Towards better patient care: drugs to avoid in 2016

Abstract

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

- Prescrire’s assessments of the harm-benefit balance of new drugs and indications are based on a rigorous procedure that includes a systematic and reproducible literature search, identification of patient-relevant outcomes, prioritisation of the supporting data based on the strength of evidence, comparison with standard treatments, and an analysis of both known and potential adverse effects.

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

- In most cases, when drug therapy is really necessary, other drugs with a better harm-benefit balance are available.

- Even in serious situations, when no effective treatment exists, there is no justification for prescribing a drug with no proven efficacy that provokes severe adverse effects. It may be acceptable to test these drugs in clinical trials, but patients must be informed of the uncertainty over their harm-benefit balance, and the trial design must be relevant. Tailored supportive care is the best option when there are no available treatments capable of improving prognosis or quality of life, beyond the placebo effect.

A reliable, rigorous and independent methodology

What data sources and methodology do we use to assess the harm-benefit balance of a given drug?

The following review concerns drugs and indications on which we published detailed analyses in our French edition over a six-year period, from 2010 to 2015. Some drugs and indications were examined for the first time, while others were re-evaluated as new data on efficacy or adverse effects became available.

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

Not all drugs are equal: some offer a therapeutic advantage, while
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- 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 for toforo treatment while others are willing to try any drug that might bring them even temporary relief, despite a risk of serious adverse effects. When the short-term prognosis is poor, some health professionals may propose last-chance treatments without properly informing the patient of the harms, either intentionally or unwittingly.

Yet patients in this situation must not be treated as guinea pigs. It is very useful to enrol patients into clinical research provided they are informed of the harms and the uncertain nature of the possible benefits, and that the results are published in order to advance medical knowledge.

But patients must be aware that they are free to refuse to participate in clinical trials or to receive last-chance treatments with an uncertain harm-benefit balance. They must also be reassured that, if they do refuse, they will not be abandoned but continue to receive the best available care. Even though they are not aimed at modifying the outcome of the underlying disease, supportive care and symptomatic treatment are key elements of patient care.

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

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

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

Antibiotics

- **Moxifloxacin** is no more effective than other fluoroquinolone antibiotics but can cause toxic epidermal necrolysis and fulminant hepatitis and has also been linked to an increased risk of cardiac disorders (Prescrire Int n° 62, 103; Rev Prescrire n° 371). Another fluoroquinolone such as ciprofloxacin or ofloxacin is a better option.

- **Telithromycin** has no advantages over other macrolide antibiotics but carries an increased risk of QT interval prolongation, hepatitis, visual disturbances and syncope (Prescrire Int n° 84, 88, 94, 106, 154). Another macrolide such as spiramycin is a better option.

Cardiology

- **Aliskiren**, an antihypertensive renin inhibitor, has not been shown to prevent cardiovascular events. On the contrary, a trial in diabetic patients showed that aliskiren was associated with an excess of cardiovascular events and renal failure (Prescrire Int n° 106, 129, 166). It is better to choose one of the many tried-and-tested antihypertensive drugs such as a thiazide diuretic or an angiotensin converting enzyme (ACE) inhibitor.

- **Bezafibrate, ciprofibrate and fenofibrate** are cholesterol-lowering drugs with no proven efficacy in the prevention of cardiovascular events (beyond the placebo effect), yet they all have
nase levels must be closely monitored.

function and serum creatine phosphoki-

vent cardiovascular complications of

only one that has been shown to pre-

a fibrate is justified,

Prescrire Int

disorders (cutaneous, haematological and renal

numerous adverse effects, including

beta-blockers or the calcium-channel

blockers amiodipine and verapamil.

There are also better options for heart

failure: one is to refrain from adding

another drug to an optimised treat-

ment regimen; another is to use a

beta-blocker with a proven impact on

mortality.

•  **Nicorandil**, a vasodilator with solely

symptomatic efficacy in the prevention

effort angina, can cause severe mucocutaneous ulceration (Prescrire Int

ª 81, 95, 110, 132). A nitrate is a better

option to prevent angina attacks.

