

Headache: One of the Most Common and Troublesome Adverse Reactions to Drugs

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Abstract: It is difficult to attribute the diagnosis of adverse drug reaction to a condition which is also a common symptom. The decision might be arduous in the case of headache, because this disorder is very frequent in the general population. The drugs that more frequently induce headache belong to a variety of therapeutic classes with different mechanisms of action and different toxicity. In the majority of cases the headache has not a typical feature, it is dose-dependent, and is associated to other symptoms of neurotoxicity. Some drugs cause, instead, a specific headache: this is the case of NO donors, which are also used in experimental studies in order to induce headache.

This review describes the classes of drugs which induce headache, analyzes the frequency of headache induction among the drugs of the same class, and discusses the possible mechanisms underlying headache induction. It is to be hoped that a better awareness of this issue would help the physician to consider it in the differential diagnosis of a recent-onset or changed headache and to avoid prescription of drugs known to cause headache to patients already suffering from this disorder.

Keywords: Adverse reaction, event, side effect, drug, headache, migraine.

INTRODUCTION

Adverse reactions to drugs and drugs' safety are of paramount importance [1]. Unwanted reactions to drugs are an important cause of morbidity and mortality [2-5]. Non serious reactions can also be very troublesome [6-9]. In patients undergoing long-lasting treatments (e.g., for hypertension or depression) they reduce compliance or even cause the interruption of the treatment [10-12]. A better understanding of such reactions is therefore essential in order to prevent or at least to reduce them, but also to be able to recognize them in clinical practice. When an adverse reaction is detected, the reduction of the dose of the drug or its replacement with another one, can provide resolution in most cases [13]. However, it is difficult to attribute the diagnosis of adverse drug reaction to a condition which is also a common symptom [14-17]. The decision might be arduous in the case of headache, because this disorder is very frequent in the general population. Headache occurs in a very large number of individuals all around the world, regardless of race and social and economic situation. Maybe everyone has experienced pain in his head. Fifty percent of the population experiences headache at least once a month, 15% at least once a week, and 5% daily [18-22]. Headache in itself is not pathognomonic of any pathological condition; it can be due to disorders of various nature and severity. The majority of headaches are primary headache disorders of three main forms: migraine, tension-type headache and cluster headache. Migraine is an idiopathic recurring headache disorder consisting in attacks lasting 4-72 hours, with unilateral location, pulsating quality, moderate to severe intensity, and it is associated with nausea, photo-and

phonophobia [23]. It affects 5 - 20% of the general population [24, 25]. Tension-type headache is characterized by recurrent episodes of headache lasting minutes to days, with pain typically pressing/tightening in quality, of mild to moderate intensity, bilateral in location. It is the most prevalent headache, affecting 78% of the general population [26]. Cluster headache is characterized by attacks of severe strictly unilateral pain, orbitally, supraorbitally and/or temporally located, lasting 15-180 minutes and occurring from once every other day to 8 times a day. Attacks occur in series lasting for weeks or months. Cluster headache is rare, occurring in less than 1% of the population [27]. Primary headaches are chronic disorders, recurring for many years, mainly in young and adult people [28]. Moreover, despite recent advances, the pathophysiology of primary headaches remains incompletely understood [29], and there are no causal and definitive therapies for these disorders [30, 31]. Secondary or symptomatic headaches constitute a minority and may be a symptom of a wide variety of conditions that adversely affect the brain: neoplastic, infectious, toxic or metabolic. Some are not serious (e.g., headache associated with fever), but others are life threatening, such as subarachnoid haemorrhage [32]. If quickly diagnosed, they can be treated and, in many cases, definitively cured. Among the innumerable types of secondary headaches are headaches as adverse reactions related to drugs, the importance of which is also recognized in the ICHD-II classification [23], which includes this issue in Chapter 8 (Headache attributed to a substance or its withdrawal).

There are no pathognomonic elements, laboratory tests or instrumental examinations to diagnose primary headache: the diagnosis is clinical [33]. Furthermore, a growing number of people take more and more drugs [34] and headache is one of the first 10 reasons to see a doctor [35-37]. Finally, the hardest, but most important task for a physician examining a headache patient, is to make a precise differential diagnosis between primary and secondary headaches [38]. For all these

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reasons, we will examine the drugs which literature considers as capable of inducing headache, in order to increase the physician's knowledge of, and attention to, this subject.

This review has some limitations, owing to the uncertainty inherent in the different sources. All the detecting methods of adverse reactions (both during the pre- and post-marketing phases) are imperfect [14, 39, 6], and the relevant literature often is biased [40, 8, 41]. Randomized double blind clinical trials, even if not sufficient to assure drug safety in clinical practice [42], offer a unique opportunity to assess the frequency and severity of adverse reactions in a controlled setting, and they are the only means to assess if adverse effects occur more often after the investigated drug than after placebo or comparator drug [43]. Furthermore, the descriptions of headaches as adverse effects reported in literature hardly ever specify the characteristics of the patient or the healthy volunteer on whom the drug was tested in the pre-marketing phase. In particular, they do not specify if the subject who developed headache as a side effect had already been suffering from it or had familiarity with this disorder. In the case of a previous headache sufferer, the precise diagnosis is uncertain, and it is not clear whether the drug was simply a "trigger" or the real cause of that particular headache. Finally, establishing a relationship of cause and effect represents the biggest problem in the analysis of drug-induced disorders [14-17]. A large number of the studies reported in literature that we examined did not specify whether headache was an "adverse reaction" or "adverse event" [44], i.e., whether the causal relationship between drug and headache was clear.

The drugs that more frequently induce headache belong to a variety of therapeutic classes with different mechanisms of action and different toxicity. We especially considered the drugs for which literature gives quantitative data about the incidence of headache as a side effect. When available we reported the percentages of headache related to the active drug, net of the percentages of headache induced by placebo. We excluded drugs inducing percentages of headache lower than those induced by placebo.

CARDIOVASCULAR DRUGS

All cardiovascular drugs, either with direct or indirect vasodilating properties, and independently of their primary mechanism of action, seem to be able to induce headache as an adverse effect, in quite a fair number of patients.

Calcium channel blockers, as a class, are potent arterial vasodilators, mainly used in the treatment of hypertension, angina pectoris, congestive heart failure, and heart arrhythmias (class IV antiarrhythmics). These drugs inhibit calcium influx through slow voltage-operated calcium channels in plasma membrane of a variety of cell types [45]. This action results in relaxation of vascular smooth muscle, with consequent vasodilatation (mainly arteriolar vasodilatation) [46]. Headache is the most frequently reported central nervous system (CNS) complaint during therapy with these agents (Table 1), particularly with dihydropyridine derivatives such as **nifedipine** [47]. Headache leads to a high rate of drug discontinuation, up to 25% in the case of **nisoldipine** [48]. Other most common

Table 1. Percentages of Headache, as an Adverse Effect, that have been Associated with Cardiovascular Drugs

Drugs	% of Headache	Notes	Ref.
<i>Calcium channel blockers</i> ^{§, &}			
Diltiazem	4	*	[51]
Felodipine	8	*	[265, 266]
Israpidine	6.6-7.9	*	[267]
Lacipidine	7-18		[268]
Lercanidipine	5		[269]
Nicardipine	3.8-12.6	*	[270]
Nifedipine	3-6	*	[271]
Nisoldipine	7	*	[48]
Nitrendipine	10	*	[272]
Verapamil	1.7	*	[50]
<i>Antiarrhythmics</i>			
Disopyramide	3-9		[52]
Flecainide	9-10		[54]
Lorcainide	10		[54]
Mexiletine	1.4	*	[53]
Propafenone	4.5		[273]
<i>Phosphodiesterase inhibitors</i> [§]			
Dipyridamole	2.3	*	[56]
Enoximone	<10		[59]
Pimobendan	27-33		[58]
<i>Alfa-2 adrenergic agonist</i>			
Clonidine	5		[60]
<i>Alfa-1 adrenergic blockers</i>			
Doxazosin	4		[61]
Prazosin	7.8	&	[62]
<i>Beta-adrenergic blockers</i> [§]			
Betaxolol	6-15		[274]
Bisoprolol	10.9		[275]
Bucindolol	20		[70]
Carteolol	4-17		[276]
Dilevalol	20		[71]
Penbutolol	1.7	*	[277]
<i>Diuretic</i>			
Amiloride	3-8		[72]
<i>ACE inhibitors</i> [§]			
Benazepril	6.2	*, &	[278]
Cilazapril	5.2	&	[279]
Enalapril	2.9-5.2	‡, &	[280]
Lisinopril	3.8	*, &	[281]
Quinapril	6.9	&	[282]
<i>Antagonists of the AT-1 receptor for angiotensin II</i> [§]			
Tasosartan	19	*	[78]
Valsartan	9.8		[77]
<i>Nitrates</i> ^{§, &}			
Nitroglycerin	45	*, ±	[283]
Isosorbide dinitrate	11-38	+, ±	[284]
Isosorbide mononitrate	23-42	*, +	[83]
Nicorandil	22-48		[87]
Molsidomine	10-25		[88]
<i>Other</i>			
Pentoxifylline	0.4	*	[89]

*percentages of headache net of percentages of headache induced by placebo.

‡all drugs of the class have been associated with headache.

§headache causing discontinuation of the drug.

¶the drug has been associated with peripheral neuropathy.

‡the drug has been associated with migraine headache.

+the drug has been associated with dose-related headache.

adverse effects observed with dihydropyridine derivatives include flushing, dizziness, and peripheral oedema; the CNS effects occur early during therapy and tend to subside with continued use [49]. **Verapamil**, a phenylalkylamine derivative, and **diltiazem**, a benzothiazepine derivative, which are less potent vasodilators than dihydropyridines, have been associated with minimal CNS toxicity and lower incidence of headache than the dihydropyridine calcium channel blockers [50, 51].

Headache is a common adverse effect of **antiarrhythmics**, such as class I A **disopyramide**, class I B **mexiletine**, class I C **lorcainide** and **flecainide**. Other CNS effects of these drugs include dizziness, ataxia, and tremor [52-54]. Class IV antiarrhythmics (calcium channel blockers) have been already mentioned, and class II antiarrhythmics (beta-blockers) will be mentioned below.

Dipyridamole inhibits phosphodiesterases, thus increasing the levels of cyclic AMP in platelets and therefore inhibiting platelet aggregation [55]. Headache, facial flushing, limb pain and weakness are common side effects of this drug [56]. Headache is more frequent during the first days of treatment; then tolerance develops [57].

Pimobendan and **enoximone** are **phosphodiesterase inhibitors** with positive inotropic and vasodilating activity. The relaxation of peripheral vascular smooth muscle due to elevation of intracellular cyclic AMP may be responsible for the vasodilator properties of these drugs and for the resultant decrease in systemic vascular resistance. The most common CNS side effects of these agents are headache, dizziness and fatigue [58, 59].

Clonidine is a centrally acting antihypertensive with alpha-2 adrenergic agonist activity. It reduces sympathetic outflow from the brain. The decrease in blood pressure is associated with reduction in peripheral vascular resistance. Headache, fatigue, lethargy are commonly reported with this drug, more often after oral than after transdermal administration. In addition, headache may develop also after withdrawal of the drug [60].

Drugs acting as **alpha-1 adrenergic antagonists** are used to control hypertension and for the management of benign prostatic hyperplasia. Selective alpha-1 blockade produces vasodilatation that may vary markedly depending on the adrenergic vasomotor tone in the different vascular beds. Dizziness, headache, and orthostatic hypotension are the most common adverse effects associated with these drugs [61-63]. **Prazosin** may cause also severe headache leading to drug discontinuation [64, 65].

Headache has been reported with **tolazoline**, a direct acting peripheral vasodilator with weak alpha-adrenergic blocking properties [66], and with **hydralazine**, a direct arterial vasodilator [67].

Beta-adrenergic blocking agents are effective in treating hypertension, angina pectoris, arrhythmias, hyperthyroidism and glaucoma. Headache and dizziness are among the most common CNS effects of the whole class [68]. However, headache has been less frequently (<10%) reported with **propranolol**, **timolol**, **nadolol**, **metoprolol** and **atenolol** that are drugs of first choice for preventive migraine treatment [68, 69]. **Bucindolol** and **dilevalol**, non

selective beta-adrenergic blocking agents with vasodilator properties, seem to cause the highest incidence of headache [70]. **Dilevalol** has been withdrawn from the market due to liver toxicity [71].

Dizziness and headache have been observed during treatment with different **diuretics** used in the treatment of hypertension and congestive heart failure, such as **amiloride**, a potassium-sparing diuretic [72], **furosemide** and **bumetanide**, loop diuretics. These side effects could be related to fluid or electrolytes abnormalities caused by these drugs [73]. In addition, diffuse headache can occur after high doses of **acetazolamide**, inhibitor of carbonic anhydrase [74].

