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.

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
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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.

One concern is the risk of haemorrhagic stroke (Prescrire Int n° 111). When best options are available, they are briefly mentioned, along with situations in which there is no suitable treatment.

When the short-term prognosis is poor, some healthcare professionals will try last-chance treatments without always informing the patient or, knowingly or unknowingly, providing incomplete information. Yet patients in this situation must not be treated like guinea pigs. They should instead be enrolled in clinical research protocols, after being fully informed of the risks and uncertain benefits. It is crucial to publish the results of these trials. Patients must also be aware 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).

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.

Cardiology

- Alikiren, an antihypertensive renin inhibitor, has not been shown to prevent...
cardiovascular events. In contrast, a trial
or the calcium channel blockers
effective in angina include beta-blockers
n° 88, 110, 118). Treatments shown to be
potentially severe bradycardia, and other
current If, can cause visual disturbances,
– Ivoabradine, an inhibitor of the cardiac
current If, can cause visual disturbances,
– Nicoranidi, a vasodilator with solely
symptomatic efficacy in the prevention of
effort angina, can cause severe muco-
symptomatic efficacy in the prevention of
– 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 use a
nitrates to prevent effort angina.
– Amlodipine, a calcium channel blocker,
is used in angina and hypertension,
– Mequitazine, a “sedative” and “atropinic”
antiarrhythmic agent, is 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-atropinic antiarrhythmic such as
verapamil. Verapamil is also far better
options for heart failure: one is to use
a beta-blocker with a proven
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,
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than placebo after 12 to 24 months).
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– Irisplatin, 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

Diabetes - Nutrition

– Dipeptidyl peptidase 4 inhibitors (gliptins) have no proven efficacy on complications of diabetes (cardiovascular events, renal failure, neurological disorders, etc.). 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 hyperglycaemia, Stevens-Johnson syndrome, infections (urticarial 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.
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than placebo after 12 to 24 months).
There is no evidence of long-term efficacy.
Gastrointestinal disorders are very frequent, along with hepatic disorders,
– Irisplatin alters the absorption of
many nutrients and can lead to deficien-
cies 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 diarrhoea 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
benefit-risk 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 alternate.
– Cox-2 inhibitors (coxibs such as cele-
coxib, etoricoxib and parecoxib) have been
linked to an excess of cardiovascular events (including myocardial infarction
and thrombosis) and skin reactions com-
pared to other, equally effective NSAIDs (Rev Prescrire n° 344 and 361).
– Floctafenine, a NSAID 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).
– Piroxicam, a NSAID, also causes more
gastrointestinal and cutaneous disorders (including Lyell’s syndrome), without
being any more effective than safer
NSAIDs (Rev Prescrire n° 321).

Osteoporosis. Several drugs author-
ised for osteoporosis should be avoided,
because their efficacy is at best modest and they have potentially serious adverse
effects. When non-steroid measures and calcium and vitamin D supplementation prove inadequate, alendronic acid (or even
tolakoxifene) has a better harm-benefit bal-
ce 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

Dermatology - Allergy

– Topical tacrolimus, an immunosuppres-
sant used in atopic eczema, increases the
risk of skin cancer and lymphoma, yet its
efficacy is barely different from that of top-
ic al corticosteroids (Prescrire Int n° 101,
110, 113). It is far more prudent to use a
topical steroid to treat exacerbations.
– Mequitazine, a “sedative” and “atropinic”
antiarrhythmic agent, is used in allergies, has only modest efficacy and carries a higher risk than other antihistamines of cardiac
arrhythmias due to QT prolongation in

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- disproportionate risk of adverse effects, including back pain, musculoskeletal pain, and serious infections (including endocarditis) due to its immunosuppressive effects (Prescrire Int n° 117 and 130). There is no satisfactory drug for “bone loss.”

- Strontium ranelate has only modest efficacy in preventing recurrent vertebral fractures. Yet its adverse effects include neuropsychiatric disorders, cardiovascular 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).

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.

- Diacerein causes gastrointestinal disorders (including gastrointestinal bleeding and colonic melanosis), angioedema, and hepatitis (Prescrire n° 282; issue 321).

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

Miscellaneous. Several drugs used primarily in rheumatology should be avoided.

- Muscle relaxants with no proven efficacy: methocarbamol has many adverse effects, including gastrointestinal and cutaneous disorders (angioedema), while thioaceticholine causes diarrhoea, stomach pain and possibly convulsions (Rev Prescrire n° 282; 321; 313). There is no justification for exposing patients with simple muscle pain to these adverse effects. It is more prudent to use an effective analgesic such as paracetamol, taken at the appropriate dosage.

- 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 to its poor efficacy (Rev Prescrire n° 337; 344). There are currently no drugs with a favourable harm-benefit balance in cramps; stretching is sometimes beneficial (Rev Prescrire n° 363).

- Colchimix (colchicine + opiyum powder + tienonium) should be avoided because the action of powdered opiyum and tienonium can mask the onset of diarrhoea, which is an early sign of potentially fatal colchicine overdose (Prescrire Int n° 147). It is far more prudent to use a nonsteroidal anti-inflammatory drug, or colchicine alone.

- The dexamethasone + salicylamide + hydroxethyl salicylate combination (Rev Prescrire n° 345) and the prednisolone + dipropylene glycol salicylate combination (Rev Prescrire n° 338), when applied to the skin, expose patients to the adverse effects of corticosteroids as well as salicylate hypersensitivity reactions. Other drugs such as oral paracetamol (respecting the dosage) and topical ibuprofen have a better harm-benefit balance in patients with painful sprains or tendinitis, in conjunction with non-drug measures (rest, ice, splints).

Gastroenterology

- Domperidone and droperidol, two neuroleptics, cause ventricular arrhythmias and sudden death, yet they are indicated for simple gastroesophageal reflux (domperidone) 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 gastroesophageal reflux disease. When an antiemetic neuroleptic is nonetheless justified, it is best to use metoclopramide, carefully, at the lowest possible dose and for the shortest possible period.

- Prucalopride, a drug chemically related to neuroleptics, is authorised for chronic constipation and shows only modest efficacy in about one in six patients. Its adverse effect profile is poorly documented, particularly with respect to its cardiovascular disorders (palpitations, ischaemic cardiovascular events, possible QT prolongation) and teratogenicity (Prescrire Int n° 116 and 137). Simple constipation does not justify exposing patients to these risks. When 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 options than prucalopride.

Haematology

- Iron dextran has no advantages over other injectable iron products and carries a higher risk of hypersensitivity reactions (Rev Prescrire n° 349).

Antibiotics

- Moxifloxacin 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 macrolide antibiotics but carries an increased risk of QT prolongation, hepatitis, visual disturbances, and loss of consciousness (Prescrire Int n° 84, 88, 94, 106). Another macrolide such as spiromycin 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 brady-cardia, malaise and syncope), and cardiac conduction disorders (Rev Prescrire n° 377; 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.
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 hepatotoxicity and pancreatitis, suicidal 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 hepatoxicity, and severe cutaneous hypersensitivity reactions such as Stevens-Johnson syndrome (Prescrire Int n° 85, 100, 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 hepatotoxicity, 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:

Asenapine, 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° 355). It is more prudent to focus on psychological and behavioural approaches.

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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References