•  **Olmesartan**, an angiotensin II recep-

tor blocker (ARB or sartan) that is no

more effective than other ARBs in

hypertension, can cause sprue-like enteropathy with chronic diarrhoea

(potentially severe) and weight loss, and,

possibly, an increased risk of card-

iovascular mortality (Prescrire Int

ª 148). It is better to choose another

of the many available ARBs, such as

losartan or valsartan, which do not

appear to have these adverse effects

•  **Trimecetazidine**, a drug with uncer-

tain properties, is used in angina

despite its only modest symptomatic

efficacy (shown mainly in stress

tests), yet it can cause parkinsonism,

hallucinations and thrombocytopenia

(Prescrire Int

ª 84, 100, 106). It is better to choose better-known treat-

ments for angina, such as certain

beta-blockers or the calcium-channel

blockers amiodipine and verapamil.

**Dermatology - Allergy**

•  **Mequitazine**, a sedating antihista-

mine with antimuscarinic properties,

used in allergies, has only modest effi-

cacy but carries a higher risk than other

antihistamines of cardiac arrhythmias
due to QT prolongation in patients who

are slow cytochrome isoenzyme P450

CYP2D6 metabolisers, and during

co-administration of drugs that inhibit

this isoenzyme (Rev Prescrire n° 337). A

non-sedating antihistamine without

antimuscarinic activity, such as lorasa-

dine or cetirizine, is a better option in

this situation.

•  **Omalizumab** in chronic spontaneous

urticaria (see the Pulmonology - ENT

section on p. 111) (Prescrire Int n° 161).

•  **Injectable promethazine**, an antihis-

tamine used to treat severe urticaria,
can cause thrombosis, skin necrosis and
gangrene following extravasation or

inadvertent injection into an artery (Rev

Prescrire n° 327). Injectable *dexchlor-

phenthiramine*, which does not appear to carry these risks, is a better option.

•  **Topical tacrolimus**, an immunosuppres-
sant used in atopic eczema, can cause skin cancer and lymphoma, yet its efficacity is barely different from that of topical corticosteroids (Prescrire Int n° 101, 110, 131; Rev Prescrire n° 367). Judi-
cious use of a topical corticosteroid to
treat flare-ups is a better option in this situation.

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

Three of the drugs that have featured in

our list of drugs to avoid since the first

version, published in 2013, were with-
drawn from the French market in 2015 by

the pharmaceutical companies concerned:
asenapine for manic episodes; iron dextran

for anaemia; and flottefanine for moderate

pain.

Pirfenidone: not listed in 2016, but

many uncertainties. All the drugs listed

in our 2015 review are also included this

year, with the exception of pirfenidone,

whose harm-benefit balance in idiopathic

pulmonary fibrosis has become more

uncertain in light of new clinical data. Its
clinical evaluation includes some favour-
nable data but still does not show whether

or not pirfenidone reduces mortality, even

after one year. It is not clear whether the

uncertain benefit of this treatment out-

weighs its harms, which markedly reduce

the quality of life of patients whose life

expectancy is short, but this does not jus-
tify its continued inclusion in our list of

drugs to avoid (Rev Prescrire n° 364).

Confirmation: thiocolchicoside, ven-
lafaxine, omalizumab. In 2015, we re-
examined certain aspects of the harm-

benefit balance of several drugs from our

list of drugs to avoid. Our re-evaluation of

thiocolchicoside, a drug with a similar

chemical structure to colchicine, confirmed

its place on the list. Thiocolchicoside has

a variety of serious hepatic, pancreatic,

muscular, haematological and neurological

adverse effects, yet has not been shown to

be more effective than placebo in mus-
cle pain (Prescrire Int n° 168).

Re-analysis also confirmed venlafaxine

as an antidepressant to be avoided. This

antidepressant with serotonergic and nor-
adrenergic activity causes more cardiovas-

cular adverse effects, and is more likely to

result in death in the event of overdose,

than many other antidepressants over

which it has no proven advantages (Rev

Prescrire n° 386 and Prescrire Int n° 170).

Omalizumab, which is authorised for use

in asthma and chronic spontaneous urti-
caria, is no more effective than a cortico-

steroid. In addition to its immunosuppres-
sant effect, this monoclonal antibody

causes hypersensitivity reactions and

cardiac disorders (Prescrire Int n° 115, 161).

Additions: drugs that are more harm-

ful than similar options. An analysis of

the cardiac adverse effects of antidepres-
sants revealed that the “selective” sero-
ton reuptake inhibitors (SSRIs) citalo-

pram and escitalopram are no more

effective than other SSRIs but cause more

cardiac disorders, including dose-

dependent prolongation of the QT interval

and torsades de pointes (Rev Prescrire

n° 386).

