor who observes 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 evaluations obtained by simply observing a small number of patients is to prioritise experimental data obtained in patients who agreed to participate in clinical trials, especially 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 if it offers the slightest chance of even temporary relief, despite a risk of serious adverse effects.

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 of course useful to enrol patients in clinical trials, provided they are aware of the known or foreseeable harms and the uncertain nature of

# Main changes in the 2024 update of Prescrire's drugs to avoid

Prescrire updates its review of drugs to avoid every year, in the interests of improving patient care.

No new drugs to avoid have been added to our 2024 review. However, it still includes a large number of drugs that are more dangerous than beneficial, indicating that health authorities are not doing enough to protect patients.

Faced with this situation, this review aims to provide crucial information to help healthcare professionals to avoid exposing patients to drugs that carry disproportionate risks. It also suggests safer therapeutic options, when they exist.

Prescrire's review of drugs to avoid in order to provide better-quality care also serves as a solid base for certain analyses. For example, Australian academics used Prescrire's drugs to avoid to analyse the authorised drugs on the Australian market in 2019 (*Prescrire Int* n° 254). Our review also made it possible to easily identify drugs that did not warrant their place on the list of "essential" drugs, published by France's Ministry of Health in mid-2023 (*Rev Prescrire* n° 478).

## The main differences between 2023 and 2024 are outlined below.

**Teriflunomide back among Prescrire's drugs to avoid.** *Teriflunomide* is an immunosuppressant authorised for use in multiple sclerosis. It was removed from Prescrire's drugs to avoid while we evaluated its harm-benefit balance in a new indication: children aged 10 years or older. Analysis of the clinical evaluation data showed that *teriflunomide*'s harm-benefit balance is also unfavourable in children. It is therefore back among Prescrire's drugs to avoid in order to provide better-quality care.

## Three drugs no longer among Prescrire's drugs to avoid: *fenfluramine*, *pholcodine* and *tixocortol mouth spray*.

**Fenfluramine** is an amphetamine that no longer features among Prescrire's drugs to avoid while we evaluate its harm-benefit balance in a new authorised indication, Lennox-Gastaut syndrome in children. It should still be avoided as an add-on to antiepileptic therapy in Dravet syndrome, a rare and serious form of infantile epilepsy (*Prescrire Int* n° 233).

Two drugs are no longer flagged as drugs to avoid because they are no longer marketed in France (nor in Belgium or Switzerland) and have not been granted marketing authorisation elsewhere in Europe through the centralised procedure: **pholcodine**, an opioid used as a cough suppressant; and **tixocortol** mouth spray, a corticosteroid used in combination with *chlorhexidine* for sore throat.

**Idebenone's removal upheld following reassessment in 2023.** *Idebenone*, a coenzyme Q10 analogue, claimed to act as an antioxidant, already no longer featured among Prescrire's drugs to avoid in 2023, because we were reassessing its harm-benefit balance in Leber hereditary optic neuropathy in light of the new data that had become available. Following this reassessment in 2023, Prescrire concluded that its harm-benefit balance was uncertain rather than unfavourable. These new, low-quality data suggest that *idebenone* slightly increases the number of patients whose visual acuity improves or stabilises, at a cost of the risk of serious hepatic adverse effects (*Prescrire Int* n° 251). *Idebenone*'s removal is therefore upheld.

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► Translated from *Rev Prescrire* December 2023  
Volume 43 N° 482 • Page 937

the possible benefits. And the results of these trials must be published in detail (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 a clinical trial or of refusing a "last-chance" treatment with an uncertain harm-benefit balance. They must be reassured that these are genuine options, and that if they do refuse, they will not be abandoned but will continue to receive the best available care. Even though support, attention and symptomatic treatments are not intended to cure or slow progression of the underlying disease, they are useful elements of patient care.

