2013 Update

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Towards better patient care: drugs to avoid

Abstract

● **Common sense dictates that one should choose tried and tested drugs with proven, concrete benefits that outweigh their adverse effects.**

● **Many new drugs are approved each year, often despite a lack of solid evidence that they are any better than existing treatments. Worse, some are approved despite being less effective or more harmful than current options. Massive promotion is used to ensure that such drugs achieve a positive image in the eyes of healthcare professionals and patients. Renowned "opinion leaders" intervene in their favour at conferences and in specialist media, and their opinions are further propagated by specialists in the field. Finally, campaigns in the lay media are used to highlight the target illness, encouraging patients to request a prescription.**

● **New data sometimes show that older, initially promising drugs are less effective or more harmful than first thought.**

● **For all these reasons, many drugs that are now present on the market are more harmful than beneficial and should be avoided.**

● **Unfortunately, negative assessment data and warnings are often drowned in the flood of promotion and advertising. Front-line healthcare professionals who are determined to act in their patients' best interests can find themselves swimming against a tide of specialist opinion, marketing authorisation, and reimbursement decisions.**

● **By leaving drugs that are more harmful than beneficial on the market and contenting themselves with simple half-measures, healthcare authorities are failing in their duty to protect patients.**

● ***Prescrire*, a journal funded solely by its subscribers, does not seek to do the work of health authorities, and does not have the means to do so. *Prescrire*'s goal is simply to help healthcare professionals provide better care. The following text lists the principal drugs that we consider more harmful than beneficial, based on our reviews published between 2010 and 2012 in our French edition. These drugs should not be used.**

● **Patients and healthcare professionals should reassess ongoing treatments and, if necessary, replace these drugs with proven treatments. Without waiting for the authorities to remove them from the market in a timely manner, as the accumulation of data showing that they are more harmful than beneficial would require.**

Rev Prescrire **2013; 33 (352): 138-142.**

Each month, *Prescrire* publishes articles designed to help the individual healthcare professional refine his or her personal list of useful drugs. This includes articles highlighting drugs that are more dangerous than beneficial and that are therefore best avoided. Many such drugs remain on the market in early 2013. Some have been available for decades, while others were authorised more recently, despite unfavourable clinical data.

How to deal with this situation?

Healthcare authorities are responsible for removing such drugs from the market. The longer they procrastinate, the longer patients remain exposed to the dangers of these drugs, that are prescribed or recommended by healthcare professionals who are unaware of their negative harm-benefit balance or who underestimate the pressure exerted by pharmaceutical companies, including on experts hired by the authorities.

Healthcare professionals are now in the difficult position of having to explain to their patients that these drugs should not be used, even though they are authorised and are prescribed by other healthcare professionals, including specialists in hospitals or in the community.

Pending a withdrawal of these drugs from the market, the authorities must at least inform healthcare professionals and patients of the dangers. In the meantime, patients must rely on healthcare professionals, especially physicians and pharmacists.

Based on our reviews of new drugs (and some older drugs) published in *Prescrire's* French edition in 2010-2012,

here is a list of the principal drugs that, pending market withdrawal, should not be used. They are presented in alphabetical order of their international non-proprietary names (INN), according to the therapeutic domain.

The drugs listed here are:
– Active substances whose adverse effects outweigh their benefits;
– Old substances that have been superseded by newer drugs with better harm-benefit balances;
– Newer drugs whose harm-benefit balance is less favourable than that of older drugs;
– Drugs whose efficacy has not been proven (beyond the placebo effect), and which carry a disproportionate risk of adverse effects;
– Fixed-dose combinations that combine the adverse effects and drug interactions of their individual components, without significantly improving their efficacy.

Better options are often available and are briefly mentioned.

