This 2022 update of Prescrire's "Drugs to avoid" replaces all prior versions.

Towards better patient care: drugs to avoid in 2022

● To make it easier to choose high-quality care, and to prevent disproportionate harm to patients, Prescrire has published its annual update of drugs to avoid.

● Prescrire's assessment of a drug's harm-benefit balance in a given situation reflects a rigorous procedure based on: a systematic and reproducible literature search; patient-relevant outcomes; prioritisation of the supporting data according to strength of evidence; comparison with standard treatment (if one exists); weighing the adverse effects, taking into account any uncertainties and gaps in our knowledge.

● This annual review of drugs to avoid covers all the drugs examined by Prescrire between 2010 and 2021 that are authorised in the European Union or in France. We have identified 105 drugs that are more harmful than beneficial in all their approved indications.

● In most cases, when drug therapy appears to be the best course of action, other drugs with a better harm-benefit balance are available. And in some situations, the most prudent option is to forgo drug therapy.

● For patients with a serious condition, who have exhausted all other treatment options, there is no justification for exposing them to drugs with severe adverse effects but no proven efficacy. It is sometimes acceptable to test these drugs in clinical trials, provided that patients are made fully aware of the uncertainties surrounding the drugs' harm-benefit balance, as well as the trial's objectives, in discussions tailored to the patient's level of understanding. For patients who 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 treatments which could improve their prognosis or quality of life.

This is Prescrire's tenth consecutive annual review of drugs to avoid (1,2). It lists drugs that are more dangerous than beneficial, along with supporting references (**a**). The aim is to make it easier to choose safe, effective treatments, and to avoid exposing patients to unacceptable harms. 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 review of drugs to avoid lists drugs and indications analysed in detail in our French edition over the 12-year period from 2010 through 2021 inclusive. Some drugs and indications were examined for the first time, while others were re-evaluated as new data on efficacy or adverse effects have become available.

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

Prescrire is structured in such a way as to guarantee the quality of the information provided to our subscribers. The Editorial Staff comprise a broad range of health professionals working in various sectors and free from conflicts of interest. We also call on an extensive network of external reviewers (specialists in the relevant area, methodologists, and practitioners representative of our readership), and each article undergoes multiple quality controls and cross-checking at each step of the editorial process (see *About Prescrire* > *How we work* at english.prescrire.org). Our editorial process is a collective one, as symbolised by the "©*Prescrire*" by-line.

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Comparison with standard treatments. The harm-benefit balance of a given drug has to be continually re-evaluated as new data on efficacy or adverse effects become available. Similarly, treatment options evolve as new drugs arrive on the market.

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

Prescrire's assessments of drugs and indications are all based on a systematic and reproducible literature search. The resulting data are then analysed collectively by our Editorial Staff, using an established procedure:

– efficacy data are prioritised 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. Adverse effects can be more difficult to analyse, as they are often less thoroughly documented than efficacy. This discrepancy must be taken into account when determining a 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 sees an improvement in certain patients cannot know how many other patients' conditions worsened when they received the same treatment (3).

The best way to minimise subjective bias caused by non-comparative 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 that might bring them even temporary relief, despite a risk of serious adverse effects.

a- *This list only includes drugs that are actually marketed in one of the following 3 countries that represent the majority of subscribers to our French edition: France, Belgium and Switzerland.*

Main changes in the 2022 update

Prescrire updates its review of drugs to avoid every year. As a result of this analysis, some drugs are added to the list, while others are removed, either because the pharmaceutical company or a health authority decided to withdraw the drug from the market, or pending the outcome of our reassessment of the drug's harm-benefit balance, which may change if new data become available in the course of our analysis. Here we outline the main differences between the 2021 and 2022 lists of drugs to avoid.

One more drug to avoid: fenfluramine. ***Fenfluramine***, an old amphetamine, has now been authorised for use in Dravet syndrome, a rare and serious form of infantile epilepsy, but it increases the incidence of convulsive status epilepticus and exposes patients to a risk of serious cardiovascular harms in the long term (*Prescrire Int* n° 233).