The primary adverse effects of several **angiotensin converting enzyme (ACE) inhibitors**, used for the treatment of hypertension and congestive heart failure, are headache, dizziness, cough and fatigue. Cough and headache are also the most common reasons for drug discontinuation. Angiotensin converting enzyme, besides being responsible for the conversion of angiotensin I into angiotensin II, is also responsible for the degradation of bradykinin. The inhibition of this enzyme leads to accumulation of bradykinin, a potent vasodilator [75]. This effect, could may have a major role in the genesis of the headache reaction. Therapy with ACE inhibitors has been associated with other CNS effects, such as depression, confusion, anxiety, and disorientation. It was suggested that these toxic effects may be due to interference with brain carboxypeptidase enzymes [76].

Headache and dizziness are also the most common adverse effects of some **angiotensin II receptor antagonists**, such as **valsartan** and **tasosartan** [77, 78]. Indeed, angiotensin II is a very potent vasoconstrictive agent and for both classes of drugs – angiotensin II receptor antagonists and ACE inhibitors – headache may be related to the vasodilator effect [79].

Organic nitrates (nitroglycerin, isosorbide, etc) readily enter vascular smooth muscle where they are converted into nitric oxide (NO) which acts as a cellular messenger eventually leading to activation of cyclic guanosine monophosphate (cGMP) and to vasodilatation. Headache is by far the most frequently reported side effect associated with organic nitrate therapy for angina or congestive heart failure [80]. Headache can be of mild to severe intensity, pulsating, and dose-related, as observed in clinical studies with sustained release dosage forms [81]. Although tolerance generally develops over 2 weeks, up to 20% of patients are unable to tolerate such headache [82]. In addition, nitroglycerin can precipitate migraine (with or without aura) in patients with a personal or family history of migraine [83, 84]. Age is independently and inversely associated with headache caused by nitrates [85]. All NO-donors can cause headache, particularly in migraine sufferers. According to ICHD-II classification [23], NO-donors can induce immediate headache (code: 8.1.1.1) which occurs in normal volunteers and in migraineurs, and delayed headache (code: 8.1.1.2) developing in primary headache sufferers one to several hours after the administration of the inducing substance. Headache is typically bilateral, pulsating and fronto-temporal in location.

Nicorandil is a nicotinamide ester with potassium channel opening and nitrate-like activity. Nicorandil

produces vascular smooth muscle relaxation by increasing potassium flux through adenosine triphosphate sensitive sarcolemmal potassium channels. The dual mechanism of action of nicorandil produces coronary vasodilatation as well as vasodilatation of both peripheral arteries and veins. Oral nicorandil is effective in the treatment of stable angina and may be used as an alternative to nitrates. The predominant adverse effect of the drug is headache which can be therapy-limiting, especially within the first 2 week [86, 87].

Molsidomine is a prodrug, rapidly converted into a nitric oxide donor. It is a coronary vasodilator used in the treatment of angina. As with other vasodilators, headache and dizziness are frequently reported adverse effect of this drug [88].

Pentoxifylline's side effects include headache and dizziness. These effects could be related to increased tissue perfusion induced by the drug. However, pentoxifylline does not appear to be a direct vasodilator; it reduces blood viscosity inhibiting phosphodiesterase and thus increasing cyclic AMP in blood cells [89].

ANTI-INFECTIVE AGENTS

Different classes of antimicrobial agents can cause headache (Table 2). Pharmacokinetic characteristics, influencing tissue distribution and brain penetration, may play a role in determining whether an anti-infective agent can or not provoke headache.

Doxycycline and **minocycline** have long half-life values and are widely distributed into various body fluids, CSF included. Cases of benign intracranial hypertension (pseudotumor cerebri), presenting with severe headache, dizziness, blurred vision (resolved upon discontinuation), have been caused by both drugs [90, 91]. However, also other tetracyclines are capable of producing elevated intracranial pressure [91]. **Quinolones**, especially **fluoroquinolones**, have been frequently associated with CNS toxicity including headache, confusion, dizziness, and seizures. These effects may be related to pharmacokinetic properties, and in particular to the high concentrations reached by the drugs in the cerebrospinal fluid, in part due to the presence of fluorine atoms [92]. CNS toxicity, in fact, can be severe with **floxacin**, which presents three fluorine atoms [93]. The elimination half-life of floxacin is approximately 10 hours, longer than many other quinolones, and cerebrospinal fluid concentrations of the drug are 20-32% of the corresponding plasma levels [94]. Headache has not been associated with **pipemidic acid**, a second-generation quinolone, with elimination half-life values of 2-4 hours. This drug accumulates in urine and does not penetrate central nervous system [95]. **Macrolides** are widely distributed in the body but do not penetrate well into CNS in the absence of meningeal inflammation. Nevertheless, these antimicrobials have been associated with headache and other central nervous system side effects [96, 97]. The incidence of headache has been somewhat higher (occasionally reaching statistical significance) with **dirithromycin**, than that observed with other macrolides, including **erythromycin** and **roxithromycin** [98]. The mechanism of action of dirithromycin is like that other macrolides but this drug presents longer elimination half-life (about 44 hours), and higher tissue penetration than both erythromycin

(elimination half-life: 1-1.5 hours) and roxithromycin (elimination half-life: 12 hours) [96, 99].

Table 2. Percentages of Headache, as an Adverse Effect, that have been Associated with Anti-Infective Agents

Drugs	% of Headache	Notes	Ref.
<i>Antimicrobics</i>			
Dirithromycin	2-9		[285]
Erythromycin	8.2		[97]
Mupirocin	9		[102]
Roxithromycin	1.5-5		[96]
Piperacillin-tazobactam	7.7		[100]
Nitrofurantoin	4-6	°	[286]
Clinfloxacin	27	°	[92]
Floxacin	40-90	°	[93]
Levofloxacin	5.4	°	[287]
Lomefloxacin	28-44	°	[288]
Ofloxacin	5.8	°	[289]
<i>Antifungals</i>			
Fluconazole	7-13		[103]
Terconazole	9	*, \$	[104]
<i>Antivirals</i> [§]			
Amantadine	1-5	+	[120]
Acyclovir	0.6-5.9		[110]
Famciclovir	5	*	[111]
Valacyclovir	2	*, #	[112]
Ganciclovir	4-6	ç	[118]
Foscarnet	26		[117]
Abacavir	7-13	*	[290]
Amprenavir	10		[291]
Didanosine	6-12	ç	[108]
Lamivudine	35	ç	[106]
Nevirapine	33		[292]
Stavudine	35-54	ç	[107]
Zidovudine	5	*, +	[293]

*percentages of headache net of percentages of headache induced by placebo.

°the drug has been associated with peripheral neuropathy.

°the drug has been associated with dose-related headache.

°the drug has been associated with benign intracranial hypertension.

°the drug has been associated with flu-like syndrome.

§all drugs of the class have been associated with headache.

the drug has been associated with aseptic meningitis.

Piperacillin, too, penetrates well into the cerebrospinal fluid through inflamed meninges. In clinical trials, headache was reported in less than 10% of patients treated with the combination of piperacillin/tazobactam [100]. **Cotrimoxazole**, an agent comprised of **trimethoprim** and **sulfamethoxazole**, has been associated with headache, aseptic meningitis, and benign intracranial hypertension [101].

Mupirocin is recommended as adjunctive therapy to infection-control programs to reduce the risk of infection among the patients during methicillin-resistant *Staphylococcus aureus* outbreaks. In clinical trials this drug has been reported to cause headache [102].

Some **antifungal agents** used for the treatment of candidiasis and other mycoses produces CNS side effects, including headache and dizziness. In addition, **fluconazole** has been reported to cause seizures [103], and **terconazole** a flu-like syndrome [104]. In the case of fluconazole, these effects may be related to the pharmacokinetic properties: low protein-binding and high levels of the drug in the cerebrospinal fluid [103].

Headache, not dose-related, is a common symptom developing during treatment of HIV infection with almost all **antiretroviral agents**. Other frequent CNS side effects of these agents are insomnia, dizziness, lethargy, asthenia, and fatigue [105]. In addition, peripheral neuropathy has been reported in association with **lamivudine, stavudine and didanosine** [106-109]. Also antiviral agents indicated in the treatment of herpes zoster and herpes simplex infections (**acyclovir, famciclovir, and valacyclovir**), can cause headache and other neurologic side effects such as dizziness, somnolence, and fatigue [110-114]. The risk of neurotoxicity seems to be higher with valacyclovir, which has been associated with cases of aseptic meningitis [115]. The primary adverse reactions of **foscarnet**, an antiviral used in the treatment of cytomegalovirus infections, are nephrotoxicity and anaemia. However, CNS side effects, such as headache, dizziness, and even seizures, have been reported with this drug [116, 117]. **Ganciclovir**, another antiviral effective in the treatment of cytomegalovirus infection, has been associated with headache, peripheral neuropathy and encephalopathy [118, 119]. Also **amantadine**, an antiviral agent for the prophylaxis of influenza (also increasing dopaminergic activity), has been associated with headache, dizziness, confusion, disorientation, depression, seizures, and mood alteration, especially in elderly patients [120, 121].

Finally, **praziquantel**, a trematocide for oral treatment of schistosome infections, has been reported to provoke headache, fever, dizziness, drowsiness and convulsions. These symptoms usually resolve by 48 hours after drug discontinuation [122].

IMMUNOSUPPRESSANT AND IMMUNOMODULATORY AGENTS

Among **immunosuppressant agents**, **tacrolimus** is the drug most commonly associated with CNS adverse effects, including headache, tremor, insomnia and dizziness (Table 3). Headache may respond to dosage reduction [123]. Severe neurotoxicity and leukencephalopathy requiring treatment withdrawal have also been reported [124]. The use of **sirolimus** has been associated with fewer than tacrolimus headache and other CNS reactions [125]. With **mycophenolic acid**, high incidence of headache (54.3%) has been observed, in particular after cardiac transplantation [126, 127]. The most common adverse effect of **cyclosporine** is nephrotoxicity; however, headache, neurotoxicity and severe leukencephalopathy with generalized tonic-clonic seizures have also been reported. These conditions have been attributed to enhance penetration of cyclosporine into the CNS [128].

Leflunomide is an immunomodulatory agent. In post marketing surveillance, sepsis and severe hepatic injury have been observed. In clinical trials, the drug was associated with

less important symptoms such as headache, dizziness and reversible peripheral neuropathy [129, 130].

Table 3. Percentages of Headache, as an Adverse Effect, that have been Associated with Immunosuppressives and Immunomodulants

Drugs	% of Headache	Notes	Ref.
Immunosuppressives			
Cyclosporine	2-15	°	[128]
Leflunomide	7	ç, #	[129]
Mycophenolate	16-21		[126]
Sirolimus	23-34		[125]
Tacrolimus	4-11*/37-64	&, +	[123]
Interleukins[§]			
Interleukin-3	20-30	&	[132]
Interleukin-4	17-100		[133]
Interleukin-6	up to 100		[134]
Interleukin-10	up to 80		[135]
Interferons[§]			
Alfa-2a Interferon	5	*, +	[141]
Alfa-2b Interferon	39-61	+	[142]
Beta-1a Interferon	3	*, +	[138]
Beta-1b Interferon	7	*, &	[143]
Gamma-1b Interferon	24	*	[294]

*percentages of headache net of percentages of headache induced by placebo.

°headache causing discontinuation of the drug.

çthe drug has been associated with peripheral neuropathy.

#the drug has been associated with dose-related headache.

°the drug has been associated with benign intracranial hypertension.

§the drug has been reported to cause flu-like syndrome.

¶the drug has been associated with aseptic meningitis.

The predominant adverse effects after intravenous or subcutaneous **interleukins** administration are flu-like symptoms such as fever, headache with neck stiffness, chills, vomiting, lethargy, fatigue. Headache usually subsides within 24 hours following the dosing interval but, in some patients, its severity precluded further treatment [131-135]. **Interferons** are naturally occurring cytokines, possessing a variety of biological functions: antitumor, antiviral, and immunomodulating activity. The most common toxicity of interferons, as a class, resembles that of interleukins: headache, fatigue, dizziness, lethargy, fever, nausea. These flu-like symptoms appear to be dose-related and usually subside after drug discontinuation [136, 137]. Headache was the most common adverse effect of **interferon beta-1a** in clinical trials, and also migraine was reported [138]. Flu-like symptoms and aseptic meningitis can develop also following **immune globulin** infusion [139]. This condition could be related to cytokine release, and it is more likely to develop in patients with a history of migraine [140]. Fatal or life-threatening neuropsychiatric disorders and peripheral neuropathy have been associated, in particular, with **interferon alfa-2a and alfa-2b** [141, 142]. Neurotoxic effects of high dose of **interferon beta-1b** caused treatment discontinuation in 10% of malignant glioma patients [143].