Analysis of the cardiovascular adverse
effects of nonsteroidal anti-inflammatory
drugs (NSAIDs) revealed that diclofenac

causes more cardiovascular adverse

effects, including myocardial infarction,

heart failure and cardiovascular deaths

than other NSAIDs, such as ibuprofen (up
to a maximum dose of 1200 mg per day)

or naproxen, but is no more effective. In

the absence of evidence to suggest

aceclofenac was considered to expose

patients to similar risks to diclofenac due
to their chemical affiliation, and should

therefore also be avoided (Prescrire Int

n° 167; Rev Prescrire n° 374).

The efficacy of defibrotide, an antithrom-

botic authorised in severe hepatic veno-
cclusive disease following haemopoietic

cell transplantation, is too uncertain

when balanced against its serious adverse

effects, in particular haemorrhages

(Prescrire Int n° 164).

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Outlook

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Diabetes - Nutrition

• Glitptins inhibit dipeptidylpeptidase-4 (DPP-4), an enzyme that catabolises the gut hormones (incretins) that stimulate postprandial insulin secretion, but these drugs have no proven efficacy against the complications of diabetes (cardiovascular events, renal failure, neurological disorders, etc.). This is the case of linagliptin, saxagliptin, sitagliptin and vildagliptin, whether used alone or in combination with metformin. These four drugs have an unfavourable adverse effect profile that includes severe hypersensitivity reactions (anaphylaxis, Stevens-Johnson syndrome), infections (urinary tract and upper respiratory tract infections), pancreatitis, biliary psephigoid and intestinal obstruction (Prescrire Int n° 121, 135, 138, 158, 167; Rev Prescrire n° 365, 366). A proven treatment such as metformin, or glibenclamide or insulin if metformin is insufficiently effective, or targeting a higher HbA1C, are more reasonable choices.

• Orlistat has only modest and transient efficacy in terms of weight loss (about 3.5 kg more than placebo after 12 to 24 months). There is no evidence of long-term efficacy. Gastrointestinal disorders are very frequent, while other adverse effects include liver damage, hyperoxaluria and bone fractures in adolescents. Orlistat alters the gastrointestinal absorption of many nutrients (fat-soluble vitamins A, D, E and K), leading to a risk of deficiency, and also reduces the efficacy of some drugs (thyroid hormones, some anti-epileptics). Oral contraceptive efficacy can be reduced if orlistat provokes severe diarrhoea (Prescrire Int n° 57, 71, 107, 110; Rev Prescrire n° 374). There are currently no drugs capable of inducing permanent weight loss. It is better to focus on dietary changes and physical activity.

Gastroenterology

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

• Prucalopride, a drug chemically related to neuroleptics, is authorised for chronic constipation but shows only modest efficacy, in about one in six patients. Its adverse effect profile is poorly documented, particularly with respect to cardiovascular disorders (palpitations, ischaemic cardiovascular events, possible QT prolongation) and teratogenicity (Prescrire Int n° 116, 137). There is no justification for exposing patients with simple constipation to such risks. If dietary measures are ineffective, then bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer than prucalopride.

Gynaecology - Endocrinology

• Tibolone, a synthetic steroid hormone used for postmenopausal replacement therapy, has androgenic, oestrogenic and progestogenic properties and carries a risk of cardiovascular disorders, breast cancer and ovarian cancer (Prescrire Int n° 83, 11, 137). When hormone therapy is chosen despite the inherent risks, the most reasonable option is an oestrogen-progestogen combination, used at the lowest possible dose and for the shortest possible period.

Neurology

Alzheimer’s disease. The drugs available for Alzheimer’s disease in early 2016 have only minimal and transient efficacy. They are also difficult to use because of their disproportionate adverse effects and many interactions with other drugs. None of the available drugs has been shown to slow progression toward dependence, yet all carry a risk of life-threatening adverse effects and severe drug interactions (Prescrire Int n° 128; Rev Prescrire n° 363, 364). It is better to focus on reorganising the patient’s daily life, keeping him or her active and providing support and help for caregivers.