The gliflozins, ciclosporin eye drops and cimetidine removed from the list of drugs to avoid. A few drugs have been removed from Prescrire's list of drugs to avoid, despite their burdensome adverse effect profiles, due to the emergence of efficacy data showing improvements in clinical outcomes.

• The **gliflozins**, or sodium-glucose cotransporter-2 (SGLT2) inhibitors, are authorised for use in various situations: type 1 or type 2 diabetes, heart failure and chronic kidney disease. Four gliflozins are authorised in the European Union: ***canagliflozin*** (alone or combined with *metformin*), ***dapagliflozin*** (alone or combined with *metformin* or *saxagliptin*), ***empagliflozin*** (alone or combined with *metformin* or *linagliptin*), and ***ertugliflozin*** (alone or combined with *metformin* or *sitagliptin*).

All the gliflozins have an unfavourable harm-benefit balance in the prevention of the complications of type 1 or type 2 diabetes. However, limited data have shown a reduction in all-cause mortality with *dapagliflozin* in patients with moderate or severe kidney disease, most of whom had diabetes; or a reduced risk of progression to end-stage kidney disease after 3 years of treatment with *canagliflozin* in patients with diabetic nephropathy, but a substantial increase in the risk of ketoacidosis (*Prescrire Int* n° 231).

In certain heart failure patients, with or without diabetes, whose physical activity remains limited despite optimised treatment, *dapagliflozin* reduced the incidence of the serious complications of heart failure, although robust evidence of a reduction in mortality is lacking (*Prescrire Int* n° 232).

All the gliflozins share a burdensome adverse effect profile, which includes urogenital infections, serious skin infections affecting the perineum, ketoacidosis, and possibly an increased risk of toe amputation. We removed gliflozins from our list of drugs to avoid in late 2021, but it is still not clear which patients are likely to derive a real benefit.

• ***Ciclosporin*** eye drops were initially authorised for the treatment of dry eye disease with severe keratitis. In this situation, they have no proven efficacy beyond that of a placebo, but they expose patients to disproportionate risks: eye pain and irritation are common, they have immunosuppressive effects and possibly cause ocular or periocular cancer (*Prescrire Int* n° 181). They therefore featured in our list of drugs to avoid in 2021. *Ciclosporin* eye drops have now also been authorised, under a different brand name, for severe forms of vernal keratoconjunctivitis, a rare form of severe seasonal allergy. In this situation, they are sometimes an option when continued use of corticosteroid eye drops is not advisable (*Prescrire Int* n° 226).

• ***Cimetidine*** is a histamine H2-antagonist authorised for use in various gastroesophageal disorders. It inhibits numerous cytochrome P450 isoenzymes. As a result, its concomitant use with many other drugs can cause these drugs to accumulate in the body, enhancing their dose-dependent adverse effects. Its harm-benefit balance is unfavourable compared with other H2-receptor antagonists that do not expose patients to these drug interactions (*Interactions Médicamenteuses Prescrire*). However, as of late 2021, as *ranitidine is* unavailable in France, *cimetidine* is the only histamine H2-antagonist marketed in a form suitable for use by infants with gastroesophageal reflux disease complicated by œsophagitis. It constitutes an alternative to *omeprazole*.

Three drugs removed from the list due to their market withdrawal. The three following drugs have an unfavourable harm-benefit balance in all the situations for which they are authorised, but we have removed them from the list of drugs to avoid because they are no longer available in France, Belgium or Switzerland as of late 2021.

• ***Attapulgite***, a medicinal clay used in various intestinal disorders, should be avoided because it is naturally contaminated with lead (*Prescrire Int* n° 203; *Rev Prescrire* n° 430).

• The fixed-dose combination of ***conjugated equine œstrogens*** + ***bazedoxifene***, which contains œstrogen and an œstrogen receptor agonist-antagonist, has an unfavourable harm-benefit balance in the treatment of menopausal symptoms, because the risks of thrombosis and hormone-dependent cancers have not been adequately evaluated (*Prescrire Int* n° 184).