ANTI-INFLAMMATORY AGENTS, ANTIHISTAMINICS, AND DRUG USED IN THE TREATMENT OF ASTHMA

Corticosteroids are used for a wide variety of clinical conditions. **Fluticasone, mometasone, budesonide** and

triamcinolone are topical corticosteroids indicated for treatment of allergic rhinitis and asthma. Mild or moderate headache is a common adverse effect after nasal administration of these drugs (Table 4), occurring usually, during the first week of treatment [144-147]. In addition, long-term use of corticosteroids, in particular of triamcinolone and prednisone, can cause benign intracranial hypertension (pseudotumor cerebri) presenting with severe headache. Intracranial hypertension seems to occur more frequently in children, and following a rapid decrease in the corticosteroid dosage [148].

Table 4. Percentages of Headache, as an Adverse Effect, that have been Associated with Anti-Inflammatory Agents, Antihistaminics and Drugs for Asthma

Drugs	% of Headache	Notes	Ref.
<i>Corticosteroids^o</i>			
Budenoside	13-14	*	[146]
Fluticasone	1.5	*	[144]
Mometasone	26		[145]
Triamcinolone	18		[147]
<i>Non Steroidal Anti-Inflammatory Drugs[§]</i>			
Fenoprofen	8.7		[295]
Indomethacin	11.7	°	[151]
Ketorolac	17	*	[296]
Diclofenac	7	#	[297]
Naproxen	3-9	#	[298]
Parecoxib	5		[299]
<i>Antihistaminics (H1 receptor antagonists[§])</i>			
Azelastine	2.1	*	[162]
Terfenadine	4.6	*	[164]
<i>Beta-2 adrenergic agonists[§]</i>			
Procaterol	13		[166]
<i>Xantine derivate</i>			
Enprofylline	20-80	+	[168]

^opercentages of headache net of percentages of headache induced by placebo.

[§]all drugs of the class have been associated with headache.

[°]the drug has been associated with dose-related headache.

^othe drug has been associated with benign intracranial hypertension.

⁺the drug has been associated with aseptic meningitis.

With **nonsteroidal anti-inflammatory drugs (NSAIDs)**, CNS complaints are less common than gastrointestinal complaints [149]. These drugs are analgesic agents, effective in a variety of pain syndromes, including acute and prophylactic treatment of migraine [150]. However, headache, dizziness and drowsiness have been reported during clinical trials with almost all NSAIDs, either with cyclooxygenase (COX)-1 selective agents, such as **fenoprofen**, or non selective agents as **nabumetone**, or COX-2 selective agents as **rofecoxib** [149]. In particular, frontal headache is the most common adverse effect of therapeutic doses of **indomethacin** [151]. Indomethacin produces vasoconstriction in the carotid area with a consequent reduction of cerebral blood flow. After withdrawal of the drug, or within 24 hours after a single dose, compensatory vasodilatation occurs. This may result in

a severe symmetrical and pulsating headache [152]. In addition, aseptic meningitis is an infrequent but well described adverse effect of **ibuprofen**, **diclofenac**, **naproxen**, and rofecoxib [153-156]. Patients present headache, fever, chills, nausea, vomiting, changes in mental status, and neck stiffness. Symptoms usually subside within 24-48 hours after stopping the drug. An antigen-specific mechanism has been suggested for this adverse reaction, not dose-related, that was especially seen in patients with lupus erythematosus and other collagen vascular disease. Most patients develop meningitis shortly after beginning a second course of an NSAID, following a period of drug discontinuation [157-160].

Antihistaminics have many pharmacological actions primarily due to their ability to inhibit physiological effects which result from histamine release. The most common side effect experienced with therapeutic dose of histamine H₁ antagonists, is sedation. However, they occasionally cause also headache [161]. In particular, headache is the most common adverse effect reported either with intranasal or ophthalmic **azelastine** [162]. **Terfenadine** has been removed from the market for serious cardiovascular toxicity (QT interval prolongation) [163]. Nevertheless, this drug has also been associated with headache [164].

Almost all **beta-2 adrenergic agonists**, bronchodilators used in the treatment of asthma, can cause headache, tremor, agitation, insomnia and dizziness. These adverse effects could be partially related to minimal effects on beta-1 receptors, even at usual doses [165-167].

Enprofylline is a xantine derivative used intravenously in the treatment of acute asthma. CNS effect of the drug include dose-related, pulsating headache and nausea, subsiding after one week of treatment. The mechanism of these adverse effects has been suggested to be adenosine antagonism [168].

GASTROINTESTINAL AGENTS

H2 receptor antagonists (Table 5), that inhibit histamine evoked gastric acid secretion and are effective in treating duodenal and gastric ulcers, have been associated with headache as the most frequent CNS adverse effect [169]. Severe headache, causing drug discontinuation, has been described with **famotidine** [170]. **Cimetidine** has been associated with more severe neurotoxicity (delirium, hallucinations, depression) in elderly and severely ill patients; in some of these cases high concentrations of cimetidine in CSF fluid were detected [171].

Also **proton-pump inhibitors**, which specifically suppress gastric acid secretion, have been associated with headache as a common adverse effect and even with tension-type and migraine headache. The symptom seems to be more frequent in female gender, and it is not dose-related [172, 173].

Headache is the most common adverse effect of selective **serotonergic (5HT₃) receptor antagonists** as a class. These drugs inhibit emesis mediated through 5HT₃ receptors both in the periphery and in CNS. Headache is generally mild or moderate, severe only in a small number of patients and not related to the dose [174-176]. However, in paediatric patients with prior history of migraine, **ondansetron** therapy

precipitated migraine attacks. Prophylaxis with topiramate and gabapentine, and analgesics such as acetaminophen, were effective in controlling headache in these patients [177].

Table 5. Percentages of Headache, as an Adverse Effect, that have been Associated with Gastrointestinal Agents

Drugs	% of Headache	Notes	Ref.
<i>H₂ receptor antagonists</i>			
Cimetidine	0.6	*, °	[171]
Famotidine	1.3-4.7	#	[300]
Nizatidine	1	*	[301]
Ranitidine	1.4		[302]
<i>Proton pump inhibitors</i>			
Lansoprazole	4.7	%	[172]
Omeprazole	0.6		[173]
<i>5HT₃ antagonists[§]</i>			
Dolasetron	5-58		[175]
Granisetron	8	*	[176]
Ondansetron	3-10	*, ±	[177]
Tropisetron	22-35		[174]
<i>Prokinetic</i>			
Cisapride	2.2	*	[178]
<i>Others</i>			
Sulfasalazine	33	ç, ±, #	[303]
Mesalamine	6.5	±	[181]

*percentages of headache net of percentages of headache induced by placebo.

[§]all drugs of the class have been associated with headache.

°the drug has been associated with benign intracranial hypertension.

#the drug has been associated with migraine headache.

çthe drug has been associated with peripheral neuropathy.

#the drug has been associated with aseptic meningitis.

In clinical trials, headache has been frequently associated also with **cisapride**. However, this prokinetic drug has been withdrawn from the market for serious and sometimes fatal cardiovascular toxicity [178].

Sulfasalazine is a conjugate of **5-aminosalicylic acid** and **sulfapyridine** used in the treatment of ulcerative colitis and in rheumatoid arthritis. The main mechanism of its action seem to be inhibition of the lipoygenase pathway. Headache, vertigo, ataxia, peripheral neuropathy, encephalopathy, and aseptic meningitis are adverse effects observed with sulfasalazine. This neurotoxicity could be due to folic acid deficiency developing during sulfasalazine therapy [179, 180]. **Mesalamine** (5-aminosalicylic acid) is believed to be the active moiety of sulfasalazine, while sulfapyridine is thought to be responsible for side effect. However, headache, dose related, and sometimes of severe intensity, has been reported in clinical trials also with this agent [181].

HORMONAL AGENTS

Different hormonal agents have been associated with headache (Table 6): mild, and controlled with common analgesics, after **mifepristone**, a progesterone receptor antagonist [182]; more rarely with **danazol**, an

antigonadotropic agent [183]; and relatively more frequently with **droloxifene**, a nonsteroidal antiestrogen [184].

Table 6. Percentages of Headache, as an Adverse Effect, that have been Associated with Hormonal Agents and Dopamine Agonists

Drugs	% of Headache	Notes	Ref.
<i>Gonadotropin inhibitors</i>			
Bicalutamide	7		[185]
Danazol	16	*	[183]
Droloxifene	1-10		[184]
Mifepristone	15		[182]
<i>Other hormonal agents</i>			
Leuprolide	26	*	[188]
Octreotide	6		[187]
Progesterone	16	°	[186]
<i>Dopamine receptor agonists</i>			
Bromocriptine	0.3	*, ±	[191]
Quinagolide	5-20	±	[189]

*percentages of headache net of percentages of headache induced by placebo.

°the drug has been associated with benign intracranial hypertension.

#the drug has been associated with migraine headache.

During therapy with **bicalutamide**, a nonsteroidal antiandrogen, indicated to treat prostate cancer, headache, dizziness, fatigue, confusion have been reported [185].

Dizziness and headache have been commonly reported also with **progesterone** [186] and with **octreotide**, a long-acting somatostatin analogue [187]. In addition, vasomotor hot flashes and headache have been frequently reported with **leuprolide**, a gonadotropin-releasing hormone analogue, especially during treatment with depot preparation [188].

Dopamine agonist drugs, **bromocriptine** and **quinagolide**, used primarily in hyperprolactinemic states, have been associated with headache, dizziness, fatigue and somnolence. The symptoms are most frequent during initiation of the treatment and tend to subside with continued use [189]. However, they occasionally cause withdrawal of the therapy [190]. In addition, bromocriptine, but not quinagolide, has been associated with unilateral neuralgiform headache attacks resembling SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) syndrome in 2 patients with pituitary adenomas [191].

During therapy with **estrogens** (alone or in combination with **progestins**), natural hormones, synthetic steroidal and nonsteroidal compounds, used for a number of purposes, headache and dizziness have been commonly reported but the incidence is not clear [192-199]. Benign intracranial hypertension has been reported with the use of combination of **mestranol** and **norethindrone** [200]. In particular, headache is a common side effect reported with **combination oral contraceptives**. Headaches that worsen in frequency or severity have been reported in 18-50% of cases, with many attacks occurring during the drug-free interval of the cycle. The mechanism of attacks of migraine that occur during pill-free interval is estrogen withdrawal [201, 202]. Migraine can begin during combination oral contraceptives

use, usually during the first cycles, and sometimes after prolonged use. New onset migraines occur more often in women with a family history of migraine [202]. Also **hormonal replacement therapy** with estrogens can exacerbate migraine or change its frequency and character [203, 204]. ICHD-II classification [23] includes "oestrogen-withdrawal headache (code: 8.4.3)", and "exogenous hormone-induced headache (code: 8.3.1)".

CENTRAL NERVOUS SYSTEM (CNS) DRUGS

Headache is a common side-effect of quite different classes of CNS drugs (Table 7). Mild or moderate headache is one of the primary adverse effects, among those involving CNS, of **tramadol**, an analgesic with low affinity for mu opioid receptors [205]. In clinical trials with controlled-release **morphine**, headache was reported in 10% of patients [206]. Also with mixed opioid agonist and antagonist analgesics, **dezocine** and **buprenorphine**, headache has been reported [207, 208].

Numerous atypical antipsychotics have been occasionally associated either with headache, dizziness and somnolence [209] or with headache, dizziness and insomnia, as is the case of **quetiapine**, a drug with less anticholinergic and antiadrenergic effects [210]. With **risperidone** migraine headache has been observed [211, 212].

Headache has been frequently associated with **adinazolam** [213], a triazolobenzodiazepine; with short or long acting hypnotics such as, respectively, **triazolam** and **quazepam** [214, 215]; and, finally, with **diazepam** and **clobazam**, benzodiazepines used also in the treatment of epilepsy [216].