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

• Memantine, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders such as hallucinations, confusion, dizziness, headache (creating a risk of violent behaviour) and seizures (Rev Prescrire n° 359, 362, 374).

Multiple sclerosis. The standard ‘disease-modifying’ treatment for multiple sclerosis is interferon beta, despite its limitations and many adverse effects. The harm-benefit balance of other such treatments is no better and sometimes clearly unfavourable. This is particularly the case of two immunosuppressants, which have disproportionate adverse effects and should be avoided.

• Natalizumab, a monoclonal antibody, can lead to life-threatening opportunistic infections, including progressive multifocal leukoencephalopathy (in about 2 per 1000 patients), potentially severe hypersensitivity reactions and liver damage (Rev Prescrire n° 330, 333, 374).

• Teriflunomide has potentially life-threatening adverse effects, including liver damage, leucopenia and infections. There is also a risk of peripheral neuropathy (Rev Prescrire n° 373).

Miscellaneous. A number of drugs used in migraine and Parkinson’s disease should also be avoided.

• Flunarizine and oxetorone, two neuroleptics used to prevent migraine attacks, have at best only modest efficacy (flunarizine prevents about one attack every two months) but can cause extrapyramidal disorders, cardiac disorders and weight gain (Prescrire Int n° 137). It is better to choose another drug such as propranolol.

• Tolcapone, an antiparkinsonian drug, can cause life-threatening liver damage (Rev Prescrire n° 330). When other treatment options have been exhaust ed, entacapone is a better option.

Oncology - Haematology

• Catumaxomab, used in malignant ascites, has serious adverse effects (possibly fatal) in more than three-quarters of patients (Prescrire Int n° 109). Paracentesis is a better option, repeated as necessary to control symptoms.

• Defibrotide, an antithrombotic approved to treat severe hepatic veno-occlusive disease following haemopoietic stem cell transplantation, had no more impact on mortality or complete disease remission

* Correction made after initial publication
than symptomatic treatment in an unblinded trial, but provokes sometimes fatal haemorrhages (Prescrire Int n° 164). It is better to focus on preventive measures and symptomatic treatments.

- **Panitumumab** does not prolong survival in metastatic colorectal cancer, yet about 90% of patients experience adverse effects, which include severe skin damage (sometimes resulting in fatal infections), gastrointestinal and ocular disorders, intermittent lung disease and hypersensitivity reactions (Prescrire Int n° 138). It is unreasonable to add panitumumab to tried-and-tested chemotherapy regimens such as those based on fluorouracil, alone or combined with other cytotoxic drugs.

- **Trabectedin** showed no tangible efficacy in comparative trials in ovarian cancer and soft-tissue sarcomas but has very frequent and severe gastrointestinal, haematological, hepatic and muscular adverse effects (Prescrire Int n° 102, 120; Rev Prescrire n° 360). It is unreasonable to add trabectedin to platinum-based chemotherapy for ovarian cancer. When chemotherapy is ineffective in patients with soft-tissue sarcomas, it is best to focus on appropriate supportive care.

- **Vandetanib** has no proven impact on survival in patients with metastatic or inoperable medullary thyroid cancer. Too many patients were lost to follow-up in placebo-controlled trials to show an increase in progression-free survival. Serious adverse effects (diarrhoea, pneumonia, hypertension) occur in about one-third of patients. There is also a risk of interstitial lung disease, torsades de pointes and cardiovascular disorders (Prescrire Int n° 112). When platinum-based chemotherapy is ineffective, it is best to focus on tailored supportive care.

- **Vinflunine** has uncertain efficacy in advanced and metastatic bladder cancer. A clinical trial provided weak evidence that vinflunine increases median survival by two months at best compared with palliative care. There is a high risk of haematological adverse effects (including aplastic anaemia), and a risk of serious infections and cardiovascular disorders (torsades de pointes, myocardial infarction, ischaemic heart disease), sometimes resulting in death (Prescrire Int n° 112). When platinum-based chemotherapy is ineffective, it is best to focus on tailored supportive care.

### Pain - Rheumatology

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

- **Cox-2 inhibitors** (coxibs) such as **celecoxib**, **etoricoxib** and **parecoxib** have been linked to an excess of cardiovascular events (including myocardial infarction and thrombosis) and skin reactions by comparison with other, equally effective NSAIDs (Prescrire Int n° 167; Rev Prescrire n° 344, 361, 374).