Cardiology

– *Aliskiren*, an antihypertensive drug with no proven preventive efficacy on cardiovascular events, exposes to an increased risk of cardiovascular and renal adverse effects (*Prescrire Int* n° 129). Better to use a proven diuretic or angiotensin-converting-enzyme (ACE) inhibitor for example;
– *Fenofibrate, bezafibrate* and *ciprofibrate*: these cholesterol-lowering drugs have no proven clinical efficacy but multiple adverse effects, including cutaneous, haematological and renal disorders (*Prescrire Int* n° 117). *Gemfibrozil*, the only fibrate with some documented efficacy, may be used, with care, when fibrate therapy is chosen;
– *Ivabradine*, a drug with no advantages in angina and heart failure, carries a risk of visual disturbances, potentially severe bradycardia, and other cardiac arrhythmias (*Prescrire Int* n° 111). Better to stick with proven treatments;
– *Nicorandil*, a vasodilator with a nitrate component, has only been shown to have a symptomatic effect in angina but can cause serious mucocutaneous ulceration (*Prescrire Int* n° 131, 132). Better to stick with a nitrate derivative for example;
– *Trimetazidine*, a drug with uncertain properties, has only a symptomatic effect in angina but carries a risk of parkinsonian syndromes, hallucinations, and thrombocytopenia (*Prescrire Int* n° 106). Better to stick with proven treatments;
– "Vasodilators", and particularly rye ergot derivatives, used in "age-related neurosensory cognitive deficits" (*dihydroergocryptine, dihydroergocristine, dihydroergotoxine* and *nicergoline*) have no proven efficacy but can cause pulmonary and retroperitoneal fibrosis (*Rev Prescrire* n° 342,343). It is best not to rely on drugs in these situations;
– A fixed-dose combination of *cafedrine* and *theodrenaline*, two sympathomimetic agents with no proven impact on hypotension, can have serious cardiovascular adverse effects and also create dependence (*Rev Prescrire* n° 344). Better to focus on non-drug treatments for hypotension (stockings, high-salt diet, etc.) and, for want of anything better, *midodrine*, used with care (*Rev Prescrire* n° 294);
– The fixed-dose combination of *amlodipine + valsartan + hydrochlorothiazide* may encourage unnecessary use of triple therapy for hypertension, while increasing adverse effects and interactions. There is also a risk of dosing errors due to poorly designed packaging (*Prescrire Int* n° 114). When triple-drug antihypertensive therapy is necessary, it is best to finely adjust the dose of each drug.

Oncology and Haematology

Among the cytotoxic drugs marketed in France, the 5 listed below should be withdrawn from the market, either because their harm-benefit balance is less favourable than that of other, better-assessed cytotoxic drugs, or because symptomatic care (without cytotoxic chemotherapy) is a better option:
– *Catumaxomab* does not prolong survival in malignant ascites and has serious adverse effects in more than three-quarters of patients (*Prescrire Int* n° 109);
– *Panitumumab* does not prolong survival in metastatic colorectal cancer but provokes adverse reactions, including hypersensitivity and cutaneous disorders, in about 90% of patients (*Rev Prescrire* n° 323);
– *Trabectedin* has no tangible efficacy in ovarian cancer or soft-tissue sarcomas but has very frequent and serious gastrointestinal, haematological and hepatic adverse effects (*Prescrire Int* n° 115, 120);
– *Vandetanib* has no proven impact on survival in medullary thyroid cancer but causes serious adverse reactions (diarrhoea, pneumonia, hypertension) in one-third of patients, as well as sudden death (*Prescrire Int* n° 131);
– *Vinflumine* has no advantages in bladder cancer but has frequent and sometimes fatal haematological adverse effects (*Prescrire Int* n° 112).
– *Iron dextran* carries a higher risk of hypersensitivity reactions than other injectable iron preparations (*Prescrire Int* n° 126).

