Towards better patient care:
drugs to avoid in 2014

Abstract

In order to help healthcare professionals and patients choose high-quality treatments and avoid harms, we have updated our list of drugs to avoid in early 2014.

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 evidence, based on the strength of evidence, comparison with standard treatments; and an analysis of both known and potential adverse effects.

Our 2014 review concerns drugs analysed in these pages over a four-year period, from 2010 to 2013. We identified 68 drugs that are potentially more harmful than beneficial in all of their authorised indications.

In most cases, other drugs with a better harm-benefit balance are available. In other cases, there is no satisfactory alternative treatment. However, even for serious diseases, this does not justify exposing patients to serious risks when a drug has no proven efficacy. Some drugs can be used within the context of clinical trials, as long as patients enrolled in such studies are informed that the harms and benefits are uncertain and that this is precisely why they are being asked to participate in clinical research. Tailored supportive care is the best option when there are no available treatments capable of improving the prognosis, beyond the placebo effect.

Our list of “drugs to avoid” published in our French edition in February 2013 attracted a great deal of interest both from concerned individuals and the media, reflecting the value that healthcare professionals and patients place in this type of information (1). The list was heavily downloaded from the Prescrire website.

We also received a number of questions, the most representative of which were published in issue 360 of our French edition (October 2013) (2).

Now, one year later in early 2014, we have updated our list of drugs that are clearly more dangerous than beneficial and should therefore be avoided. Our goal remains the same: to help healthcare professionals and patients choose the best healthcare options and to avoid harm from dangerous drugs.

A reliable, rigorous and independent methodology

How do we determine the harm-benefit balance of a given drug, and why do we consider some drugs to be more dangerous than beneficial? The following review focuses on the drugs that we have analysed in depth over a four-year period, from 2010 to 2013. Some were new drugs or indications, while others were existing products for which new data on efficacy or adverse effects had become available.

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Comparison with standard treatments. The harm-benefit balance of a given drug may be modified by new data on efficacy or adverse effects, and the choice of treatment options evolves as new drugs arrive on the market.

Not all drugs are created equal. Some offer a therapeutic advantage, while others are more harmful than beneficial and are therefore best avoided (2).

Prescrire’s evaluations are based on a systematic and reproducible literature search, followed by team-based analysis through an established procedure:

- Efficacy data are prioritised, with most weight given to studies providing high-quality supporting evidence: in...
Towards better patient care: drugs to avoid in 2014

that they are free to refuse clinical trial participation and last-chance treatments that have a poorly known harm-benefit balance; if they do so, they must nonetheless be assured of receiving high-quality care. Accompaniment and symptomatic care are key elements of patient care, even though they are not aimed at curing the underlying disease or even slowing its progression.

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 adverse effect profile compatible with the patient’s situation. In general, little additional information on efficacy is collected once marketing authorisation has been granted (2).

68 drugs more dangerous than beneficial

Between 2010 and 2013, we identified 68 drugs marketed in France that are more dangerous than beneficial. They are listed below, first based on their therapeutic class and then in alphabetical order according to their international non-proprietary name (INN).

The drugs concerned may be:
- Active substances with adverse effects that are disproportionate to the benefits they provide;
- Older drugs that have been superseded by new drugs with a better harm-benefit balance;
- Newer drugs that have a less favourable harm-benefit balance than existing options;
- Drugs that have no proven efficacy (beyond the placebo effect) but that carry a risk of serious adverse effects.

The main reasons for which a drug is considered to have an unfavourable harm-benefit balance are explained in each case. When better options are available, they are briefly mentioned, along with situations in which there is no suitable treatment.

Nine of the drugs listed in 2013 have since been withdrawn (or are in the process of being withdrawn) from the French market, either by regulatory agencies or by drug companies, and are therefore no longer listed (a). Two other drugs (natalizumab and nefopam) are not listed because we are currently reassessing them in the light of new data (b).