Antidepressants, too, even with quite different suggested mechanism of antidepressant action, have been associated with headache. **Bupropion**, lacking anticholinergic activity, has been commonly associated with headache and also migraine [217]. Headache is among the most frequent CNS side effects of **clovoxamine**, and **milnacipram**, inhibitors of neural reuptake of both serotonin and norepinephrine [218, 219]; headache has been reported during treatment with **fluvoxamine**, **fluoxetine**, **paroxetine**, and **sertraline** [220-223], specific inhibitors of serotonin reuptake [224]. Headache is a frequent adverse effect of **rolipram**, a selective phosphodiesterase inhibitor [225] and also of **tianeptine**, whose mechanism of action is unclear [226]; in addition, **venlafaxine**, an inhibitor of serotonin, norepinephrine, and dopamine reuptake [227], and **nefazodone**, that also possesses 5-HT₂ antagonist properties, and that may have a rationale to be used in migraine prophylaxis [228], and even **trazodone**, used in headache prophylaxis, nevertheless have been commonly associated with headache [229]. Headache, not related to increases in blood pressure, was seen even with **moclobemide**, a selective and reversible inhibitor of monoamine oxidase-A [230]. Finally, **viloxazine**, an inhibitor of norepinephrine but not of serotonin reuptake, caused also migraine headache with nausea in the absence of history of migraine [231].

Finally, headache, dizziness, agitation and insomnia are common, dose-related, events with **modafinil**, a central nervous system stimulant (alfa-1 adrenoceptor agonist), indicated for treatment of excessive daytime sleepiness associated with narcolepsy [232].

Table 7. Percentages of Headache, as an Adverse Effect, that have been Associated with Central Nervous System (CNS) Drugs

Drugs	% of Headache	Notes	Ref.
<i>Opioid analgesics</i>			
Buprenorphine	1-5		[208]
Dezocine	16-35		[207]
Morphine	10		[206]
Tramadol	10-15		[205]
<i>Antipsychotics</i>			
Clozapine	7-9		[304]
Olanzapine	2	*	[305]
Quetiapine	14		[210]
Risperidone	2	*, ±	[212]
Ziprasidone	up to 30		[306]
Zotepine	7-10		[307]
<i>Sedative-Hypnotics</i>			
Adinazolam	up to 30		[213]
Clobazam	11		[216]
Diazepam	2	*	[216]
Quazepam	2.3-4.5	*	[215]
Triazolam	1.3	*	[214]
<i>Antidepressants</i>			
Bupropion	3.1	*, ±, &	[217]
Clovoxamine	22-50		[218]
Fluoxetine	4.8	*	[221]
Fluvoxamine	22	*	[220]
Milnacipram	8		[219]
Moclobemide	5-15		[230]
Nefazodone	3	*	[228]
Paroxetine	0.2	*	[222]
Rolipram	up to 20		[225]
Sertraline	1.3	*	[223]
Tianeptine	up to 18		[226]
Trazodone	3.2-7	*	[229]
Venlafaxine	25	±	[227]
Viloxazine		±	[231]
<i>Stimulant</i>			
Modafinil	50	+	[232]

*percentages of headache net of percentages of headache induced by placebo.

†the drug has been associated with migraine headache.

‡headache causing discontinuation of the drug.

§the drug has been associated with dose-related headache.

MISCELLANEOUS AGENTS

Sibutramine is a nonamphetamine appetite suppressant that may also have antidepressant properties (Table 8). It blocks neuronal reuptake of norepinephrine, serotonin, and to a lesser extent, dopamine. Headache, insomnia, constipation, irritability, tachycardia are among the most common side effects of the drug in the treatment of obesity [233].

Table 8. Percentages of Headache, as an Adverse Effect, that have been Associated with Miscellaneous Agents

Drugs	% of Headache	Notes	Ref.
<i>Anti-obesity agent</i>			
Sibutramine	30.3	±	[233]
<i>Smoking cessation aid</i>			
Nicotine	20-29		[234]
<i>Statin</i>			
Lovastatin	4.4	*, †	[235]
<i>Erythropoietins[§]</i>			
Epoetin alfa	4-5		[238]
Darboepoetin alfa	16		[239]
<i>Retinoids analogs[§]</i>			
Alitretinoin	40-70	°, &	[240]
Tretinoin	30-85	°, &	[242]
<i>Antineoplastic</i>			
Tegafur	70	&	[243]
<i>Prostaglandins[§]</i>			
Alprostadil	20		[248]
Dinoprostone	10		[251]
Enprostil	9.8		[250]
Iloprost	70	+	[249]
<i>Agents for erectile dysfunction[§]</i>			
Sildenafil	11-16	*, ±	[246]
Tadalafil	16.7	+, &	[244]
Vardenafil	9	+, &	[245]

*percentages of headache net of percentages of headache induced by placebo.

†all drugs of the class have been associated with headache.

°the drug has been associated with migraine headache.

‡headache causing discontinuation of the drug.

§the drug has been associated with dose-related headache.

¶the drug has been associated with peripheral neuropathy.

⊕the drug has been associated with benign intracranial hypertension.

Headache is also a reported effect with the use of **nicotine** transdermal patch. Other neurologic reactions during therapy of smoking cessation with transdermal nicotine include sleep disturbances, dizziness and nervousness. However, all these symptoms resemble those which develop also during nicotine abstinence syndrome [234].

Lovastatin is an inhibitor of 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol synthesis. The drug effectively lowers plasma cholesterol and is generally well tolerated. However, transient headache, insomnia, dizziness, irritability, and peripheral neuropathy have been reported with lovastatin [235]. Headache has been occasionally observed also during treatment with other statins, such as **simvastatin** and **pravastatin**. It is unclear whether these effects are related to statin therapy or result from lowered cholesterol [236, 237].

The most prevalent adverse effect associated with **epoetin alfa** and **darboepoetin alfa** therapy is hypertension, but headache has been also reported [238]. The drugs are forms of erythropoietin, indicated for the treatment of

anaemia due to chronic renal failure or antitumoral chemotherapy administration [239].

Tretinoin (all-trans-retinoic acid) is a retinoid derived from naturally occurring all-trans retinol (Vitamin A1). Following oral tretinoin, toxicity is similar to that of vitamin A, including increased CSF pressure and severe occipital headache, in the majority of patients with acute promyelocytic leukaemia [240]. Some patients, particularly children, develop frank pseudotumor cerebri and papilledema. This condition can be treated with acetazolamide, an agent able to decrease CSF production [241]. **Alitretinoin** action and toxicity profile is similar to tretinoin [242].

Even if **tegafur** is considered to be a prodrug of 5-fluorouracil, its toxicity is different from the latter drug. Neurotoxicity, including headache, dizziness, confusion, sedation, and lethargy, is common, in particular following intravenous administration. Neurologic adverse reactions can be dose-limiting in numerous patients treated with tegafur for gastrointestinal and other malignancies [243].

Headache and facial flushing are the most frequent adverse effects of phosphodiesterase type 5 (PDE5) inhibitors used for the treatment of **erectile dysfunction** [244-246]. The drugs are selective but not specific for PDE5 and therefore inhibition of other phosphodiesterase isoenzymes could be responsible for the adverse effects including headache and changes in colour vision. For example, **sildenafil** also weakly inhibits phosphodiesterase type-6 and 11. This last phosphodiesterase isoenzyme 11, is present in CNS and its inhibition could lead to cerebral vasodilatation [247]. In migraine patients, sildenafil, usually induces a migraine attack. ICHD-II classification [23] includes criteria for phosphodiesterase (PDE) inhibitor induced headache (code: 8.1.2.).

During **alprostadil** administration the most common adverse reactions are headache, dizziness, flushing, nausea and tachycardia. These effects are related to the vasodilatation induced by the drug, which is identical to the naturally occurring prostaglandin E 1 (PGE 1) [248]. Also with **iloprost** infusion, as with alprostadil, the most common adverse effects include flushing and headache as a consequence of vasodilatation. In fact the drug is analogue of prostacyclin (PGI 2), a potent vasodilating agent. Headache is dose-related and subsides rapidly after discontinuance of the infusion [249]. Diarrhoea is the most common adverse effect reported with **enprostil** in the treatment of peptic ulcers. However, either with this synthetic prostaglandin E 2 (PGE 2) analogue [250] or with **dinoprostone**, a natural PGE 2 used for induction of labor, mild headache is a relatively frequent side effect [251].

DISCUSSION

Headache as an adverse effect to drugs is extraordinarily common. More than one thousand drugs, with quite different mechanisms of action, can induce headache. Headache is also one of the most frequent complaints attributed to placebo [252]. Two major pathogenetic mechanisms of headache as an adverse reaction have been classically considered: vasodilatation and intracranial hypertension [253]. The first, vasodilatation, explains headache induced by most cardiovascular drugs, for example calcium channel

blockers and ACE inhibitors. Here, headache is often an extension of the primary pharmacological action of the drug and appear a true side-effect ("any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug") [254]. Headache induced by intracranial hypertension secondary to drugs really is a true adverse reaction. It is a cardinal symptom of benign intracranial hypertension (pseudotumor cerebri) and is progressive, diffuse, worsened by coughing or straining. Other symptoms or signs include nausea, vomiting, intracranial noises, tinnitus, papilloedema or visual field defect (progressive if untreated), and sixth nerve palsy. CSF pressure is increased but chemistry and cellularity are normal. The prognosis is generally good but the progressive visual loss and eventual blindness are a major risk. The pathogenesis of benign intracranial hypertension is not completely understood [255-257]. In the case of corticosteroids it is possible that the sodium retaining properties of these hormones may be involved in the development of this condition [253].

The mechanism of headache is yet unknown for many classes of drugs. Perhaps, a complete understanding of primary headaches pathogenesis could help also to explain drug-induced headache and why agents such as some beta-blockers reduce the frequency of migraine but can induce headache as an adverse effect [68, 69]. The mode of action of beta-blockers in migraine prophylaxis is not clear; one hypothesis involves reduction of brain catecholaminergic hyperactivity. Only agents without intrinsic sympathomimetic activity are effective against migraine [258].

Considerable evidence suggests that there is a link between migraine and the female sex hormones [259]. Migraine occurrence is strongly influenced by the hormonal fluctuations of the female reproductive cycle; at least 60% of women affected by migraine relate the periodicity of their attacks to the menstrual cycle [260]. Hormonal contraceptive use during the reproductive years or hormone replacement in menopause are interventions that may cause a change in headache prevalence or intensity [202]. It is speculated that the estrogens could alter sympathetic control of cerebral vasculature [201] but little research has been undertaken on the possible mechanisms for these adverse changes in migraine [202].

Beyond drugs, individual variations in pharmacogenetic profiles, the immune system, drug metabolic pathways, are some important factors that could play a role in the likelihood of headache as an adverse effect [13].

Headache as an adverse reaction to drugs occurs at therapeutic dose levels. However, headache is a symptom typical of many intoxications, such as local anaesthetic intoxications [261]. There are also headaches that develop after abrupt withdrawal of antihypertensive drugs such as clonidine, beta-blockers, methyldopa, and guanabenz, and are associated with other symptoms of sympathetic overactivity including nervousness, tachycardia, agitation, and nausea [262].

Most headaches as adverse reactions are dose-related, as occurs generally for the majority of the other adverse reactions [1, 13]. As a consequence, they can be treated by

simply decreasing drug dosage to that minimal effective; on the other hand, they can also result from pharmacokinetic drug-interaction when a drug (for instance, by means of enzymatic inhibition) increases plasma concentrations of another one with the potential of inducing headache.

Headache caused by aseptic meningitis is rare and not dose-related. The clinical presentation includes fever, neck stiffness, confusion, nausea and vomiting. The diagnosis is difficult and infectious aetiologies must be excluded. Examination of CSF shows lymphocytic pleocytosis, mildly elevated protein and normal glucose in the absence of infectious organisms. The major categories of causative agents are non-steroidal anti-inflammatory drugs, antimicrobials and also intravenous immunoglobulins. The most likely mechanism seems to involve an immunological response [157-160].

Headache, as an adverse reaction, has not a typical feature or is not well defined in the literature but most such headaches are dull, continuous, diffuse and moderate to severe in intensity. In several cases, the headache is associated with other symptom such as dizziness, fatigue, drowsiness or agitation, tremors, and insomnia. Besides headache, many drugs have been associated with peripheral neuropathy, seizures, and encephalopathy. Here, headache may be an early signal of serious conditions that, if recognized, can be resolved discontinuing the causal drug.

Some drugs, indicated in the tables, are able to provoke true migraine attacks, especially in migraineurs. This is the case of NO donors used in order to induce and study migraine [263].

Even when headache is an adverse effect of a whole class of drugs, there are differences among single substances that allow to prescribe the one inducing the lowest incidence of headache to an headache prone-patient. Migraineurs in particular are vulnerable to a variety of internal and external stimuli, including drugs. However, in a prospective 3 months study, drugs have been indicated as headache triggers by 1% of both 366 migraineurs and 169 nonmigraineurs [264].

Fortunately, even if headache is a very common adverse effect of drugs, it is usually a non serious symptom; however, mild adverse reactions, such as nausea or headache, often have substantial effect on the patient and can lead to limiting the dose, changing the therapy, or decreasing compliance [7]. In addition, a recent-onset or changed headache may induce clinician to prescribe laboratory or instrumental examinations to diagnose it and further drugs to treat it, while the solution is another one: to discontinue drugs.