• Topical ***prednisolone*** + ***dipropylene glycol salicylate*** has an unfavourable harm-benefit balance in the treatment of pain associated with a sprain or tendinitis, because it exposes patients to the adverse effects of corticosteroids and to the risk of *salicylate* hypersensitivity reactions (*Rev Prescrire* n° 338, 452).

Reintroduction of ulipristal 5 mg: once again authorised, but best avoided in all circumstances. ***Ulipristal* 5 mg** (Esmya°), an antagonist and partial agonist of progesterone receptors, authorised for use in uterine fibroids, has an unfavourable harm-benefit balance because it can cause serious liver injury, sometimes requiring liver transplantation. Esmya°'s marketing authorisation was suspended in the European Union in March 2020, and we removed it from our list of drugs to avoid because it was no longer available in the European Union. However, *ulipristal* 5 mg has once again been authorised and is marketed in Belgium, and is therefore back on our list of drugs to avoid.

► Translated from *Rev Prescrire* December 2021
Volume 41 N° 458 • Pages 938-939

When the short-term prognosis is poor, some health professionals feel justified in proposing "last-chance" treatments without necessarily informing the patient, or only partially informing them, either intentionally or unintentionally, without taking into account their level of understanding.

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 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 supportive care and symptomatic treatment 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 under evaluation in clinical trials, drugs used for routine care must have a reasonable 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 late 2021, 105 of the drugs examined by Prescrire between 2010 and 2021 that are authorised in France or in the European Union have been identified as more dangerous than beneficial in all their authorised indications (**b**).

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

These 105 drugs comprise:

– Active substances with adverse effects that, given the clinical situations in which they are used, are disproportionate to the benefits they provide;

– Older drugs that have been superseded by newer drugs with a better harm-benefit balance;

– Recent drugs that have a less favourable harm-benefit balance than existing options;

– Drugs that have no proven efficacy beyond that of a placebo, but that carry a risk of particularly severe adverse effects.

The main reasons why these drugs are considered to have an unfavourable harm-benefit balance are explained on a case-by-case basis. When available, better options are briefly mentioned, as are situations (serious or non-serious) in which there is no suitable treatment.

The differences between this year's and last year's lists are detailed in "Main changes", on page 50-3.

Cardiology

• ***Aliskiren***, a blood pressure-lowering 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 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 in preventing the cardiovascular complications of hypercholesterolaemia, provided that renal function and serum creatine phosphokinase levels are closely monitored.

• ***Dronedarone***, an antiarrhythmic drug 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* or *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.

b- *89 of these drugs are marketed in France.*

• ***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 for 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, and possibly an increase in cardiovascular mortality (*Prescrire Int* n° 148, 171). Among the many other ARBs available, it is better to choose *losartan* or *valsartan*, which do not appear to have these adverse effects.
• ***Ranolazine***, an antianginal 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 œdema (*Prescrire Int* n° 102; *Rev Prescrire* n° 350; *Interactions Médicamenteuses Prescrire*).
• ***Trimetazidine***, a drug with uncertain properties, is used in angina despite its modest effect on symptoms (shown mainly in stress tests). Yet it can cause parkinsonism, hallucinations and thrombocytopenia (*Prescrire Int* n° 84, 100, 106; *Rev Prescrire* n° 404, 457). It is better to choose better-known treatments for angina: certain beta-blockers or, as an alternative, calcium-channel blockers such as *amlodipine* and *verapamil*.
• ***Vernakalant***, an injectable antiarrhythmic used in atrial fibrillation, has not been shown to reduce mortality or the incidence of thromboembolic or cardiovascular events. Its adverse effects include various arrhythmias (*Prescrire Int* n° 127). *Amiodarone* is a more prudent choice for pharmacological cardioversion.

Dermatology - Allergy

• ***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; *Rev Prescrire* n° 335). When a pharmacological approach is chosen, topical *minoxidil* is less dangerous, although certain precautions must be taken (**c**).
• ***Mequitazine***, a sedating antihistamine with antimuscarinic 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° 101, 110, 131, 224; *Rev Prescrire* n° 367, 428) (**d**). 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.