- **Diclofenac** and **aceclofenac** cause more cardiovascular adverse effects (including myocardial infarction and heart failure) and cardiovascular deaths than other, equally effective NSAIDs (Prescrire Int n° 167; Rev Prescrire n° 362, 374).

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

- **Piroxicam**, when used systemically, is associated with an increased risk of gastrointestinal and cutaneous disorders (including toxic epidermal necrolysis (Lyell’s syndrome)) but is not more effective than other NSAIDs (Rev Prescrire n° 321).

### Osteoporosis

Several drugs authorised for osteoporosis should be avoided because their efficacy is at best modest and they have potentially serious adverse effects. When non-drug measures plus calcium and vitamin D supplementation prove inadequate, **alendronic acid** or an alternative, **raloxifene**, have a better harm-benefit balance than other options, despite the significant limitations of both drugs.

- **Denosumab** 60 mg in osteoporosis has very modest efficacy in the prevention of osteoporotic fractures and no efficacy for “bone loss” during prostate cancer, but carries a disproportionate risk of adverse effects, including back pain, musculoskeletal pain, and serious infections (including endocarditis) due to the immunosuppressive effects of this monoclonal antibody (Prescrire Int n° 117, 130, 168). There is no known satisfactory drug treatment for “bone loss” (a).

- **Strontium ranelate** has only modest efficacy in the prevention of recurrent vertebral fractures. Yet its adverse effects include neuropsychiatric disorders, cardiovascular disorders (including venous thrombosis and pulmonary embolism, myocardial infarction and cardiovascular death), and hypersensitivity reactions including toxic epidermal necrolysis and DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) (Prescrire Int n° 117, 125, 139, 142, 156).

### Osteoarthritis

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

- **Diclofenac** causes gastrointestinal disorders (including gastrointestinal bleeding and melanosi coli), angioedema and hepatitis (Rev Prescrire n° 282, 321; Rev Prescrire n° 159).

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

### Miscellaneous

A number of other drugs used primarily in rheumatology should be avoided.

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

- **Pegloticase**, a recombinant urate oxidase used in severe gout, has modest short-term symptomatic efficacy and disproportionate adverse effects, including severe reactions during infusion (despite premedication), anaphylaxis, severe skin infections and, possibly, severe cardiac disorders (Rev Prescrire n° 365). When treatment is not justified, denosumab offers no tangible clinical advantage, but its harms do not clearly outweigh its benefits (Prescrire Int n° 130).
Outlook

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• with the first-choice drug allopurinol and the alternative probenecid is inadequate or risky, it is better to manage attacks with symptomatic treatments, pending a better solution.
• Quinine, used to treat cramps, can have life-threatening adverse effects including anaphylactic reactions, haematological disorders (including thrombocytopenia, haemolytic anaemia, agranulocytosis, and pancytopenia) and cardiac arrhythmias. These adverse effects are disproportionate in view of their poor efficacy (Rev Prescrire n° 338, 344). There are no drugs with a favourable harm-benefit balance for patients with cramps. Stretching is sometimes beneficial (Rev Prescrire n° 363).
• Colchimax® (colchicine + opium powder + tiemonium) should be avoided in gout attacks because the action of powdered opium and tiemonium can mask the onset of diarrhoea, which is an early sign of potentially fatal colchicine overdose (Prescrire Int n° 147). A nonsteroidal anti-inflammatory drug, or colchicine alone, are better options in this situation.
• The dexamethasone + salicylamide + hydroxethyl salicylate combination (Prescrire Int n° 345) and the prednisolone + dipropylene glycol salicylate combination (Prescrire Int n° 338), when applied to the skin, expose patients to the adverse effects of corticosteroids and to salicylate hypersensitivity reactions. Other drugs such as oral paracetamol (at the appropriate dosage) and topical ibuprofen have a better harm-benefit balance in patients with painful sprains or tendinopathy, in conjunction with non-drug measures (rest, ice, splints).