When a clinician faces with a patient who complains of headache, the possibility of an adverse reaction to a drug should always be taken into consideration, and the collection of a thorough history of prior and/or current drug intake should be customary procedure. Finally, it should be borne in mind that a very close temporal relation to the drug exposure does not prove causation, because headache can occur just on the basis of chance.

CONCLUSION

Headache has been reported following the intake of a number of drugs, but the mechanism is generally unknown.

Headache is so ordinary a symptom that it has been often disregarded; it does not obtain the same emphasis as more striking and rare adverse reaction. Nevertheless, it may be highly disturbing, particularly if it is long-lasting and worrisome for the patient, and may be a signal of further serious neurotoxicity. Therefore, it would be of great interest to clinicians to know what drugs are quite frequently associated with headache as an adverse reaction.

REFERENCES

- [1] Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. *Br J Clin Pharmacol* 1992; 34: 377-95.
- [2] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; 279: 1200-5.
- [3] Bates DW, Miller EB, Cullen DJ, *et al.* Patient risk factors for adverse drug events in hospitalized patients. ADE prevention study group. *Arch Intern Med* 1999; 159: 2553-60.
- [4] van den Bemt PM, Egberts AC, Lenderink AW, *et al.* Risk factors for the development of adverse drug events in hospitalized patients. *Pharm World Sci* 2000; 22: 62-6.
- [5] Gurwitz JH, Field TS, Harrold LR, *et al.* Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; 289: 1107-16.
- [6] Kaufman DW, Shapiro S. Epidemiological assessment of drug-induced disease. *Lancet* 2000; 356: 1339-43.
- [7] Neidig JL, Koletar SL. Safety reporting in clinical trials. *JAMA* 2001; 285: 2077-8.
- [8] Ioannidis JPA, Lau J. Improving safety reporting from randomised trials. *Drug Saf* 2002; 25: 77-84.
- [9] Gandhi TK, Weingart SN, Borus J, *et al.* Adverse drug events in ambulatory care. *N Engl J Med* 2003; 348: 1556-64.
- [10] Feldman R, Bacher M, Campbell N, Drover A, Chockalingam A. Adherence to pharmacologic management of hypertension. *Can J Public Health* 1998; 89: 116-8.
- [11] Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol* 1995; 14: 88-90.
- [12] Davies SJC, Jackson PR, Ramsay LE, Ghahramani P. Drug intolerance due to nonspecific adverse effects related to psychiatric morbidity in hypertensive patients. *Arch Intern Med* 2003; 163: 592-600.
- [13] Atuah KN, Hughes D, Pirmohamed M. Clinical pharmacology: special safety considerations. *Drug Saf* 2004; 27: 535-54.
- [14] Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; 356: 1255-9.
- [15] Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002; 287: 622-7.
- [16] Tierney WM. Adverse outpatient drug events—a problem and an opportunity. *N Engl J Med* 2003; 48: 1587-9.
- [17] Trontell A. Expecting the unexpected - drug safety, pharmacovigilance, and prepared mind. *N Engl J Med* 2004; 351: 1385-7.
- [18] Goldstein M, Chen TC. The epidemiology of disabling headache. *Adv Neurol* 1982; 33: 377-90.
- [19] Kryst S, Sherl E. A population-based survey of the social and personal impact of headache. *Headache* 1994; 34: 344-50.
- [20] Rasmussen BK. Epidemiology of headache. *Cephalalgia* 1995; 15: 45-68.
- [21] Mannix LK. Epidemiology and impact of primary headache disorders. *Med Clin North Am* 2001; 85: 887-95.
- [22] Boardman HF, Thomas E, Croft PR, Millson DS. Epidemiology of headache in an English district. *Cephalalgia* 2003; 23: 129-37.
- [23] Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia* 2004; 24 (Suppl. 1): 9-160.
- [24] Henry P, Aurray JP, Gandin AF, *et al.* Prevalence and clinical characteristics of migraine in France. *Neurology* 2002; 59: 232-7.
- [25] MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment patterns: the global migraine and zolmitriptan evaluation survey. *Headache* 2003; 43: 19-26.
- [26] Jensen R. Diagnosis, epidemiology, and impact of tension-type headache. *Curr Pain Headache Rep* 2003; 7: 455-9.
- [27] Finkel AG. Epidemiology of cluster headache. *Curr Pain Headache Rep* 2003; 7: 144-9.
- [28] Osterhaus JT, Gutterman DL, Plachetka JR. Healthcare resource and lost labour costs of migraine headache in the United States. *Pharmacoeconomics* 1992; 2: 67-76.
- [29] Welch KM. Contemporary concepts of migraine pathogenesis. *Neurology* 2003; 61(Suppl. 4): S2-S8.
- [30] Adelman JU, Adelman RD. Current options for prevention and treatment of migraine. *Clin Ther* 2001; 23: 772-88.
- [31] Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl J Med* 2002; 346: 257-70.
- [32] Leicht MJ. Non-traumatic headache in the emergency department. *Ann Emerg Med* 1980; 9: 404-9.
- [33] Smetana GW. The diagnostic value of historical features in primary headache symptoms. *Arch Intern Med* 2000; 160: 2729-37.
- [34] Friedman MA, Woodcock J, Lumpkin MM, Shuren EJ, Hass AE, Thompson LJ. The safety of newly approved medicines. Do recent market removals mean there is a problem? *J Am Med Assoc* 1999; 28: 1728-34.
- [35] Task Force of the International Headache Society. Organization and delivery of services to headache patients. *Cephalalgia* 1977; 17: 702-10.
- [36] Rasmussen BK. Epidemiology of headache. *Cephalalgia* 2001; 21: 774-7.
- [37] Smith TR. Epidemiology and impact of headache: an overview. *Prim Care* 2004; 31: 237-41.
- [38] Ryan RE Jr, Pearlman SH. Common headache misdiagnoses. *Prim Care* 2004; 31: 395-405.
- [39] Ray WA. Population-based studies of adverse drug effects. *N Engl J Med* 2003; 17: 1592-4.
- [40] Ioannidis JPA, Lau G. Completeness of safety reporting in randomized trials. An evaluation of 7 medical areas. *J Am Med Assoc* 2001; 285: 437-43.
- [41] Austin PC, Mamdani M, Williams IJ. Adverse effects of observational studies when examining adverse outcomes of drugs. *Drug Saf* 2002; 25: 677-87.
- [42] Wood AJJ, Stein CM, Woosley R. Making medicines safer—the need for an independent drug safety board. *N Engl J Med* 1998; 339: 1851-4.
- [43] Ross SD. Drug-related adverse events. A readers' guide to assessing literature reviews and meta-analyses. *Arch Intern Med* 2001; 161: 1041-6.
- [44] World Health Organization (1969) Tech Rep 425.
- [45] Sica DA. Calcium channel blocker class heterogeneity: select aspects of pharmacokinetics and pharmacodynamics. *J Clin Hypertens* 2005; 7(Suppl. 1): 21-6.
- [46] Friedel HA, Sorkin EM. Nisoldipine: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of angina pectoris, hypertension, and related cardiovascular disorders. *Drugs* 1988; 36: 682-731.
- [47] Frohlich ED. Calcium antagonists: their physiological differences. *Am J Hypertens* 1991; 4: 430-4.
- [48] Daniels AR, Opie LH. Monotherapy with the calcium channel antagonist nisoldipine for systemic hypertension and comparison with diuretic drugs. *Am J Cardiol* 1987; 60: 703-7.
- [49] Endersby CA, Brown EG, Perelman MS. Safety profile of lacidipine: a review of clinical data. *J Cardiovasc Pharmacol* 1991; 17(Suppl. 4): S45-S47.
- [50] White WB, Sica DA, Calhoun D, Mansoor GA, Anders RJ. Preventing increases in early-morning blood pressure, heart rate, and the rate-pressure product with controlled onset extended release verapamil at bedtime versus enalapril, losartan, and placebo on arising. *Am Heart J* 2002; 144: 657-65.
- [51] Product Information: Cardizem CD(R), diltiazem HCl. Aventis Pharmaceuticals Inc., Kansas City, MO (PI revised 07/2000).
- [52] Kim SY, Benowitz NL. Poisoning due to class I A antiarrhythmic drugs quinidine, lorcaïnamide and disopyramide. *Drug Saf* 1990; 5: 393-420.
- [53] Kerin NZ, Aragon E, Marinescu G, Faitel K, Frumin H, Rubenfire M. Mexiletine: long-term efficacy and side effects in patients with chronic drug-resistant potentially lethal ventricular arrhythmias. *Arch Intern Med* 1990; 150: 381-4.