While a great deal of uncertainty surrounds the harm-benefit balance of drugs that are undergoing evaluation in clinical trials, drugs used for routine care must have a favourable harm-benefit balance. It is in the common interest that drugs should only

be granted marketing authorisation on the basis of proven efficacy relative to standard care, along with an adverse effect profile that is acceptable in the situation concerned, because 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 early 2024, 105 of the drugs examined by Prescrire between 2010 and 2023 that are authorised in France or in the European Union are more dangerous than beneficial in all their authorised indications (a).

**a-** *Nintedanib* is mentioned twice in this review, in lung cancer (*Vargatef*<sup>®</sup>) and idiopathic pulmonary fibrosis (*Ofev*<sup>®</sup>), but has been counted as only one of the 105 drugs 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.

For each drug, we give the main reasons why it is considered to have an unfavourable harm-benefit balance, together with one or more *Prescrire* references where subscribers will find further details and the external references on which our analysis was based. 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 versions are detailed in "Main changes in the 2024 update of *Prescrire*'s drugs to avoid", on page 50-3.



## Cardiology

• **Aliskiren**, a blood pressure-lowering renin inhibitor, has not been shown to prevent cardiovascular events. Furthermore, 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; *Rev Prescrire* n° 349). It is better to choose one of the many well-established blood pressure-lowering 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 the use of a fibrate is justified, *gemfibrozil* is the only one with a degree of proven efficacy against the cardiovascular complications of hypercholesterolaemia, provided that renal function and serum creatine phosphokinase levels are closely monitored.

• **Dronedarone**, an antiarrhythmic chemically related to *amiodarone*, is less effective than *amiodarone* at preventing atrial fibrillation recurrence. Yet it 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**, a cardiac If current inhibitor, 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 the prevention of effort angina, can cause severe mucocutaneous ulceration (*Prescrire Int* n° 81, 95, 110, 131, 132, 163, 175, 241; *Rev Prescrire* n° 336, 419). A nitrate is a better option for the prevention of angina attacks.

• **Olmesartan**, an angiotensin II receptor blocker (ARB or sartan) marketed alone or in combination with *hydrochlorothiazide* or *amlodipine*, is no more effective than other ARBs against the complications of hypertension. However, it can cause sprue-like enteropathy leading to chronic diarrhoea (potentially severe) and weight loss, autoimmune hepatitis, and possibly an increase in cardiovascular mortality (*Prescrire Int* n° 148, 171, 242; *Rev Prescrire* n° 324, 374). 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 agent 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° 342, 357, 404, 457). It is better to choose treatments for angina with a better-established harm-benefit balance: 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

• **Finasteride 1 mg**, a 5-alpha reductase inhibitor, has very modest efficacy against male-pattern baldness in men, slightly increasing hair density on the crown of the head (by about 10%), but only while treatment continues. Notable adverse effects include sexual dysfunction (erectile dysfunction, ejaculatory disorders, decreased libido), depression, suicidal ideation and breast cancer (*Prescrire Int* n° 175, 196,

248; *Rev Prescrire* n° 335). When a pharmacological approach is chosen, topical *minoxidil* is less dangerous, although certain precautions must be taken (b).

• **Mequitazine**, a sedating antihistamine with anti-muscarinic activity, authorised for allergies, has only modest efficacy. However, it carries a higher risk of cardiac arrhythmias through QT prolongation than other antihistamines, in particular in patients whose cytochrome P450 isoenzyme CYP2D6 metabolises the drug slowly (a characteristic patients and doctors are generally unaware of), 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.

• **Topical pimecrolimus** and **topical tacrolimus**, two immunosuppressants used in atopic eczema, can cause skin cancer and lymphoma. These adverse effects are disproportionate as their efficacy is barely different from that of high-potency topical corticosteroids (*Prescrire Int* n° 71, 101, 110, 118, 131, 224; *Rev Prescrire* n° 311, 331, 343, 367, 428) (c). Judicious use of a topical corticosteroid to treat flare-ups is a better option in this situation. Hardly any comparative evaluation data are available on *pimecrolimus* or *tacrolimus* in patients in whom a topical corticosteroid has failed.