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* is insufficiently effective, other options to consider are: a sulfonylurea such as *glibenclamide*, an insulin, adding a GLP-1 receptor agonist (by subcutaneous injection) such as *liraglutide* or *semaglutide to metformin*, or, in some patients, slightly raising the HbA1c target.
• Gliptins (dipeptidyl peptidase-4 (DPP-4) inhibitors), i.e. ***alogliptin***, ***linagliptin***, ***saxagliptin***, *sitagliptin* and ***vildagliptin***, marketed alone or in combination with other drugs, 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° 365, 379).
• ***Pioglitazone*** has a burdensome adverse effect profile, including heart failure, bladder cancer and bone fractures (*Prescrire Int* n° 129, 160).

Weight loss. As of late 2021, 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.

c- *Prescrire plans to reassess the harm-benefit balance of finasteride 5 mg in benign prostatic hyperplasia.*

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

• The weight loss product ***bupropion*** + ***naltrexone*** combines a substance chemically related to certain amphetamines (*bupropion*) with an opioid receptor antagonist (also see *bupropion* in the Smoking cessation section) (*Prescrire Int* n° 164).
• ***Orlistat*** has only a modest and transient effect on weight loss: patients lost about 3.5 kg compared with placebo over 12-24 months, with no evidence of long-term efficacy. Gastrointestinal disorders are very common, while other adverse effects include liver damage, hyperoxaluria, and bone fractures in adolescents. *Orlistat* alters the gastrointestinal absorption of many nutrients (fat-soluble vitamins A, D, E and K), leading to a risk of deficiency, and also reduces the efficacy of 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).
• The medicinal clays ***beidellitic 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 treatment with moderate doses of a clay-free antacid, for example *sodium bicarbonate + sodium alginate*.
• 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, 193, 230; *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 withdrawal is planned from the outset, explaining to the patient the importance of switching to a different treatment if withdrawal symptoms arise. In the rare situations in which treatment with an antiemetic neuroleptic appears justified, *metoclopramide* is a less risky option. *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), closely monitor patients, and take interactions into account.
• ***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, and includes in particular 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, bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer choices than *prucalopride*.
• ***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, œstrogenic and progestogenic properties and 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 œstrogen-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 (**e**). 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 alter-

e- *In postcoital contraception, ulipristal is taken as a single 30-mg dose. 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).*

native 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; *Rev Prescrire* n° 371). Another fluoroquinolone such as *ciprofloxacin* or *ofloxacin* is a better option.

Neurology

Alzheimer's disease. The drugs available in late 2021 for Alzheimer's disease have only minimal and transient efficacy. They are also difficult to use 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 reorganise 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 the rate of exposure to psychotropic drugs among patients who had previously been regularly exposed to at least one such drug (*Prescrire Int* n° 228).

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

• ***Memantine***, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders (hallucinations, confusion, dizziness 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).

• ***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 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.

• ***Fenfluramine*** is an amphetamine authorised in combination with antiepileptic therapy in Dravet syndrome, a rare and serious form of infantile epilepsy. *Fenfluramine* increases the incidence of convulsive status epilepticus, despite a decrease in the incidence of convulsive seizures as a whole. Its long-term impact on children's psychomotor development and mortality is unknown as of late 2021. *Fenfluramine* can provoke heart valve disease and pulmonary arterial hypertension, which is why its use as an appetite suppressant was discontinued. It can also cause neuropsychiatric disorders and other cardiovascular disorders (*Prescrire Int* n° 233).

• ***Flunarizine*** and ***oxetorone***, two neuroleptics used to prevent migraine attacks, have at best only modest efficacy (*flunarizine* prevents about one attack every two months), but can cause extrapyramidal disorders, cardiac disorders and weight gain (*Rev Prescrire* n° 321, 359). *Oxetorone* also causes chronic diarrhoea (*Prescrire Int* n° 193). Other options, such as *propranolol*, are preferable.