- [54] McDevitt DG. The clinical pharmacology of lidocaine congeners - Review of encainide, flecainide, lorainide and tocainide. *Eur Heart J* 1984; 5(Suppl. B): 63-6.
- [55] Moncada S, Korbut R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. *Lancet* 1978; 1: 1286.
- [56] Product Information: Persantin(R), dipyridamole intravenous. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, 1995.
- [57] Theis JGW, Deichsel G, Marshall S. Rapid development of tolerance to dipyridamole-associated headaches. *Br J Clin Pharmacol* 1999; 48: 750-5
- [58] Hagemeljer F. Calcium sensitization with pimobendan: pharmacology, haemodynamic improvement, and sudden death in patients with chronic congestive heart failure. *Eur Heart J* 1993; 14: 551-66.
- [59] Vernon MW, Heel RC, Brogden RN. Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991; 42: 997-1017.
- [60] Spah F, Grosser KD. Treatment of hypertensive urgencies and emergencies with nitrendipine, nifedipine, and clonidine: effect on blood pressure and heart rate. *J Cardiovasc Pharmacol* 1988; 12 (Suppl. 4): S154-S156.
- [61] Product Information: Cardura(R), doxazosin. Pfizer Inc, New York, NY (PI revised 06/2000).
- [62] Product Information: Minipress(R), prazosin. Pfizer, New York, NY (PI revised 6/1996).
- [63] Product Information: Flomax(R), tamsulosin. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT (PI revised 9/2000).
- [64] Rasmussen K, Jensen HA. Prazosin in treatment of hypertension. *Br Med J* 1975; 4: 346.
- [65] Stokes GS, Weber MA. Prazosin: preliminary report and comparative studies with other antihypertensive agents. *Br Med J* 1974; 2: 298
- [66] Bush A, Busst CM, Knight WB, *et al.* Cardiovascular effects of tolazoline and ranitidine. *Arch Dis Child* 1987; 62: 241-6.
- [67] Kaplan NM. South western internal medicine conference: difficult-to-treat hypertension. *Am J Med Sci* 1995; 309: 339-46.
- [68] Eichhorn EJ. Do beta-blockers have a role in patients with congestive heart failure? *Cardiol Clin* 1994; 12: 133-42.
- [69] Silberstein SD. Practice parameter: evidenced-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Committee of the American Academy of Neurology. *Neurology* 2000; 55: 754-863
- [70] Rosendorff C, Goodman C, Coull A. Short- and long-term studies of bucindolol in mild to moderate hypertension: efficacy, safety, and exercise responses. *J Clin Pharmacol* 1985; 25: 223-36.
- [71] Glover DR, Tarbit WJ. Overview of clinical trials of dilevalol in essential hypertension. *J Hum Hypertens* 1990; 4(Suppl. 2): 49-53.
- [72] Product Information: Midamor(R), amiloride HCl. Merck & Co., Inc., West Point, PA (PI revised 8/96).
- [73] Reeves WB, Molony DA. The physiology of loop diuretic action. *Semin Nephrol* 1988; 8: 225-33.
- [74] Dahl A, Russell D, Rootwelt K, Nyberg-Hansen R, Kerty E. Cerebral vasoreactivity assessed with transcranial doppler and regional cerebral blood flow measurements: dose, serum concentration, and time course of the response to acetazolamide. *Stroke* 1995; 26: 2302-6.
- [75] Fuller RW, Choudry NB. Increased cough reflex associated with angiotensin converting enzyme inhibitor cough. *Br Med J* 1987; 295: 1025-6.
- [76] Tarlow MM, Scoyni R, Wolf-Klein G. Quinapril-associated acute psychosis in an older woman (letter). *J Am Geriatr Soc* 2000; 48: 1533.
- [77] Oparil S, Dyke S, Harris F, *et al.* The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996; 18: 797-810
- [78] Feldman R, Chattman MS, Lonigro A, *et al.* Tasosartan in patients with essential hypertension: a randomized, double-blind, dose-titration study. *Adv Ther* 1997; 14: 290-303.
- [79] Carson PE. Rationale for the use of combination angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker therapy in heart failure. *Am Heart J* 2000; 140: 361-6
- [80] Baxter T, Eadie CJ. Twenty-four hour plasma profile of sustained-release isosorbide mononitrate in healthy volunteers and in patients with chronic stable angina; two open label trials. *Br J Clin Pharmacol* 1997; 43: 333-5.
- [81] Cleophas TJM, Niemeijer MG, van der Wall EE, *et al.* Nitrate-induced headache in patients with stable angina pectoris: beneficial effect of starting on a low dosage. *J Vasc Dis* 1996; 47: 679-85.
- [82] Olsson G, Allgen J. Is there an optimal prophylactic nitrate therapy? *Eur Heart J* 1991; 12(Suppl. A): 21-3.
- [83] Iversen HK, Olesen J. Nitroglycerin-induced headache is not dependent on histamine release: support for a direct nociceptive action of nitric oxide. *Cephalalgia* 1994; 14: 437-42.
- [84] Bank J. Migraine with aura after administration of sublingual nitroglycerin tablets. *Headache* 2001; 41: 84-7.
- [85] Pahor M, Cecchi E, Fumagalli S, *et al.*, for the Gruppo Italiano di Farmacogilanza nell'anziano (GIFA). Association of serum creatinine and age with headache caused by nitrates. *Clin Pharmacol Ther* 1995; 58: 470-81
- [86] Kukovetz WR, Holzmann S, Poch G. Molecular mechanism of action of nicorandil. *J Cardiovasc Pharmacol* 1992; 20 (Suppl. 2): S1-S7.
- [87] Krumenacker M, Roland E. Clinical profile of nicorandil: an overview of its hemodynamic properties and therapeutic efficacy. *J Cardiovasc Pharmacol* 1992; 20 (Suppl. 3): S93-S102.
- [88] Bertel O, Noll G. Additional molsindomine in refractory unstable angina pectoris. *Cardiovasc Drugs Ther* 1988; 2: 107-111
- [89] Lucas MA. Prevention of post-operative thrombosis in peripheral arteriopathies. Pentoxifylline vs conventional antiaggregants: a six-month randomized follow-up study. *Angiology* 1984; 35: 443-50.
- [90] Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *Br Med J* 2003; 326: 641-2.
- [91] Nagarajan L, Lam GC. Tetracycline-induced benign intracranial hypertension. *J Paediatr Child Health* 2000; 36: 82-3
- [92] Goldstein EJC. Possible role for the new fluoroquinolones (levofloxacin, grepafloxacin, trovafloxacin, cinafloxacin, sparfloxacin, and DU-6859a) in the treatment of anaerobic infections: review of current information on efficacy and safety. *Clin Infect Dis* 1996; 23 (Suppl. 1): S25-S30.
- [93] Wolfhagen MJHM, Hoepelman AIM, Verhoff J. Double-blind, dose-range-finding study of fleroxacin (RO 23-6240; AM-833) for treatment of complicated urinary tract infections. *Antimicrob Agents Chemother* 1990; 34: 409-12
- [94] Stuck AE, Kim DK, Frey FJ. Fleroxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1992; 22: 116-31.
- [95] Klinge E, Mannisto PT, Mantyla J, Hanninen U. Single- and multiple-dose pharmacokinetics of pipemidic acid in normal human volunteers. *Antimicrob Agents Chemother* 1984; 26: 69-73.
- [96] Worm AM. Roxithromycin and erythromycin in chlamydia-negative non-gonococcal urethritis. *Acta Derm Venereol* 1990; 70: 269-71.
- [97] Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. *Drug Saf* 1993; 9: 346-64.
- [98] Derriennic M, Escande JP. Dirithromycin in the treatment of skin and skin structure infections. *J Antimicrob Chemother* 1993; 31(Suppl. C): 159-68
- [99] Sides GD, Cerimele BJ, Black HR, Busch HR, De Sante KA. Pharmacokinetics of dirithromycin. *J Antimicrob Chemother* 1993; 31(Suppl. C): 65-75.
- [100] Product Information: Zosyn(R), piperacillin/tazobactam. Lederle Piperacillin, Inc., Carolina, Puerto Rico (PI revised 4/2003).
- [101] Muller MP, Richardson DC, Walmsley SL. Trimethoprim-sulfamethoxazole induced aseptic meningitis in a renal transplant patient. *Clin Nephrol* 2001; 55: 80-4.
- [102] Product Information: Bactroban(R), mupirocin, 2%. SmithKline Beecham Pharmaceuticals, Philadelphia, PA (revised 5/99).
- [103] Product Information: Diflucan(R), fluconazole. Roerig Division of Pfizer Inc, New York, NY, 1999.
- [104] Product Information: Terazol 3(R), terconazole vaginal cream 0.8% and 80-mg vaginal suppositories. Ortho McNeil Pharmaceutical, Inc, Raritan, NJ, 1998.
- [105] Crowe S, Cooper DA, Chambers D. Antiretroviral therapies for HIV. *Med J Aust* 1996; 164: 290-5.
- [106] Product Information: Epivir(R), lamivudine. GlaxoSmithKline, Research Triangle Park, NC (PI revised 06/2002).
- [107] Product Information: Zerit XR(R), stavudine. Bristol-Myers Squibb Company, Princeton, NJ (PI revised 12/2002).

- [108] Product Information: Videx(R) EC, didanosine delayed-release capsules. Bristol-Myers Squibb, Princeton, NJ (PI revised 01/2004).
- [109] Kelleher T, Cross A, Dunkle L. Relation of peripheral neuropathy to HIV treatment in four randomized clinical trials including didanosine. *Clin Ther* 1999; 2: 1182-92.
- [110] Product Information: Zovirax(R) acyclovir capsules, tablet, suspension. Glaxo Wellcome, Research Triangle Park, NC (PI revised 11/2001).
- [111] Product Information: Famvir(R), famciclovir tablets. SmithKline Beecham Pharmaceuticals, Philadelphia, PA, 2000.
- [112] Product Information: Valtrex(R), valacyclovir hydrochloride caplets. GlaxoWellcome Inc, Research Triangle Park, NC (PI revised 08/2003).
- [113] Wagstaff AJ, Faulds D, Goa KL. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; 47: 153-205.
- [114] Stott GA. Famciclovir: a new systemic antiviral agent for herpesvirus infections. *Am Fam Physician* 1997; 55: 2501-4.
- [115] Olin JL, Gugliotta JL. Possible valacyclovir-related neurotoxicity and aseptic meningitis. *Ann Pharmacother* 2003; 37: 1814-7.
- [116] Wagstaff AJ, Bryson HM. Foscarnet: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs* 1994; 48: 199-226.
- [117] Chatelain E, Deminiere C, Lacut JY, Potaux L. Severe renal failure and polyneuritis induced by foscarnet. *Nephrol Dial Transplant* 1998; 13: 2368-9.
- [118] Product Information: Cytovene(R), ganciclovir injection and capsules. Roche Laboratories, Inc, Nuttley, NJ (PI revised 09/2000).
- [119] Whitley RJ, Jacobson MA, Friedberg DN, *et al.* Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. International AIDS Society-USA. *Arch Intern Med* 1998; 158: 957-69.
- [120] Product Information: Symmetre(R), amantadine tablets and syrup. Endo Pharmaceuticals, Chadds Ford, PA (PI revised 07/2004).
- [121] Keyser LA, Karl M, Nafziger AN, Bertino JS Jr. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. *Arch Intern Med* 2000; 160: 1485-8.
- [122] Watt G, White NJ, Padre L, *et al.* Praziquantel pharmacokinetics and side effects in *Schistosoma japonicum* - infected patients with liver disease. *J Infect Dis* 1988; 157: 530-5.
- [123] Product Information: Prograf(R), tacrolimus. Fujisawa Healthcare, Inc., Deerfield, IL (PI revised 05/2004).
- [124] Neu AM, Furth SL, Case BW, *et al.* Evaluation of neurotoxicity in pediatric renal transplant recipients treated with tacrolimus (FK506). *Clin Transplantation* 1997; 11: 412-4.
- [125] Product Information: Rapamune(R), sirolimus. Wyeth Laboratories, Division of Wyeth-Ayerst Pharmaceuticals Inc. Philadelphia, PA (PI revised 01/2001).
- [126] Product Information: CellCept(R), mycophenolate mofetil. Roche Laboratories, Nutley, New Jersey (PI revised 7/2000).
- [127] Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin Exp Rheumatol* 1993; 11(Suppl. 8): S117-S119.
- [128] Product Information: Sandimmun(R), cyclosporine. Novartis S.p.A, Milan, Italy, 1998.
- [129] Product Information: Arava(R), leflunomide. Aventis Pharmaceuticals Inc., Kansas City, MO (PI revised 1/2003).
- [130] Cohen JD, Jorgensen C, Sany J. Leflunomide-induced aseptic meningitis. *Joint Bone Spine* 2004; 71: 243-5.
- [131] Lindemann A, Ganser A, Herrmann F, *et al.* Biologic effects of recombinant human interleukin-3 *in vivo*. *J Clin Oncol* 1991; 9: 2120-7.
- [132] Ganser A, Lindemann A, Seipelt G, *et al.* Clinical effects of recombinant human interleukin-3. *Am J Clin Oncol* 1991; 14(Suppl. 1): S51-S63.
- [133] Prendiville J, Thatcher N, Lind M, *et al.* Recombinant human interleukin-4 (rhu IL-4) administered by the intravenous and subcutaneous routes in patients with advanced cancer-a phase I toxicity study and pharmacokinetic analysis. *Eur J Cancer* 1993; 29A: 1700-7.
- [134] Van Gameren MM, Willems PHB, Mulder NH, *et al.* Effects of recombinant human interleukin-6 in cancer patients: a phase I-II study. *Blood* 1994; 85: 1434-41.
- [135] Huhn RD, Radwanski E, O'Connell SM, *et al.* Pharmacokinetics and immunomodulatory properties of intravenously administered recombinant human interleukin-10 in healthy volunteers. *Blood* 1996; 87: 699-705.
- [136] Chofflon M. Recombinant human interferon beta in relapsing-remitting multiple sclerosis: a review of the major clinical trials. *Eur J Neurol* 2000; 7: 369-80.
- [137] Balmer CM. The new alpha interferons. *Drug Intell Clin Pharm* 1985; 19: 887-93.
- [138] Product Information: Avonex(R) (interferon beta-1a). Biogen, Inc., Cambridge MA (PI revised 05/2003).
- [139] Rio J, Nos S, Bonaventura I, *et al.* Corticosteroids, ibuprofen, and acetaminophen for IFN beta-1a flu symptoms in MS: a randomized trial. *Neurology* 2004; 63: 525-28.
- [140] Dalakas MC. The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: evidence-based indications and safety profile. *Pharmacol Ther* 2004; 102: 177-93.
- [141] Product Information: Roferon-A(R), interferon alfa-2a recombinant. Roche Laboratories, Nutley, NJ (revised 03/1998).
- [142] Product Information: Intron(R) A, interferon alfa-2b, recombinant. Schering Corporation, Kenilworth, NJ (PI revised 2/2001).
- [143] Product Information: Betaseron(R), interferon beta-1b. Berlex Laboratories, Richmond, CA (PI revised 04/2003).
- [144] Product Information: Flonase(R), fluticasone propionate. Genesoft Pharmaceuticals, San Francisco, CA (PI revised 07/2003).
- [145] Product Information: Elocon(R), mometasone furoate. Schering Corporation, Kenilworth, NJ, revised, 1998; 2002.
- [146] Product Information: Pulmicort(R), budesonide inhalation powder. AstraZeneca LP, Wilmington, DE (PI revised 03/2003).
- [147] Product Information: Nasacort(R) nasal inhaler, triamcinolone acetate. Rhone-Poulenc Rorer Pharmaceuticals, Inc, Collegeville, PA (revised 10/1998).
- [148] Neville BGR, Wilson J. Benign intracranial hypertension following corticosteroid withdrawal in childhood. *Br Med J* 1970; 3: 554-6.
- [149] FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; 345: 433-42.
- [150] Rasmussen MK, Binzer M. Non-steroidal anti-inflammatory drugs in the treatment of migraine. *Curr med Res Opin* 2001; 16(Suppl. 1): s26-9.
- [151] Product Information: Indocin(R), indomethacin, Merck & Co., Inc, West Point, PA, 1999.
- [152] Wenmalm A, Carlsson F, Edlund A, Eriksson S, Kaijser L, Nowak J. Central and peripheral haemodynamic effects of non-steroidal anti-inflammatory drugs in man. *Arch Toxicol* 1984; (Suppl. 7): 350-9.
- [153] Nguyen HT, Juurlink DN. Recurrent ibuprofen-induced aseptic meningitis. *Ann Pharmacother* 2004; 38: 408-10.
- [154] Chazan B, Weiss A, Weiner Z, Rimbrot S, Raz R. Drug induced aseptic meningitis due to diclofenac. *J Neurol* 2003; 250: 1503-4.
- [155] Lee P, Rose BS, Anderson JA, *et al.* Naproxen in the treatment of rheumatoid arthritis. *N Z Med J* 1978; 87: 425-7.
- [156] Jacob S, Rajabally YA. Intracranial hypertension induced by rofecoxib. *Headache* 2005; 45: 75-6.
- [157] Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf* 2000; 22: 215-26.
- [158] Ostensen M, Villiger PM. Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. *Lupus* 2001; 10: 135-9.
- [159] Nettis E, Colagiuri G, Colanardi MC, Ferrannini A, Tursi A. Drug-induced aseptic meningitis. *Curr Drug Targets Immune Endocr Metabol Disord* 2003; 3: 143-9.
- [160] Horizon AA, Wallace DJ. Risk. benefit ratio of nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. *Expert Opin Drug Saf* 2004; 3: 273-8.
- [161] Gehanno P, Desfougeres JL. Fluticasone propionate aqueous nasal spray compared with oral loratadine in patients with seasonal allergic rhinitis. *Allergy* 1997; 52: 445-50.
- [162] Product Information: Optivar(R), azelastine hydrochloride. Muro Pharmaceutical, Inc., Tewksbury, MA (PI revised 07/2004).
- [163] Marchiando RJ, Cook MD. Probable terfenadine-fluoxetine-associated cardiac toxicity. *Ann Pharmacother* 1995; 29: 937.