Dermatology and Allergy

– Topical *tacrolimus*, an immunosuppressant used in eczema, can cause skin cancer and lymphoma, a risk disproportionate to the discomfort of this skin condition (*Prescrire Int* n° 110, 131). Exacerbations are best treated with a well-managed topical corticosteroid;
– *Mequitazine*, a "sedative" and "atropinic" antihistamine, has only modest efficacy in allergies but carries a higher risk of cardiac arrhythmias than other antihistamines (*Prescrire Int* n° 126). Better to use a non-sedative and non-atropinic antihistamine such as *loratadine* or *cetirizine*;
– Injectable *promethazine*, an antihistamine used in severe urticaria, can cause cutaneous necrosis and gangrene (*Prescrire Int* n° 109). Better to use injectable *dexchlorpheniramine*.

Diabetes and Nutrition

– Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) such as *saxagliptin, sitagliptin* and *vildagliptin* have no proven efficacy on complications of diabetes (cardiovascular, renal, neurological, etc.), while their adverse effects include immune disorders, pancreatitis and hypersensitivity reactions (*Prescrire Int* n° 113, 134). Better to use proven therapies such as *metformin, glibenclamide* and *insulin*;
– *Orlistat* has disproportionate adverse effects (very frequent gastrointestinal disorders, liver damage, etc.) and interactions in view of its only modest and transient impact on weight loss, with no evidence of a long-term benefit (*Rev Prescrire* n° 349). Better to avoid weight-loss drugs altogether and to focus on dietary measures and physical exercise.

Gynaecology and Endocrinology

– *Tibolone*, a synthetic steroid hormone used for post-menopausal hormone replacement therapy, has androgenic adverse effects, in addition to those of its oestrogen and progestin components (cardiovascular disease, breast and ovarian cancer, etc.) (*Prescrire Int* n° 111). When a woman opts for hormone therapy despite the risks, it is best to use the lowest-dose oestrogen + progestin combination for the shortest possible time. ▶▶

Gastroenterology

– *Domperidone*, a neuroleptic, causes ventricular arrhythmias and sudden death, a risk clearly disproportionate to the conditions it is used to treat, namely gastroesophageal reflux and nausea and vomiting (*Prescrire Int* n° 129). Other drugs have better harm-benefit balances: for example, antacids and *omeprazole* in gastroesophageal reflux disease;
– *Prucalopride*, a neuroleptic-related drug authorised in constipation, can cause cardiovascular disorders (*Prescrire Int* n° 116). Better to use a carefully chosen laxative when dietary measures fail.

Infections

– *Moxifloxacin* is no more effective than other fluoroquinolones but carries a risk of Lyell's syndrome, fulminant hepatitis, and more frequent cardiac disorders (*Rev Prescrire* n° 327);
– *Telithromycin*, a drug with no advantages over other macrolides, causes more cardiac, hepatic and visual disorders (*Prescrire Int* n° 106).

Neurology

– *Flunarizine* and *indoramin*, two neuroleptics used to prevent migraine attacks, are potentially more harmful than beneficial (*Rev Prescrire* n° 318, 321). Better to use *propranolol* for example;
– *Natalizumab*, an immunosuppressant, is no more effective than interferon beta in multiple sclerosis but carries a risk of life-threatening leukoencephalopathy and hypersensitivity reactions; in addition, its long-term effects are poorly documented (*Prescrire Int* n° 122);
– *Tolcapone*, an antiparkinsonian drug, carries a risk of life-threatening liver damage (*Rev Prescrire* n° 330). *Entacapone* is an option for last-resort treatment.

Psychiatry and Addiction

Several drugs currently used to treat depression should be removed from the market, as many other antidepressants have a better harm-benefit balance.
– *Agomelatine* has doubtful efficacy but carries a risk of hepatic, pancreatic, muscular and cutaneous disorders (*Prescrire Int* n° 136);
– *Duloxetine* can cause liver damage (*Prescrire Int* n° 111);
– *Milnacipran* exposes to an increased risk of cardiac and urinary disorders (*Rev Prescrire* n° 338);
– *Tianeptine* carries a risk of dependence, as well as hepatic and cutaneous adverse effects (*Prescrire Int* n° 132);
– *Venlafaxine* causes more cardiovascular disorders than other antidepressants (*Rev Prescrire* n° 343).