• ***Ginkgo biloba***, used in cognitive impairment in elderly patients, has no proven efficacy beyond that of a placebo, but can cause haemorrhage, gastrointestinal disorders, skin disorders, seizures, hypersensitivity reactions and possibly arrhythmias (*Prescrire Int* n° 205, 224; *Rev Prescrire* n° 365). *Ginkgo biloba* is also used in some countries 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, œsophagitis, mouth ulceration, skin disorders, kidney stones and potentially severe hepatic disorders (*Prescrire Int* n° 192; *Rev Prescrire* n° 427). A walking exercise programme is an effective and less risky treatment.

• ***Piracetam***, a "psychostimulant", is authorised for use in various clinical situations, including vertigo, cognitive or neurosensory impairment in elderly patients, 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 antiepileptics, *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 haemopoietic stem cell transplantation, was no more effective in reducing mortality or inducing complete disease remission than symptomatic treatment in a non-blinded trial, yet 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 for osteosarcoma, but has not been shown to prolong survival and can provoke serious hypersensitivity reactions, pleural and pericardial effusions, neurological adverse effects and hearing loss (*Prescrire Int* n° 115; *Rev Prescrire* n° 341). It is more prudent to propose chemotherapy without *mifamurtide*.

• ***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).

• ***Trabectedin*** showed no tangible efficacy in comparative trials in ovarian cancer or soft-tissue sarcoma, but 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 even 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).

Ophtalmology

• ***Idebenone*** was no more effective than placebo in a trial in Leber's hereditary optic neuropathy, and carries a risk of adverse effects including hepatic disorders (*Prescrire Int* n° 179). As of late 2021, there are no treatments with a favourable harm-benefit balance for this rare disease.

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 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): ***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*** provokes drowsiness, nausea, vomiting, hypersensitivity reactions (including rash and anaphylactic shock), abuse and addiction; *mephenesin* ointment provokes severe skin disorders, including erythema multiforme and acute generalised exanthematous pustulosis (*Prescrire Int* n° 125, 138; *Rev Prescrire* n° 414, 430).

• ***Methocarbamol*** has many adverse effects, in particular 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, 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 late 2021, there are no drugs known to have efficacy against joint degeneration as well as 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).

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 (**f**). 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 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 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 ***colchicine*** + ***opium powder*** + ***tiemonium*** (Colchimax°) 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) (**g**).

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 that of a placebo, but can cause hepatitis and pancreatitis, suicide and aggressive behaviour, rhabdomyolysis, and serious skin disorders including

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

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

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 and torsade de pointes than other SSRIs, as well as worse outcomes in the event of overdose (*Prescrire Int* n° 170, 174; *Rev Prescrire* n° 369).

• ***Duloxetine***, ***milnacipran*** and ***venlafaxine*** are serotonin and noradrenaline (norepinephrine) reuptake inhibitors that, as well as provoking the adverse effects of SSRI antidepressants, carry a risk of cardiac disorders due to their noradrenergic activity, including hypertension, tachycardia, arrhythmias, and QT prolongation. In addition, *venlafaxine* overdose is associated with a high risk of cardiac arrest (*Prescrire Int* n° 131, 170, 206; *Rev Prescrire* n° 338; *Interactions Médicamenteuses Prescrire*). *Duloxetine* can also cause hepatitis and severe cutaneous adverse reactions such as Stevens-Johnson syndrome (*Prescrire Int* n° 85, 100, 111, 142; *Rev Prescrire* n° 384).

• ***Esketamine*** nasal spray is authorised for use in "treatment-resistant" depression, but its efficacy is highly uncertain. Its neuropsychiatric adverse effects are common and include dissociative symptoms. Addiction and misuse are likely (*Prescrire Int* n° 222). In this difficult clinical situation, it is more prudent to consider other less dangerous options, even if their efficacy is uncertain: psychotherapy; increasing the dose of the initial antidepressant; switching to an antidepressant from a different pharmacological class; adding a so-called atypical neuroleptic; or electroconvulsive (electroshock) therapy. The choice of treatment will mainly depend on the adverse effect profile.