• **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.

• Powdered peanut seed, containing **peanut protein**, taken orally to desensitise patients with peanut allergy, reduced the incidence and intensity of allergic reactions to peanuts in a test conducted in hospital. However, it increases the incidence of allergic reactions in patients' everyday life, including reactions that require *adrenaline* administration (*Prescrire Int* n° 238). In the absence of a better alternative, the first-choice measures are still a peanut-avoidant diet, access to *adrenaline* injector pens, and for patients and their carers to learn to use these pens correctly.



## 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 have many adverse effects. The first-choice glucose-lowering drug for type 2 diabetes is *metformin*. If *metformin* alone is insufficiently effective, the other options to consider are: to continue using *metformin*, with the addition of a GLP-1 receptor agonist such as *liraglutide* or *semaglutide* (by subcutaneous injection); or addition of a gliflozin such as *dapagliflozin* for patients with heart failure or moderate renal impairment with proteinuria; or

addition of an insulin if avoiding weight gain is not a priority; or alternatively, raising the HbA1c target slightly.

• **Gliptins** (dipeptidyl peptidase-4 (DPP-4) inhibitors), i.e. *alogliptin*, *linagliptin*, *saxagliptin*, *sitagliptin* and *vildagliptin*, have a burdensome 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, 152, 158, 167, 186, 216; *Rev Prescrire* n° 349, 352, 354, 362, 365, 379, 473, 478).

• **Pioglitazone** also has a burdensome adverse effect profile, including heart failure, bladder cancer and bone fractures (*Prescrire Int* n° 129, 160).

**Weight loss.** As of early 2024, 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 combination of **bupropion** + **naltrexone** contains a substance chemically related to certain amphetamines (*bupropion*) and an opioid receptor antagonist (see also *bupropion* in the Smoking cessation section of this article) (*Prescrire Int* n° 164).

• **Orlistat** has only a modest and transient effect on weight: 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 certain 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 when used either 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).

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b- *Finasteride* 5 mg is sometimes an option in benign prostatic hyperplasia, when alpha-1-adrenoceptor blockers provide insufficient relief of urinary symptoms, are unsuitable or provoke unacceptable adverse effects (*Prescrire Int* n° 248).

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

- The **medicinal clays**, i.e. ***beidellite montmorillonite, diosmectite, hydrotalcite*** and ***kaolin***, used alone or in multi-ingredient products to treat various intestinal disorders, including diarrhoea, heartburn and gastroesophageal reflux disease, should be avoided because they are naturally contaminated with lead. 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 uncomplicated gastroesophageal reflux disease, when pharmacological treatment seems helpful, other drugs have a positive harm-benefit balance, such as a short course of moderate doses of a clay-free antacid, e.g. *sodium bicarbonate + sodium alginate*.

- The neuroleptics ***domperidone, droperidol*** and ***metopimazine*** can provoke arrhythmias and sudden death, and *domperidone* and *metopimazine* at least increase the risk of ischaemic stroke. 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, 193, 230, 243; *Rev Prescrire* n° 403, 404). 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, provided its discontinuation is planned from the outset, explaining to the patient the importance of switching to a different treatment if withdrawal symptoms occur. In the rare situations in which treatment with an antiemetic neuroleptic appears justified, *metoclopramide* has a better harm-benefit balance. *Metoclopramide* also provokes serious cardiac events, but has proven efficacy against nausea and vomiting. It is essential however to keep exposure to a minimum (by using modest daily doses and avoiding continuous use), to closely monitor patients, and to take interactions into account.

- Prucalopride***, a drug chemically related to neuroleptics, is authorised for chronic constipation but has only modest efficacy, and only in about one in six patients. Its adverse effect profile is poorly documented, and includes in particular cardiovascular disorders (palpitations, ischaemic cardiovascular events, possible QT prolongation), depression, 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 insufficiently effective, bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer choices than *prucalopride*.