Oncology
- Catumaxomab, in malignant ascites, provokes serious adverse effects in more than three-quarters of patients; it also increases the risk of hospitalisation and, possibly, death (Prescrire Int n° 109). It is more prudent to drain symptomatic ascites, at intervals guided by symptoms.
- Panitumumab does not prolong survival in metastatic colorectal cancer, yet about 90% of patients experience adverse effects, including severe skin damage that sometimes results in fatal infections, gastrointestinal and ocular disorders, interstitial pneumonia, and hypersensitivity reactions (Prescrire Int n° 138). It is unwise 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 and 120; Rev Prescrire n° 360). It is unwise 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. As too many patients were lost to follow-up, placebo-controlled trials failed to show convincing evidence of 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 pneumonia, torsades de pointes, and sudden death (Prescrire Int n° 131). Once again, it is best to focus on tailored supportive care.
- Vinflunine has uncertain efficacy in advanced-stage and metastatic bladder cancer. A weak-evidence clinical trial showed a survival advantage of no more than two months compared to palliative care. There is a high risk of haematological adverse effects (including aplastic anaemia), 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.

Cardiology
- Aliskiren, an antihypertensive renin inhibitor, has not been shown to prevent...
cardiovascular events. In contrast, a trial in diabetic patients showed that alogliptin was associated with an excess of cardiovascular events (Prescrire Int n° 106 and 129). It is more prudent to choose one of the many tried-and-tested antihypertensive drugs such as a diuretic or an angiotensin-converting enzyme (ACE) inhibitor.

- Fentisib, bezafibrate and ciprofibrate are cholesterol-lowering drugs with no proven efficacy in the prevention of cardiovascular events (beyond the placebo effect), yet they all have numerous adverse effects including cutaneous, haematological and renal disorders (Prescrire Int n° 85 and 117). Gemfibrozil is the only fibrate that has been shown to prevent cardiovascular complications of hypercholesterolaemia, although it must be used with care.

- Ilopradine, an inhibitor of the cardiac current If, can cause visual disturbances, potentially severe bradycardia, and other cardiac arrhythmias. It has no advantages in angina or heart failure (Prescrire Int n° 88, 110, 118). Treatments shown to be effective in angina include beta-blockers or the calcium channel blockers amlodipine and verapamil. There are also far better options for heart failure; one is to refrain from adding another drug to an optimal treatment regimen; another is to use a beta-blocker with a proven impact on mortality.

- Nicorandil, a vasodilator with solely symptomatic efficacy in the prevention of effort angina, can cause severe mucocutaneous ulceration (Prescrire Int n° 81, 95, 110, 132). It is more prudent to use a nitrate to prevent effort angina.

- Trimetazidine, a drug with uncertain properties, is used in angina despite its only modest symptomatic efficacy (shown mainly in stress tests), yet it can cause parkinsonian syndromes, hallucinations and thrombocytopenia (Prescrire Int n° 84, 100, 106). It is far more prudent to choose better-known treatments for angina, such as certain beta-blockers or the calcium channel blockers amlodipine and verapamil.

### Dermatology - Allergy

- Topical tacrolimus, an immunosuppressant used in atopic eczema, increases the risk of skin cancer and lymphoma, yet its efficacy is barely different from that of topical corticosteroids (Prescrire Int n° 101, 110, 131). It is far more prudent to use a topical steroid to treat exacerbations.

- Mequitazine, a “sedative” and “atropinic” antihistamine used in allergies, has only modest efficacy and carries a higher risk than other antihistamines of cardiac arrhythmias due to QT prolongation in patients with low cytochrome P450 isoenzyme CYP2D6 activity, or during co-administration of drugs that inhibit this isoenzyme (Rev Prescrire n° 337). It is far more prudent to choose a non-sedative and non-atopinic antihistamine such as loratadine or cetirizine.

- Injectable promethazine, an antihista-mine used to treat severe urticaria, can cause thrombosis, skin necrosis and gangrene following extravasation or inadvertent injection into an artery (Rev Prescrire n° 327). It is more prudent to use injectable deschlorpheniramine, which does not appear to carry these risks (4).

### Diabetes - Nutrition

- Dipeptidyl peptidase 4 inhibitors (glitizins) have no proven efficacy on complications of diabetes (cardiovascular events, renal failure, neurological disorders, etc.). This is the case for 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), and pancreatitis (Prescrire Int n° 121, 135, 138). A proven treatment such as metformin, glibenclamide or insulin is a more reasonable choice.

- Orlitast has only modest and transient efficacy in 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, along with hepatic disorders, hyperparalutina, and bone fractures in adolescents. Orlitast alters the absorption of many nutrients and can lead to deficiencies and reduce the efficacy of certain drugs (fat-soluble vitamins A, D, E and K; thyroid hormones; some antiepileptics).