Other psychotropic drugs should also be removed from the market:
– *Asenapine* is less effective than other antipsychotics on manic episodes in patients with bipolar disorder and can cause oral hypoaesthesia and severe hypersensitivity reactions (*Prescrire Int* n° 131);
– *Etifoxine*, a drug with uncertain efficacy in anxiety, can damage the liver (*Prescrire Int* n° 136). Better to use a benzodiazepine, for as short a period as possible, when anxiolytic drug therapy is needed;
– *Meprobamate*, still used in France as an anxiolytic in Kaologeais° (combination therapy of functional gastrointestinal disorders with anxiety) and in Precyclan° (combination therapy of premenstrual syndrome), carries a risk of severe cutaneous and haematological adverse effects and of withdrawal syndromes (*Rev Prescrire* n° 336). Better to use a benzodiazepine when anxiolytic drug therapy is needed.

Drugs indicated for smoking cessation should also be withdrawn, because they are no more effective than nicotine but have more adverse effects:
– *Bupropion*, an amphetamine, can cause neuropsychiatric disorders, congenital heart defects, and dependence (*Prescrire Int* n° 126, 131);
– *Varenicline* can provoke suicide (*Prescrire Int* n° 131).

Pneumology and ENT

– *Almitrine*, used as an "oxygenator" (without proven efficacy) in chronic obstructive pulmonary disease, carries a risk of severe neuropathy and weight loss (*Rev Prescrire* n° 345);
– *Pholcodine*, an opioid, can cause sensitization to neuromuscular blocking agents (*Rev Prescrire* n° 349). This risk is disproportionate to the discomfort of cough;
– Oral and nasal vasoconstrictive decongestants (*ephedrine, naphazoline, oxymetazoline, pseudoephedrine* and *tuaminoheptane*) carry a disproportionate risk of cardiovascular adverse effects when used to treat mild conditions such as the common cold (*Prescrire Int* n° 136);
– *Omalizumab*, a monoclonal antibody used in severe persistent asthma, carries a risk of infections, hypersensitivity and cardiac disorders (*Prescrire Int* n° 121). Better to use a corticosteroid;
– *Pirfenidone*, an immunosuppressant with no proven efficacy in idiopathic pulmonary fibrosis, carries a risk of serious adverse effects, including cardiac and cutaneous disorders (see May issue). For want of anything better, it is best to focus on symptom management;
– *Tixocortol* (combined with *chlorhexidine* in Thiovalone °) carries a risk of allergic reactions such as mucocutaneous facial oedema, glossitis, and even angioedema (*Rev Prescrire* n° 320). Better to use *paracetamol* for throat pain.

Analgesia and Rheumatology

Analgesia. Many painkillers and anti-inflammatory drugs should be taken off the market. Treatments with better harm-benefit balances are available. *Paracetamol* (*acetaminophen*) is the analgesic of first choice: it is effective and poses little danger when the recommended dosage is respected. Some nonsteroidal anti-inflammatory drugs (NSAIDs) such as *ibuprofen* and *naproxen*, used at the lowest effective dose and for the shortest time possible, are an alternative.
– The cox-2 inhibitors *celecoxib, etoricoxib* and *parecoxib* carry a higher risk of cutaneous and cardiovascular effects than other NSAIDs (*Rev Prescrire* n° 344);
– *Floctafenine*, a NSAID used as an analgesic, can cause hypersensitivity reactions such as bronchospasm and angioedema (*Rev Prescrire* n° 321);
– *Ketoprofen* gel carries a higher risk of cutaneous disorders than other topical NSAIDs (*Prescrire Int* n° 109, 112);
– *Nefopam*, an analgesic, carries a risk of atropinic adverse effects, seizures, liver damage and dependence (*Rev Prescrire* n° 324);
– *Nimesulide*, a NSAID, can cause life-threatening liver damage (*Prescrire Int* n° 116);
– *Piroxicam*, a NSAID, carries an increased risk of cutaneous and gastrointestinal disorders (including Lyell's syndrome) (*Rev Prescrire* n° 321).