- [164] Napke E, Biron P. Nervous reactions after first dose of terfenadine in adults. *Lancet* 1989; 2: 615-6.
- [165] Rasmussen JB, Lunell E. Additive bronchodilator effects of terbutaline and enprofylline in asthma. *Eur J Clin Pharmacol* 1987; 32: 23-6.
- [166] Siegel SC, Katz RM, Rachelefsky GS, *et al.* A placebo-controlled trial of procaterol: A new long-acting oral beta2-agonist in bronchial asthma. *J Allergy Immunol* 1985; 75: 698-705.
- [167] Storms WW, Bodman SF, Nathan RA, *et al.* Procaterol metered-dose inhaler in adults with asthma. *Ann Allergy* 1985; 55: 476-8.
- [168] Chapman KR, Bryant D, Marlin GE, *et al.* A placebo-controlled dose-response study of enprofylline in the maintenance therapy of asthma. *Am Rev Respir Dis* 1989; 139: 688-93.
- [169] Cloud ML. Safety of nizatidine in clinical trials conducted in the USA and Europe. *Scand J Gastroenterol* 1987; 22(Suppl. 136): 29-36.
- [170] Hirsch E: Famotidine and ranitidine, but not cimetidine, cause severe, disabling headache (letter). *Am J Gastroenterol* 1989; 84: 202-3.
- [171] Humphries T, Myerson RM, Gifford LM, *et al.* A unique post marketing outpatient surveillance program of cimetidine, report on phase II and final summary. *Am J Gastro* 1984; 79: 593-5.
- [172] Claessens A, Heerdink E, van Eijk JT, Lamers CB, Leufkens HG. Determinants of headache in lansoprazole users in the Netherlands. Results from a nested case-control study. *Drug Saf* 2002; 25: 287-95.
- [173] Product Information: Prilosec(R), omeprazole delayed-release capsules. AstraZeneca, Wilmington, DE (PI revised 11/2001).
- [174] de Bruijn KM. Tropisetron: a review of the clinical experience. *Drugs* 1992; 43(Suppl. 3): 11-22.
- [175] Kris MG, Grunberg SM, Gralla RJ, *et al.* Dose-ranging evaluation of the serotonin antagonist dolasetron mesylate in patients receiving high-dose cisplatin. *J Clin Oncol* 1994; 12: 1045-9.
- [176] Product Information: Kytril(R), granisetron hydrochloride tablets. SmithKline Beecham Pharmaceuticals, Philadelphia, PA, 2000.
- [177] Khan RB. Migraine-type headaches in children receiving chemotherapy and ondansetron. *J Child Neurol* 2002; 17: 857-8.
- [178] Rosch W. Cisapride in non-ulcer dyspepsia: results of a placebo controlled trial. *Scand J Gastroenterol* 1987; 22: 161-4.
- [179] Alloway JA, Mitchell SR. Sulfasalazine neurotoxicity: a report of aseptic meningitis and a review of the literature (letter). *J Rheumatol* 1993; 20: 409-11.
- [180] Hanauer S. Inflammatory Bowel Disease. *N Engl J Med* 1996; 334: 841-8.
- [181] Guarino J, Chatzinoff M, Berk T, Friedman LS. 5-Aminosalicylic acid enemas in refractory distal ulcerative colitis: long-term results. *Am J Gastroenterol* 1987; 82: 732-7.
- [182] Mishell DR, Shoupe D, Brenner PF, *et al.* Termination of early gestation with the anti-progestin steroid RU 486: medium versus low dose. *Contraception* 1987; 35: 307-21.
- [183] Asch RH, Greenblatt RB. The use of impeded androgen-danazol in the management of benign breast disorders. *Am J Obstet Gynecol* 1977; 127: 130.
- [184] Bruning PF. Droloxifen, a new anti-oestrogen in postmenopausal advanced breast cancer: preliminary results of a double-blind dose-finding phase II trial. *Eur J Cancer* 1992; 28: 1404-7.
- [185] Product Information: Casodex(R), bicalutamide. Zeneca Pharmaceuticals, Wilmington, DE (PI revised 09/2000).
- [186] Product Information: Prometrium(R), progesterone, USP. Solvay Pharmaceuticals, Marietta, GA (PI revised 9/99).
- [187] Product Information: Sandostatin(R), octreotide. Novartis Pharmaceuticals, East Hanover, NJ (PI revised 5/1999).
- [188] Product Information: Lupron Depot(R)-3 Month 11.25 mg, leuprolide acetate. TAP Pharmaceuticals, Lake Forest, IL (PI revised 05/2002).
- [189] van der Heijden PFM, Lappohn RE, Corbey RS, de Goeij WB, Brownell J, Rolland R. The effectiveness safety, and tolerability of CV 205-502 in hyperprolactinemic women: a 12-month study. *Fertil Steril* 1989; 52: 574-9.
- [190] Shoham Z, Homburg R, Jacobs HS. CV 205-502 - effectiveness, tolerability, and safety over 24-month study. *Fertil Steril* 1991; 55: 501-6.
- [191] Massiou H, Launay JM, Levy C, El-Amrani M, Emperauger B, Bousser MG. SUNCT syndrome in two patients with prolactinomas and bromocriptine-induced attacks. *Neurology* 2002; 58: 1698-9.
- [192] Lauritzen C. Clinical use of oestrogens and progestogens. *Maturitas* 1990; 12: 199-214.
- [193] Product Information: TACE(R), chlorotrianisene. Merrell Dow Pharmaceuticals, Inc. Cincinnati, OH, 1990.
- [194] Product Information: Estrovis(R), quinestrol. Parke-Davis, Morris Plains, NJ, 1996.
- [195] Product Information: Ortho(R), dienestrol. Ortho Pharmaceutical Corporation, Raritan, NJ (PI revised 10/96).
- [196] Bogerlt-Hansen L. Oral contraceptives: an update on health benefits and risks. *J Am Pharm Assoc* 2001; 2001; 41: 875-86.
- [197] Fluck E, File SE, Rymer J. Cognitive effects of 10 years of hormone-replacement therapy with tibolone. *J Clin Psychopharmacol* 2002; 22: 62-7.
- [198] Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. *N Engl J Med* 2002; 346: 340-52.
- [199] Wright LJ, Kalantaridou SN, Calis KA. Update on the benefits and risks of hormone replacement therapy. *Formulary* 2002; 37: 78-93.
- [200] Saarikoski S, Yliskoski M, Pentilla I. Sequential use of norethisterone and natural progesterone in pre-menopausal bleeding disorders. *Maturitas* 1990; 12: 89-97.
- [201] Welch KM. Migraine and pregnancy. *Adv Neurol* 1994; 64: 77-81.
- [202] Massiou U, MacGregor EA. Evolution and treatment of migraine with oral contraceptives. *Cephalalgia* 2000; 20: 170-4.
- [203] Silberstein SD, de Lignieres B. Migraine, menopause and hormonal replacement therapy. *Cephalalgia* 2000; 20: 214-22.
- [204] de Lignieres B, MacGregor EA. Risks and benefits of hormone replacement therapy. *Cephalalgia* 2000; 20: 164-9.
- [205] Rodrigues N, Rodrigues Pereira E. Tramadol in cancer pain. *Curr Ther Res* 1989; 46: 1142-8.
- [206] Product Information: Avinza(TM), morphine sulfate extended-release capsules. Ligand Pharmaceuticals, Inc., San Diego, CA, 92121 (PI revised 03/2002).
- [207] Romagnoli A, Keats AS. Ceiling respiratory depression by dezocine. *Clin Pharmacol Ther* 1984; 35: 367-73.
- [208] Product Information: Subutex(TM), buprenorphine. Reckitt Benckiser Pharmaceuticals, Inc, Richmond, VA (PI issued 2002).
- [209] Zarate CA. Antipsychotic drug side effect issues in bipolar manic patients. *J Clin Psychiatry* 2000; 61: 52-61.
- [210] Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *J Clin Psychopharmacol* 1996; 16: 158-69.
- [211] Marder SR. Clinical experience with risperidone. *J Clin Psychiatry* 1996; 57 (Suppl. 9): 57-61.
- [212] Product Information: Risperdal(R) Consta(TM), risperidone long-acting injection. Janssen Pharmaceutica Products, L.P., Titusville, NJ, January, 2004.
- [213] Smith WT, Glaudin V. Double-blind efficacy and safety study comparing adinazolam mesylate and placebo in depressed inpatients. *Acta Psychiatr Scand* 1986; 74: 238-45.
- [214] Kales A, Bixler EO, Vgontzas AN. Triazolam safety (letter). *Lancet* 1993; 341: 1602.
- [215] Mendels J, Stern S. Evaluation of the short-term treatment of insomnia in outpatients with 15 milligrams of quazepam. *J Int Med Res* 1983; 11: 155-61.
- [216] Jacobson AF, Goldstein BJ, Dominguez RA, Steinbook RM. A placebo-controlled, double-blind comparison of clobazam and diazepam in the treatment of anxiety. *J Clin Psychiatry* 1983; 44: 296-300.
- [217] Product Information: Zyban(R), bupropion. GlaxoSmithKline, Research Triangle Park, NC (PI revised 3/2003).
- [218] Gelenberg AJ, Wojcik JD, Falk WE, Spring B, Brotman AW, Galvin-Nadeau M. Clovoxamine in the treatment of depressed outpatients: a double-blind, parallel-group comparison against amitriptyline and placebo. *Compr Psychiatry* 1990; 31: 307-14.
- [219] Puech A, Montgomery SA, Prost JF, Solles A, Briley M. Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. *Intern Clin Psychopharmacol* 1997; 12: 99-108.
- [220] Product Information: Luvox(R), fluvoxamine. Solvay Pharmaceuticals, Marietta, GA, 1998.
- [221] Product Information: Prozac(R), fluoxetine. Eli Lilly and Company, Indianapolis, IN, 2001.
- [222] Product Information: Paxil(R) CR(TM), paroxetine hydrochloride controlled-release tablets. SmithKline Beecham Pharmaceuticals, Philadelphia, PA, USA (PI issued 04/2002).