Oral contraceptive efficacy can be reduced if severe diarrhea occurs (Prescrire Int n° 57, 71, 107, 110). There are currently no drugs capable of inducing permanent weight loss. It is best to focus on dietary changes and increased physical activity.

### Pain - Rheumatology

#### Analgesics

Many analgesics and anti-inflammatory drugs should be avoided, especially as alternatives with a better harm-benefit balance are available. Paracetamol is the first-choice analgesic: it is effective on moderate pain and poses little danger when the maximum recommended dose is not exceeded. Some nonsteroidal anti-inflammatory drugs (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, valdecoxib and parecoxib) have been linked to an excess of cardiovascular events (including myocardial infarction and thrombosis) and skin reactions compared to other, equally effective NSAIDs (Rev Prescrire n° 344 and 361).

- Floctafenine, a NSAIID authorised for use as an analgesic, can cause severe hypersensitivity reactions (including bronchospasm and angioedema), yet is no more effective than other options (Prescrire Int n° 137).

### 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 and calcium and vitamin D supplementation prove inadequate, alendronic acid (or even raloxifene) has a better harm-benefit balance than other options, despite the major limitations of these drugs.

- Denosumab, a monoclonal antibody, has very modest efficacy in the prevention of osteoporotic fractures and no proven impact on “bone loss” associated with prostate cancer. It also carries a

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**a** These drugs are: oral almitrine, an “oxygenator” used in chronic obstructive pulmonary disease; the fixed-dose combination of cefadroxil + theodrenaline, sympathomimetic drugs with no proven benefit in hypotension; indomethacin, a non-steroidal anti-inflammatory drug; and ergot derivatives (dihydroergocristine, dihydroergocryptine, dihydroergotoxine and ergonoveline) used in “age-related neurosensor-y cognitive deficits”.

**b** Natalizumab, an immunosuppressant used in multiple sclerosis, was included on our 2013 list of drugs to avoid because of its serious adverse effects, including leukoencephalopathy and life-threatening hypersensitivity reactions (Prescrire Int n° 122). Veprosen, a centrally acting non-opioid analgesic, was listed because of its serious adverse effects, including seizures, potentially severe hypersensitivity reactions (including anaphylaxis and angioedema), hepatic and renal toxicity and addiction (Prescrire Int n° 125). Two other drugs are no longer listed because their adverse effects appear less severe than initially thought. The fixed-dose combination of amlopidine + valsartan + hydrochlorothiazide was listed mainly because it encour-aged prescribers to start antihypertensive treatment immediately with a triple-drug combination (Rev Prescrire n° 125). Tramiprosate, a peripherally acting parathyroid hormone, was listed mainly because it provoked bone tumours in experimental animals (Rev Prescrire n° 315).
Towards better patient care: drugs to avoid in 2014

- **Osteoarthritis.** Drugs authorised for long-term treatment of osteoarthritis should be avoided because they have significant adverse effects but no proven efficacy beyond the placebo effect. Paracetamol is a more prudent first-choice treatment for pain, provided patients do not exceed the recommended dose. A carefully chosen and closely monitored nonsteroidal anti-inflammatory drug is sometimes an acceptable option.
- **Diuretics** cause gastrointestinal disorders (including venous thrombosis and pulmonary embolism, myocardial infarction, and cardiovascular death), hypersensitivity reactions, including Lyell’s syndrome and DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) (Prescrire Int n° 117, 125, 139, 142).

**Gastroenterology**

- **Doxycycline** and tetracyclines, two tetracyclines, cause ventricular arrhythmias and sudden death, yet they are indicated for simple gastrointestinal reflux (doxycycline) and nausea and vomiting (Prescrire Int n° 129 and 144). Other drugs such as antacids and omeprazole have a much better harm-benefit balance in patients with painful sprains or tendinitis, in conjunction with non-drug measures (rest, ice, splints).

**Antibiotics**

- **Levofloxacin** is no more effective than other fluoroquinolone antibiotics but can cause Lyell’s syndrome and fulminant hepatitis; it has also been linked to an increased risk of cardiac disorders (Prescrire Int n° 62 and 103). It is far more prudent to choose another fluoroquinolone such as ciprofloxacin or ofloxacin.
- **Telithromycin** has no advantages over other macroline antibiotics but carries an increased risk of QT prolongation, hepatitis, visual disturbances, and loss of consciousness (Prescrire Int n° 84, 88, 94, 106). Another macroline such as spiramycin is a far more prudent option.