- Opium tincture***, a “soup” containing a variety of constituents of the poppy *Papaver somniferum* L., is authorised for severe diarrhoea. As an adjunct to rehydration, the opioid *loperamide* alone is a more

prudent choice in this situation than a multitude of poppy-derived substances (*Rev Prescrire* n° 466).

- ***Glyceryl 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

- ***Tibolone***, a synthetic steroid hormone authorised in postmenopausal hormone replacement therapy, has androgenic, oestrogenic and progestogenic properties. It carries a risk of cardiovascular disorders, breast cancer and endometrial cancer (*Prescrire Int* n° 83, 111, 137; *Rev Prescrire* n° 427). 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 duration.

- ***Ulipristal 5 mg***, an antagonist and partial agonist of progesterone receptors, authorised for uterine fibroids, has an unfavourable harm-benefit balance because it can cause serious liver injury, sometimes requiring liver transplantation (d). When drug treatment appears necessary while awaiting menopause or when surgery is not an option, other less risky options are available: insertion of a *levonorgestrel* intrauterine device (IUD) is the first choice; an alternative is an oral progestogen, taken for a limited duration due to the uncertain harm-benefit balance of treatment lasting more than a few months (*Prescrire Int* n° 198, 225, 231; *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, 117; *Rev Prescrire* n° 371). Another fluoroquinolone such as *ciprofloxacin* or *ofloxacin* is a better option.

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**d-** In postcoital contraception, ulipristal is taken as a single 30-mg dose (*EllaOne*®). Although there is no evidence of a risk of hepatitis when used in this way, levonorgestrel would be a more cautious choice in this situation, especially since interactions between ulipristal and hormonal contraceptives can reduce the efficacy of ulipristal or the contraceptive (*Prescrire Int* n° 198, 212).



**Alzheimer's disease.** The drugs available in early 2024 for Alzheimer's disease have only minimal and transient efficacy. They are also difficult to manage because of their disproportionate adverse effects and multiple 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 dangerous drug interactions (*Prescrire Int* n° 128, 150; *Rev Prescrire* n° 363). The priorities in the management of Alzheimer's disease are to help organise the patient's daily life, keep him or her active, and provide support and help for caregivers and family members. In France, when the national health insurance system stopped reimbursing drugs for Alzheimer's disease, no increase was found in the number of consultations or rates of exposure to psychotropic drugs among patients who had previously been regularly exposed to at least one of these delisted drugs (*Prescrire Int* n° 228).

- The cholinesterase inhibitors ***donepezil***, ***galantamine*** and ***rivastigmine*** can provoke gastrointestinal disorders, including sometimes severe vomiting, neuropsychiatric disorders, and cardiac disorders including rhythm and conductance disorders, bradycardia, faintness and syncope. *Donepezil* can also cause compulsive sexual behaviour (*Prescrire Int* n° 162, 166, 192, 204, 243; *Rev Prescrire* n° 337, 340, 344, 349, 398, 416).
- ***Memantine***, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders (hallucinations, confusion, dizziness or headache), sometimes leading to violent behaviour, seizures, psychotic disorders, as well as heart failure or bradyarrhythmia (*Prescrire Int* n° 204, 225, 227; *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 uncertain efficacy and no demonstrated advantages over *interferon beta-1a*. It has many serious and sometimes fatal adverse effects, in particular: infusion-related reactions (including atrial fibrillation and hypotension), infections, frequent autoimmune disorders (including autoimmune thyroid disorders, immune thrombocytopenic purpura, cytopenia, nephropathy and hepatitis), myocardial infarction, pulmonary haemorrhage, stroke, and cervicocephalic arterial dissection (*Prescrire Int* n° 158, 218; *Rev Prescrire* n° 384, 428).