Osteoporosis. Several drugs marketed for osteoporosis should be withdrawn, as their efficacy is at best modest and their adverse effects are potentially serious. *Alendronic acid* may be used with care when non-drug measures and *calcium + vitamin D3* supplementation is inadequate:
– *Denosumab*, a monoclonal antibody marketed to prevent osteoporotic fractures and "bone loss" in patients with prostate cancer, can cause back pain and musculoskeletal pain, as well as infections due to its immunosuppressive effects (*Prescrire Int* n° 117, 130). There is no satisfactory drug for "bone loss";
– *Strontium ranelate* can cause neuropsychiatric disorders and hypersensitivity reactions, including Lyell's syndrome and Dress syndrome (drug reaction with

eosinophilia and systemic symptoms.), and also venous thromboembolism (*Prescrire Int* n° 125);
– *Teriparatide*, a peptide, carries a risk of gastrointestinal disorders, syncope secondary to hypotension and, possibly, bone tumours (*Rev Prescrire* n° 315).

Osteoarthritis. Some drugs used in osteoarthritis should be withdrawn because they have no proven efficacy. *Paracetamol* is the first-choice analgesic in this setting:
– *Diacerein* carries a risk of gastrointestinal disorders, severe cutaneous disorders, and hepatitis;
– *Glucosamine* can cause allergic reactions and hepatic disorders (*Rev Prescrire* n° 323).

Miscellaneous. Other drugs used primarily in rheumatology should be withdrawn, including:
– Muscle relaxants with no proven efficacy: *methocarbamol* has multiple adverse effects including gastrointestinal and cutaneous disorders, while *thiocolchicoside*, a *colchicine* derivative, causes diarrhoea, gastralgia and, possibly, seizures (*Rev Prescrire* n° 313, 321). Other symptomatic treatments are preferable;
– *Quinine* used in muscle cramp carries a risk of hypersensitivity reactions, haematological disorders and cardiac disorders that largely outweigh its marginal effect (*Rev Prescrire* n° 344). There are no drugs with a favourable harm-benefit balance in muscle cramp;
– The proprietary drug Colchimax° (*colchicine* + *opium powder* + *tiemonium*) should be withdrawn because the effects of powdered *opium* and *tiemonium* can mask the onset of diarrhoea, which is one of the first signs of potentially fatal *colchicine* overdose (*Rev Prescrire* n° 350). Better to use *colchicine* alone;
– The *dexamethasone* + *salicylamide* + *hydroxyethyl salicylate* combination (*Rev Prescrire* n° 345), and the *prednisolone* + *dipropylene glycol salicylate* combination (*Rev Prescrire* n° 338) both expose patients to the adverse effects of corticosteroids and to the risk of hypersensitivity reactions to salicylates; better to use oral *paracetamol* or topical *ibuprofen* to relieve pain due to sprains and tendinopathy, in addition to non-drug measures (rest, ice, splinting).

Healthcare professionals and patients should start to prepare for the market withdrawal of drugs with unfavourable harm-benefit balances. This means first deciding precise therapeutic goals and then choosing the treatment strategy accordingly. This will help to avoid harmful drugs (1).

Selected references from Prescrire's literature search.
1- Prescrire Editorial Staff "Treatment goals: discuss them with the patient" *Prescrire Int* 2012; **21** (132): 276-278.

Prescrire IN ENGLISH — Coming soon...

New Products

– *Pirfenidone*
– *Panitumumab* adjunctive therapy
– *Tegafur* + *gimeracil* + *oteracil*

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– Heparin-induced thrombocytopenia
– Anaphylactic reactions during anaesthesia
– Weekly oral *methotrexate* therapy

Reviews

– Deep venous thrombosis and pulmonary embolism - part II
– Botulinum toxin type A and tension-type headache

Outlook

– 2012 drug packaging review
– Exceptions to and deviations from the INN common stem system
– The FDA is spying on whistle-blowers