Psychiatry - Addiction

Antidepressants. Several drugs authorised for depression carry a greater risk of severe adverse effects but are no more effective than alternative treatments. In general, antidepressants have only modest efficacy and often take some time to work. It is better to choose an antidepressant with an adequately documented adverse effect profile.
• Agomelatine has no proven efficacy beyond the placebo effect, but can cause hepatitis and pancreatitis, suicide and aggression, as well as serious skin disorders including Stevens-Johnson syndrome (Prescrire Int n° 136, 137).
• Duloxetine, a serotonin and noradrenaline reuptake inhibitor, not only has the adverse effects of the so-called “selective” serotonin reuptake inhibitors (SSRIs) but also carries a risk of cardiac disorders (hypertension, tachycardia, arrhythmias, etc.) due to its noradrenergic activity. Duloxetine can also cause hepatitis and severe cutaneous hypersensitivity reactions such as Stevens-Johnson syndrome (Prescrire Int n° 85, 100, 111, 142; Rev Prescrire n° 384).
• Citalopram and escitalopram are SSRI antidepressants that increase the incidence of QT prolongation and torsades de pointes compared with other SSRI antidepressants (Rev Prescrire n° 369, 386).
• Milnacipran and venlafaxine, two non-tricyclic, non-SSRI, non-monoamine oxidase inhibitor (MAOI) antidepressants, have both serotoninergic and noradrenergic activity. Not only do they have the adverse effects of SSRI antidepressants, they also cause cardiac disorders (hypertension, tachycardia, arrhythmias, QT prolongation) due to their noradrenergic activity. In addition, venlafaxine overdoses are associated with a high risk of cardiac arrest (Rev Prescrire n° 338, 343, 386 and Prescrire Int n° 170).
• Tianeptine, a drug with no proven efficacy, can cause hepatitis, life-threatening skin reactions (including bullous rash), abuse and addiction (Prescrire Int n° 127, 132).

Other psychotropic drugs. Some other psychotropic drugs have unacceptable adverse effects.
• Dapoxetine, a “selective” SRI, is used for premature ejaculation with sexual dissatisfaction. Its adverse effects are disproportionate to its very modest efficacy and include aggressive outbursts, serotonin syndrome and syncope (Prescrire Int n° 105; Rev Prescrire n° 355). A psychological and behavioural approach is a better option in this situation.
• Etifoxine, a drug poorly evaluated in anxiety, can cause hepatitis and severe hypersensitivity reactions (including DRESS syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis) (Prescrire Int n° 136; Rev Prescrire n° 376). When an anxiolytic drug is justified, it is better to choose a benzodiazepine, for the shortest possible period.

Smoking cessation. Some drugs authorised to assist with smoking cessation are no more effective than nicotine and have more adverse effects. When a drug is needed to help with smoking cessation, nicotine is a better choice.
• Buproprion, an amphetamine, can cause neuropsychiatric disorders (including aggressiveness, depression...
and suicidal ideation), potentially severe allergic reactions (including angioedema and Stevens-Johnson syndrome), addiction, and congenital heart defects in children exposed to the drug in utero (Prescrire Int n° 131; Rev Prescrire n° 377).

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

### Pulmonology - ENT

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

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

- **Pholcodine**, an opioid used as an antitussive, can cause sensitisation to neuromuscular blocking agents (Rev Prescrire n° 349). This serious adverse effect is not known to occur with other opioids. Cough is a minor ailment that does not warrant taking such risks. When drug therapy is required for cough, it is better to choose dextromethorphan, despite its limitations (Rev Prescrire n° 358).

- **Tixocortol** (sometimes combined with chlorhexidine), a corticosteroid authorised for sore throat, can cause allergic reactions such as facial mucocutaneous oedema, glossitis and even angioedema (Rev Prescrire n° 320). When a drug is needed to relieve sore throat, paracetamol is a better option, when taken at the appropriate dosage.

### Putting patients first

Our analyses show that the harm-benefit balance of the drugs listed here is unfavourable in all their authorised indications. Yet some have been marketed for many years and are commonly used. How can one justify exposing patients to drugs that have more adverse effects than other members of the same pharmacological class or other similarly effective drugs? And what justification is there for exposing patients to drugs with severe adverse effects but no proven impact (beyond the placebo effect) on patient-relevant clinical outcomes?

It is necessary but not sufficient for health professionals to remove these drugs from their list of useful treatments: regulators and health authorities must also take concrete steps to protect patients and promote the use of treatments that have an acceptable harm-benefit balance.

The drugs listed above are more dangerous than beneficial. There is no valid reason for them to remain on the market.

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

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Selected references from Prescrire’s literature search.