- ***Natalizumab***, another monoclonal antibody, can lead to potentially 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, 464).

• ***Teriflunomide***, an immunosuppressant, has uncertain efficacy and no demonstrated advantages over *interferon beta-1a*. It has serious and potentially fatal adverse effects, including liver damage, leukopenia and infections. It also carries a risk of peripheral neuropathy (*Prescrire Int* n° 158, 253; *Rev Prescrire* n° 482).

**Miscellaneous.** A number of other drugs used in particular in a severe form of epilepsy, migraine, cognitive impairment, vertigo, 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 older adults, has no proven efficacy beyond that of a placebo, but can cause haemorrhage, gastrointestinal disorders, skin disorders, seizures, hypersensitivity reactions and possibly arrhythmias (*Prescrire Int* n° 205, 224; *Rev Prescrire* n° 365). *Ginkgo biloba* is also used for venous insufficiency, as part of a fixed-dose combination with *heptaminol* and *troxerutin*, but its efficacy in this indication is no better (*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 it can cause headache, oesophagitis, mouth ulceration, skin disorders, kidney stones and potentially severe hepatic disorders (*Prescrire Int* n° 192; *Rev Prescrire* n° 427, 459). A walking exercise programme is an effective and less risky treatment.

• ***Piracetam***, a "psychostimulant", is authorised for use in various clinical situations, including vertigo, cognitive or neurosensory impairment in older adults, dyslexia in children, and myoclonus of cortical origin. *Piracetam*'s efficacy in these situations has not been established, but it can provoke haemorrhage, nervousness, agitation and weight gain (*Rev Prescrire* n° 294, 342, 443). No drugs are known to have a favourable harm-benefit balance in vertigo, cognitive or neurosensory impairment, or dyslexia. The anti-epileptic drugs *valproic acid* and *clonazepam* are options for cortical myoclonus.

• ***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 - Transplantation Haematology

• **Defibrotide**, an antithrombotic authorised for severe hepatic veno-occlusive disease following haematopoietic stem cell transplantation, was no more effective in reducing mortality or inducing complete disease remission than symptomatic treatment in a non-blinded trial, yet it 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 quality of life is a prudent choice.

• **Mifamurtide** is authorised in combination with other chemotherapy drugs for osteosarcoma, but it 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**, a tyrosine kinase inhibitor with anti-angiogenic activity, authorised in combination with *docetaxel* for certain types of non-small cell lung cancer, has not been shown to prolong survival. It can provoke liver injury and 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 vital functions, hastening the death of many patients (*Prescrire Int* n° 176).

• **Roxadustat**, authorised for use in anaemia associated with chronic kidney disease, is no more effective in correcting anaemia than epoetins, overall, but it seems to increase mortality, especially in patients on dialysis. Its adverse effect profile appears similar to that of epoetins, but a number of potentially serious effects seem more frequent, in particular: thrombosis of vascular access (essential for performing dialysis), sepsis and hepatic disorders (*Prescrire Int* n° 425; *Rev Prescrire* n° 475). An epoetin remains a better option.

• **Trabectedin** showed no tangible efficacy in comparative trials in ovarian cancer or soft-tissue sarcoma, but it has very frequent and severe gastrointestinal, haematological, hepatic and muscular adverse effects (*Prescrire Int* n° 102, 115, 229; *Rev Prescrire* n° 360, 426). It is not reasonable to add *trabectedin* to platinum-based chemotherapy for ovarian cancer. When chemotherapy is ineffective in patients with soft-tissue sarcoma, it is best to focus on symptomatic treatments in order 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).



## Pain Rheumatology

**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, the least risky options are *ibuprofen* and *naproxen*, provided that patients' exposure is limited (by using modest daily doses and avoiding continuous use).

• **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).

• **Cox-2 inhibitors** (coxibs), i.e. **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).