- [223] Product Information: Zolof(R), sertraline, Pfizer, Inc., New York, NY (revised 5/2002).
- [224] Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* 1999; 57: 507-33.
- [225] Fleischhacker WW, Hinterhuber H, Bauer H. A multicenter double-blind study of three different doses of the new cAMP-phosphodiesterase inhibitor rolipram in patients with major depressive disorder. *Neuropsychobiology* 1992; 26: 59-64.
- [226] Wilde MI, Benfield P. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* 1995; 49: 411-39.
- [227] Product Information: Effexor(R) XR, venlafaxine. Wyeth-Ayerst Laboratories, Philadelphia, PA, 2000.
- [228] D'Amico MF, Roberts DL, Robinson DS, *et al.* Placebo-controlled dose-ranging trial designs in phase II development of nefazodone. *Psychopharmacol Bull* 1990; 26: 147-150.
- [229] Product Information: Desyre(R), trazodone, Apothecon, Princeton, NJ, 1988.
- [230] Gex-Febry M, Balant-Gorgia AE, Balant LP. Potential of concentration monitoring data for a short half-life drug: analysis of pharmacokinetic variability of moclobemide. *Ther Drug Monit* 1995; 17: 39-46.
- [231] Barnes TRE, Kidger T. Viloxazine and migraine. *Lancet* 1979; 2: 1368.
- [232] Product Information: Provigil(R), modafinil tablets. Cephalon, Inc, West Chester, PA, 1998.
- [233] Product Information: Meridia(R), sibutramine. Abbott Laboratories, North Chicago, IL (PI revised 10/2003).
- [234] Kadakia S C, De La Baume HR, Shaffer RT. Effects of transdermal nicotine on lower esophageal sphincter and esophageal motility. *Dig Dis Sci* 1996; 41: 2130-4.
- [235] Product Information: Mevacor(R), lovastatin. Merck & Co., Inc., Whitehouse Station, NJ (PI revised 6/2002).
- [236] Product Information: Zocor(R), simvastatin. Merck & Co., Inc., Whitehouse Station, NJ (PI revised 5/2002).
- [237] Product Information: Pravachol(R), pravastatin. Bristol-Myers Squibb Company, Princeton, NJ, 1998.
- [238] Finelli PF, Carley MD. Cerebral venous thrombosis associated with epoetin alfa therapy. *Arch Neurol* 2000; 57: 260-2.
- [239] Joy MS. Novel erythropoiesis-stimulating protein. An erythropoietin analogue with an extended half-life and less frequent dosing. *Formulary* 2001; 36: 19-25.
- [240] Kurie JM, Lee JS, Griffin T, *et al.* Phase I trial of 9-cis-retinoic acid in adults with solid tumors. *Clin Cancer Res* 1996; 2: 287-93.
- [241] Ganguly S. All-trans retinoic acid related headache in patients with acute promyelocytic leukemia: prophylaxis and treatment with acetazolamide. *Leu Res* 2005; 29: 721.
- [242] Product Information: Vesanoind(R), tretinoin. Roche Laboratories Inc., Nutley, New Jersey (PI revised 3/2003).
- [243] Friedman MA, Ignoffo RJ. A review of the United States clinical experience of the fluoropyrimidine, florafur (NSC-148958). *Cancer Treat Rev* 1980; 7: 205-13.
- [244] Young JM, Feldman RA, Auerbach SM, *et al.* Tadalafil improved erectile function at twenty-four and thirty-six hours after dosing in men with erectile dysfunction: US trial. *J Androl* 2005; 26: 310-8.
- [245] Porst H, Rosen R, Padma-Nathan H, *et al.* The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction. *Formulary* 2003; 38: 131-48.
- [246] Moreira SG, Brannigan RE, Spitz A, Orejuela FJ, Lipshultz LI, Kim ED. Side-effect profile of sildenafil citrate (Viagra) in clinical practice. *Urology* 2000; 56: 474-6.
- [247] Conti CR, Pepine CJ, Sweeney M: Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease. *Am J Cardiol* 1999; 83 (Suppl. 5A): 29C-34C.
- [248] Schramek P, Waldmauser M. Dose dependent effect and side-effect of prostaglandin E1 in erectile dysfunction. *Br J Clin Pharmacol* 1989; 28: 567-71.
- [249] Rademaker M, Cooke ED, Almond NE, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *Br Med J* 1989; 298: 561-4.
- [250] Lauritsen K, Laursen LS, Havelund T, *et al.* Enprostil and ranitidine in duodenal ulcer healing: double blind comparative trial. *Br Med J* 1986; 292: 864-6.
- [251] Product Information: Prostin E2(R), dinoprostone vaginal suppository. Pharmacia & Upjohn Company, Kalamazoo, MI (PI revised 08/1999).
- [252] Aznar-Ramos R, Giner-Velazquez J, Lara-Ricalde R, Martinez-Manatou J. Incidence of side effects with contraceptive-placebo. *Am J Obst Gynecol* 1969; 105: 1144-9.
- [253] Asmark H, Lundberg PO, Olsson S. Drug-related headache. *Headache* 1989; 29: 441-4.
- [254] World Health Organization 1972; Tech Rep 498.
- [255] Ramadan NM. Headache caused by raised intracranial pressure and intracranial hypotension. *Curr Opin Neurol* 1996; 9: 214-8.
- [256] Lorberboym M, Lampl Y, Kesler A, Sadeh M, Gadot N. Benign intracranial hypertension: correlation of cerebral blood flow with disease severity. *Clin Neurosurg* 2001; 103: 33-6.
- [257] Salman MS, Kirkham FJ, MacGregor DL. Idiopathic "benign" intracranial hypertension: case series and review. *J Child Neurol* 2001; 16: 465-70.
- [258] Massiou H, Bousser MG. Beta-blockers and migraine. *Pathol Biol* 1992; 40: 373-80.
- [259] Silberstein SD, Merriam GR. Physiology of menstrual cycle. *Cephalalgia* 2000; 20: 148-54.
- [260] Allais G, Benedetto C. Update on menstrual migraine: from clinical aspects to therapeutic strategies. *Neurol Sci* 2004; 25 (Suppl. 3): s229-31.
- [261] Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anaesthesia. *Drug Saf* 1990; 5: 179-94.
- [262] Karachalios, GN, Charalabopoulos A, Papatimneou V, Kiortsis D, Dimicco P, Kostoula OK, Charalabopoulos K. Withdrawal syndrome following cessation of antihypertensive drug therapy. *Int J Clin Pract* 2005; 59: 562-70.
- [263] Jones MG, Lever I, Bingham S, Read S, McMahon SB, Parsons A. Nitric oxide potentiates response of trigeminal neurones to dural or facial stimulation in the rat. *Cephalalgia* 2001; 21: 643-55.
- [264] Chabriat H, Danchot J, Michel P, Joire JE, Henry P. Precipitating factors of headache. A prospective study in a national control-matched survey in migraineurs and nonmigraineurs. *Headache* 1999; 39: 335-8.
- [265] Salties E, Ellrodt AG, Monk JP, Langley MS. Felodipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. *Drugs* 1988; 36: 387-428.
- [266] Product Information: Plendil(R), felodipine. AstraZeneca LP, Wilmington, DE (PI revised 11/2003).
- [267] Product Information: Dynacirc(R)CR, isradipine. Novartis Pharmaceuticals Corp, East Hanover, NY (PI revised 10/1998).
- [268] Endersby CA, Brown EG, Perelman MS. Safety profile of lacidipine: a review of clinical data. *J Cardiovasc Pharmacol* 1991; 17(Suppl 4): S45-S47.
- [269] Rimoldi E, Lumina C, Giunta L, *et al.* Evaluation of the efficacy and tolerability of two different formulations of lercanidipine versus placebo after once-daily administration in mild to moderate hypertensive patients. *Curr Ther Res* 1993; 54: 248-52.
- [270] Product Information: Cardene SR(R), nicardipine. Roche, Nutley, NJ (PI revised 05/1999).
- [271] Rosenfeld JB, Zabudowski J. The efficacy and tolerability of nifedipine (NIF) and nisoldipine (NIS) both alone and combined with a beta-blocker in patients with essential hypertension: a multicenter, parallel-group study. *J Clin Pharmacol* 1989; 29: 1013-6.
- [272] Goa KL, Sorkin EM. Nitrendipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. *Drugs* 1987; 33: 123-55.
- [273] Product Information: Rythmol(R), propafenone. Abbott Laboratories, North Chicago, IL (PI revised 07/2003).
- [274] Product Information: Kerlone(R), betaxolol. GD Searle, Chicago, IL (PI revised 05/1999).
- [275] Frithz, Weiner L. Effects of bisoprolol on blood pressure, serum lipids and HDL-cholesterol in essential hypertension. *Eur J Clin Pharmacol* 1987; 32: 77-80.
- [276] Von Rosprich G, Solter H. For treatment of essential hypertension with the beta-receptor antagonist carteolol. A multicentre study. *Arzneimittelforschung* 1983; 33: 334-9.

- [277] Hayes G. Single-blind comparison of penbutolol and long-acting propranolol in general practice. *Pharmatherapeutica* 1983; 3: 456-63.
- [278] Product Information: Lotensin HCT(R), benazepril hydrochloride and hydrochlorothiazide. Novartis, East Hanover, NJ (PI revised 02/1999).
- [279] Product Information: Inhibace(R), cilazapril. Hoffman-LaRoche Ltd, Mississauga, Ontario, Canada (PI revised 01/1997).
- [280] Product Information: Vasotec(R), enalapril maleate. Merck & Co., Inc, Whitehouse Station, NJ (PI revised 10/2000).
- [281] Goa KL, Balfour JA, Zuanetti G. Lisinopril: a review of its pharmacology and use in the management of acute myocardial infarction. *Drugs* 1996; 52: 564-88.
- [282] Frank GJ, Knapp LE, McLain RW. Overall tolerance and safety of quinapril in clinical trials. *Angiology* 1989; 40: 405-15.
- [283] Product Information: Transderm-Nitro(R), nitroglycerin transdermal therapeutic system. Novartis Pharmaceuticals, Summit, NJ (PI revised 1/1997).
- [284] Product Information: Isordil(R), isosorbide dinitrate. Wyeth-Ayerst Laboratories, Philadelphia, PA, USA, 1994.
- [285] Derriennic M, Conforti PM, Sides GD. Dirithromycin in the treatment of streptococcal pharyngitis. *J Antimicrob Chemother* 1993; 31(Suppl C): 89-95.
- [286] Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden and Holland. *Br Med J* 1982; 284: 1440-2.
- [287] Product Information: Levaquin(R), levofloxacin tablets and injection. Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ (PI revised 07/2004).
- [288] Hunt TL, Adams MA. Pharmacokinetics and safety of lomefloxacin following multiple doses. *Diagn Microbiol Infect Dis* 1989; 12: 181-7.
- [289] Todd PA, Faulos D. Ofloxacin: a reappraisal of its antimicrobial activity, pharmacology and therapeutic use. *Drugs* 1991; 42: 825-76.
- [290] Product Information: Ziagen(R), abacavir sulfate tablets and oral solution. GlaxoSmithKline Inc, Research Triangle Park, NC (PI revised 07/2003).
- [291] Adkins JC, Faulds D. Amprenavir. *Drugs* 1998; 55: 837-42.
- [292] Cheeseman SH, Hattox SE, McLaughlin MM, *et al.* Pharmacokinetics of nevirapine: initial single-rising dose study in humans. *Antimicrob Agents Chemother* 1993; 37: 178-82.
- [293] Product Information: Retrovir(R) zidovudine IV infusion. GlaxoSmithKline, Research Triangle Park, NC (PI revised 04/2003).
- [294] Product Information: Actimmune(R), interferon gamma-1b. InterMune Pharmaceuticals, Inc, Burlingame, CA (PI revised 3/2000).
- [295] Brogden RN, Pinder RM, Speight TM, Avery GS. Fenoprofen: a review of its pharmacological properties and therapeutic efficacy in rheumatic diseases. *Drugs* 1977; 13: 241-65.
- [296] Product Information: Toradol(R), ketorolac tromethamine. Roche Laboratories, Nutley, NJ, 2002.
- [297] Kirchheiner B, Trang L, Wollheim FA. Diclofenac sodium (Voltaren(R)) in rheumatoid arthritis: a double-blind comparison with indomethacin and placebo. *Int Clin Pharmacol* 1976; 13: 292-7.
- [298] Product Information: EC-Naprosyn(R), Delayed-Release Naproxen. Roche Laboratories, Inc., Nutley, NJ, USA, 5/2003.
- [299] Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; 61: 1133-43.
- [300] Product Information: Pepcid(R), famotidine. Merck & Co, Inc., West Point, PA (PI revised 12/2004).
- [301] Product Information: Axid(R), nizatidine. Eli Lilly and Company, Indianapolis, IN, 1988.
- [302] Product Information: Zantac(R), ranitidine. Glaxo Wellcome Inc., Research Triangle Park, NC (PI revised 11/1999).
- [303] Product Information: Azulfidine EN-tabs(R), sulfasalazine delayed release tablets. Pharmacia & Upjohn, Kalamazoo, MI, (PI revised 9/2000).
- [304] Product Information: Clozaril(R), clozapine. Novartis, East Hanover, NJ, (PI revised 09/2002).
- [305] Corya SA, Andersen SW, Detke HC, *et al.* Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: a 76-week open-label study. *J Clin Psychiatry* 2003; 64: 1349-56.
- [306] Product Information: Geodon(R), ziprasidone hydrochloride. Pfizer Inc., New York, NY, (PI revised 6/2002).
- [307] Kondo T, Otani K, Ishida M, Tanaka O, Kaneko S, Fukushima Y. Adverse effects of zotepine and their relationship to serum concentrations of the drug and prolactin. *Ther Drug Monit* 1994; 16: 120-4.