• ***Tianeptine***, a drug with no proven efficacy beyond that of a placebo, can cause hepatitis, life-threatening skin reactions (including bullous rash) and addiction (*Prescrire Int* n° 127, 132; *Rev Prescrire* n° 349).

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

• ***Dapoxetine***, a so-called selective serotonin reuptake inhibitor (SSRI) antidepressant, is used for sexual dissatisfaction related to premature ejaculation. Its adverse effects are disproportionate to its very modest efficacy and include aggressive behaviour, 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*** has no proven efficacy against anxiety beyond that of a placebo, but it 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, 445, 458) (**h**). When an anxiolytic drug is justified, a benzodiazepine, used for the shortest possible duration, is a better choice. It is prudent to discuss with the patient when and how the drug will be discontinued at the time it is prescribed, in order to reduce the risks associated with prolonged use.

Pulmonology – ENT

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).

• ***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; *Interactions Médicamenteuses Prescrire*).

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

• ***Pholcodine***, an opioid authorised as an antitussive, can cause sensitisation to neuromuscular blocking agents used in general anaesthesia (*Prescrire Int* n° 184; *Rev Prescrire* n° 349, 441, 456). This serious adverse effect is not known to occur with other opioids.

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

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

• ***Tixocortol*** **mouth spray** (sometimes combined with *chlorhexidine*), a corticosteroid authorised for sore throat, can cause allergic reactions such as facial mucocutaneous œdema, glossitis or angioedema (*Rev Prescrire* n° 320) (**i**).

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

• ***Ephedrine***, ***naphazoline***, ***oxymetazoline***, ***phenylephrine***, ***pseudoephedrine***, ***tuaminoheptane*** and ***xylometazoline*** (decongestants for oral or nasal use) are sympathomimetic vasoconstrictors. They can cause serious and even life-threatening cardiovascular

h- *The French national health insurance system stopped reimbursing etifoxine in mid-November 2021.*

i- *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.*

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).

• ***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.

• ***Roflumilast***, a phosphodiesterase type-4 inhibitor with anti-inflammatory effects, has not been shown to reduce mortality or improve the quality of life of patients with severe chronic obstructive pulmonary disease (COPD), but it can provoke gastrointestinal adverse effects, weight loss, mental 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-like drug 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 has serious adverse effects, including pigmentary maculopathy with visual disturbances, and immune-mediated thrombocytopenia with a consequent risk of arterial thrombosis (*Prescrire Int* n° 204; *Rev Prescrire* n° 443) (**j**). In the absence of a better alternative, it is more prudent to offer these patients analgesic medication and non-drug measures with a low risk of adverse effects, such as applying heat or cold to the bladder or perineum, and avoiding foods or activities that exacerbate symptoms.

Putting patients first

Our analyses show that the harm-benefit balance of the drugs listed here is unfavourable in all their authorised indications (apart from a few exceptions, explained in a footnote). Yet some have been marketed for many years and are in common use. From the patient's viewpoint, 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.

The drugs listed above are more dangerous than beneficial. There is no valid reason why they should retain their marketing authorisations.

Review produced collectively by the Editorial Staff: no conflicts of interest

► Translated from *Rev Prescrire* December 2021
Volume 41 N° 458 • Pages 935-947

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

Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Towards better patient care: drugs to avoid in 2021" *Prescrire Int* 2021; **30** (223): 51-53.
2- Prescrire Editorial Staff "Towards better patient care: drugs to avoid" *Prescrire Int* 2013; **22** (137): 108-111.
3- Prescrire Rédaction "Des médicaments à écarter pour mieux soigner: pourquoi?" *Rev Prescrire* 2013; **33** (360): 792-795.
4- Prescrire Editorial Staff "Determining the harm-benefit balance of an intervention: for each patient" *Prescrire Int* 2014; **23** (154): 274-277.
5- Prescrire Editorial Staff "Treatment goals: discuss them with the patient" *Prescrire Int* 2012; **21** (132): 276-278.