• **Ketoprofen gel** causes more photosensitivity reactions (eczema, bullous rash) than other equally effective topical NSAIDs (*Prescrire Int* n° 109, 137, 193).

• **Meloxicam**, **piroxicam** and **tenoxicam**, when used **systemically**, expose patients to an increased risk of gastrointestinal disorders 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).

**“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** can cause drowsiness, nausea, vomiting, hypersensitivity reactions (including rash and anaphylactic shock), abuse and addiction; *mephenesin* ointment can provoke severe cutaneous adverse reactions, including erythema multiforme and acute generalised exanthematous pustulosis (*Prescrire Int* n° 125, 138; *Rev Prescrire* n° 414, 430).

- **Methocarbamol** has many adverse effects, in particular gastrointestinal and cutaneous disorders (including angioedema) (*Rev Prescrire* n° 282, 338, 468, 480).

- **Thiocolchicoside**, which is related to *colchicine*, can cause diarrhoea, stomach pain, photodermatoses and possibly convulsions, and it is genotoxic and teratogenic (*Prescrire Int* n° 168; *Rev Prescrire* n° 282, 313, 321, 367, 400, 412).

**Osteoarthritis.** Some 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 early 2024, there are no drugs known to have efficacy against joint degeneration as well as a favourable harm-benefit balance.

- **Diacerein** can cause gastrointestinal disorders (including gastrointestinal bleeding and melanosis coli), angioedema and hepatitis (*Prescrire Int* n° 159; *Rev Prescrire* n° 282, 321).

- **Glucosamine** can provoke allergic reactions (angioedema, acute interstitial nephritis) and hepatitis (*Prescrire Int* n° 84, 137; *Rev Prescrire* n° 380).

**Osteoporosis.** Two drugs used in osteoporosis have an unfavourable harm-benefit balance. When non-drug measures, plus *calcium* and *vitamin D* supplementation are insufficiently effective, *alendronic acid*, or *raloxifene* as an alternative, have a better harm-benefit balance in reducing the incidence of clinical fractures, despite their considerable limitations. There is no known satisfactory drug treatment for “bone loss”.

- **Denosumab 60 mg** has very modest efficacy in the prevention of osteoporotic fractures and no efficacy for “bone loss” during prostate cancer (e). This monoclonal antibody 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 its immunosuppressive effects (*Prescrire Int* n° 117, 130, 168, 198).

- **Romosozumab** is authorised for severe osteoporosis in postmenopausal women, on the basis of a trial in several thousand women that showed a slightly lower risk of clinical fractures than with *alendronic acid*. This slight gain must be weighed against a possible increase in the risk of cardiovascular events, with higher mortality among patients aged 75 years and older (*Prescrire Int* n° 223).

**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 (Qutenza<sup>®</sup>) for neuropathic pain, is barely more effective than placebo, but can provoke irritation, severe pain and second-degree burns (*Prescrire Int* n° 108, 180; *Rev Prescrire* n° 425, 455). *Capsaicin* remains an unreasonable choice even when systemic pain medications or local ones such as *lidocaine* medicated plasters fail to provide adequate relief.

- The combination of **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, 211). A nonsteroidal anti-inflammatory drug, or a corticosteroid as an alternative, is a better option for gout attacks.

- **Quinine**, authorised for cramps, can have life-threatening adverse effects including anaphylactic reactions, haematological effects (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) (f).



## Psychiatry Addiction

**Drugs for depression.** A number of drugs authorised for depression carry a greater risk of severe adverse effects than others, without offering greater efficacy. Antidepressants generally have only modest efficacy and often take some time to work. It is better to choose one of the antidepressants with a longer history of use and 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 behaviour, rhabdomyolysis, and severe cutaneous adverse reactions 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 (SSRI) antidepressants that expose patients to a higher incidence of QT prolongation, torsade de pointes and sudden death than other SSRIs, as well as worse outcomes in the event of overdose (*Prescrire Int* n° 170, 174, 221; *Rev Prescrire* n° 369).