**Neurology**

**Alzheimer’s disease.** Drugs available for Alzheimer’s disease in 2014 have only minimal and transient efficacy. They are also difficult to use because of their disproportionate adverse effects and the risk of drug-drug interactions. None of these drugs has been shown to slow progression toward dependence, yet all carry a risk of life-threatening adverse effects and dangerous interactions (Prescrire Int n° 128 and Rev Prescrire n° 363). It is better to focus on reorganising the patient’s daily life, keeping him or her active, and providing support and help for family members and relatives.
- **Donepezil, galantamine and rivastigmine,** three cholinesterase inhibitors, can cause gastrointestinal disorders (including severe vomiting), neuropsychiatric disorders, cardiac disorders (including bradycardia, malaise and syncope), and cardiac conduction disorders (Rev Prescrire n° 337; 340: 344; 349; 362).
- **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).

**Miscellaneous.** Other drugs used in migraine and Parkinson’s disease should be avoided.

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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 more prudent to use 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 exhausted, it is far more prudent to use entacapone.

**Psychiatry - Addiction**

**Antidepressants.** Some drugs authorised for depression carry a greater risk of severe adverse effects but are no more effective than other drugs used in depression. In general, antidepressants have only modest efficacy and often take some time to work. It is best to choose a well-established antidepressant with an adequately documented adverse effect profile.

- **Agomelatine** has no proven efficacy but can cause hepatitis and pancreatitis, suicide attempts and physical assaults, and serious skin disorders (including Stevens-Johnson syndrome) (Prescrire Int n° 136 and 137).
- **Duloxetine**, a serotonin and norepinephrine reuptake inhibitor, not only has the adverse effects of selective serotonin reuptake inhibitors (SSRIs) but also carries a risk of cardiac disorders (arterial 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, 110, 111, 142).
- **Milnacipran** and venlafaxine, two non-tricyclic, non-SSRI, non-monoamine oxidase inhibitor (MAOI) antidepressants, have both serotonergic and noradrenergic activity. Not only do they have the adverse effects of SSRIs antidepressants, they also cause cardiac disorders (arterial hypertension, tachycardia, arrhythmias) due to their noradrenergic activity; venlafaxine also causes QT prolongation (Rev Prescrire n° 338; 343; 362).
- **Tianeptine**, a drug with no proven efficacy, can cause hepatitis, life-threatening skin reactions (including bullous rash) and abuse and addiction (Prescrire Int n° 127 and 132).

Other psychotropic drugs. Other psychotropic drugs with unacceptable adverse effects include:

- **Aserpine**, a drug somewhat less effective than other neuroleptics in manic episodes associated with bipolar disorder, can cause potentially severe hypersensitivity reactions (angioedema, hypotension, tongue swelling) as well as hypoaesthesia, in addition to the usual adverse effects of neuroleptics (Prescrire Int n° 131).
- **Dapoxetine**, an SSRI, is used in the treatment of premature ejaculation. Its adverse effects are disproportionate to its very modest efficacy, and include aggressive outbursts, serotonin syndrome, and syncope (Prescrire Int n° 105 and Rev Prescrire n° 335). It is more prudent to focus on psychological and behavioural approaches.

- **Etifoxine**, a drug poorly evaluated in anxiety, can cause hepatitis and severe hypersensitivity reactions (including DRESS, Stevens-Johnson and Lyell’s syndromes) (Prescrire Int n° 136). When an anxiolytic drug is needed, it is far more prudent to prescribe a benzodiazepine, for the shortest possible period.

**Smoking cessation.** 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 the most prudent choice.

- **Bupropion**, 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 if used during pregnancy (Prescrire Int n° 131).
- **Varenicline** can cause depression, suicide, serious skin rash (including Stevens-Johnson syndrome) and cardiac disorders (angina, myocardial infarction, atrial fibrillation) (Prescrire Int n° 124 and 131).

**Putting patients first**

It is necessary but not sufficient for individual healthcare professionals to remove these drugs from their therapeutic list: health authorities must also take concrete steps to protect patients and encourage prescribers to adopt treatments with a favourable harm-benefit balance. Our analysis shows that the harm-benefit balance of the drugs mentioned in this article is unfavourable in all of their approved indications. These drugs are more dangerous than beneficial, and there is no valid reason to keep them on the market.

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