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**e**-A 120-mg strength denosumab product is authorised in various situations, including 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).

**f**-Quinine is sometimes useful for certain patients with malaria (*Prescrire Int* n° 145).



**Cough.** 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 that of a placebo. Yet they carry a risk of anaphylactic reactions and serious, sometimes fatal, cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (*Prescrire Int* n° 159, 184, 192; *Rev Prescrire* n° 462).

• **Oxomemazine** 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, 462; *Interactions Médicamenteuses Prescrire*).

• **Pentoxyverine**, a centrally-acting cough suppressant, can cause cardiac disorders including QT prolongation, and serious allergic reactions (*Prescrire Int* n° 208; *Rev Prescrire* n° 462).

**Sore throat.** When a drug appears necessary to relieve sore throat, in conjunction with non-drug measures such as sipping water or sucking on 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 sometimes severe cutaneous or allergic disorders, including urticaria, pruritus, angioedema, maculopapular rash and erythema (*Rev Prescrire* n° 426).

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

• The oral or nasal **decongestants ephedrine, naphazoline, oxymetazoline, pseudoephedrine** and **tuaminoheptane**, as well as **phenylephrine** and **xylometazoline**, are sympathomimetic vasoconstrictors (g). They can cause serious and even life-threatening cardiovascular disorders (hypertensive crisis, stroke, and arrhythmias, including atrial fibrillation), as well as ischaemic colitis and ischaemic optic neuropathy. 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, 231; *Rev Prescrire* n° 312, 342, 345, 348, 361, 424).

g- *Phenylephrine* for ocular use is sometimes an option as a mydriatic (*Rev Prescrire* n° 387).

• **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 with anti-angiogenic activity, has not been shown to improve clinical outcomes in any of its authorised indications: various types of pulmonary fibrosis, and systemic sclerosis-associated interstitial lung disease. It can provoke liver injury and many severe adverse effects due to its inhibitory effect on angiogenesis, including venous thromboembolism, bleeding, hypertension, gastrointestinal perforation and impaired wound healing (*Prescrire Int* n° 173, 231, 237). It is better to focus on symptomatic treatments, despite their limitations.

• **Roflumilast**, a phosphodiesterase type-4 inhibitor with anti-inflammatory effects, has not been shown to reduce mortality or improve quality of life in patients with severe chronic obstructive pulmonary disease (COPD). Yet it can provoke gastrointestinal adverse effects, weight loss, psychiatric disorders (including depression and suicide), and possibly cancer (*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.



## 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° 126, 131; *Rev Prescrire* n° 221, 377). When a drug is needed to help with smoking cessation, *nicotine* is a better choice, despite its limitations.



## 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 it has serious adverse effects, including pigmentary maculopathy with visual disturbances, and immune-mediated thrombo-

cytopenia with a consequent risk of arterial thrombosis (*Prescrire Int* n° 204; *Rev Prescrire* n° 443, 477). 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 analysis shows that the harm-benefit balance of the drugs listed above is unfavourable in all their authorised indications (apart from a few exceptions, explained in a footnote). Yet some have been marketed for many years and are in common use. From the patients' perspective, what possible justification is there for exposing them to drugs that have more adverse effects than other drugs belonging to the same pharmacological class, or other similarly effective drugs? And how can one justify exposing patients to a drug with severe adverse effects, when it has not been shown to be more effective than a placebo, or to improve patient-relevant clinical outcomes?

Healthcare professionals need to actively remove these drugs, which pharmaceutical companies persist in marketing, from their list of useful treatments. But 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.

There is no valid reason why these drugs, which are more dangerous than beneficial, should retain their marketing authorisations.

**Review produced collectively  
by the Editorial Staff: no conflicts of interest  
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► Translated from *Rev Prescrire* December 2023  
Volume 43 N° 482 • Pages 934-945

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