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EDUCATION AND DEBATE

Evidence of the principle of similitude in modern fatal iatrogenic events

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Samuel Hahnemann attributed fundamental importance to the principle of similitude, promoting it to a 'natural law'. Observing that enantiopathic or allopathic treatment produced enduring aggravation of the disease symptoms after a brief and transitory initial relief, he systematised homeopathic treatment, prescribing substances that provoke similar symptoms in healthy individual. Based on clinical and experimental observations, he anticipated the concept of homeostasis, dividing the effects of substances into: primary action of the medicine followed by secondary action or reaction of the organism. This reaction, known as the rebound effect or paradoxical action by modern pharmacology, used to awake the curative response of the body when the principle of similitude is applied, is responsible for several iatrogenic diseases when used on the basis of the principle of contraries. This study discusses the role of this paradoxical reaction of the organism in the fatal side effects of four important drugs, used according to the model of enantiopathic treatment of the symptoms. I present evidence relating to acetylsalicylic acid, rofecoxib, antidepressants and long-acting bronchodilators. The consequences of the allopathic treatment could be decreased if health professionals valued homeostasis, minimising the rebound effect of the organism by gradual suspension of palliative drugs. *Homeopathy* (2006) **95,** 229–236.

Keywords: similitude; homeostasis; rebound effect; paradoxical reaction; compensatory response; fatal iatrogenic event

Introduction

Samuel Hahnemann, in paragraphs 22–70 of the *Organon of Medicine*,[1] discourses on the particularities of the principle of similitude, raising it to the status of a 'natural law'. Relating the principle of similitude to the symptomatic manifestation of diseases, he discusses the homeopathic and antipathetic (allopathic, enantiopathic or palliative) methods of treatment (paragraphs 51–70): administering the medicines that produce, respectively, symptoms opposite or similar to those of patients. On the basis of transitory relief produced by allopathic treatment, followed by evident aggravation of the disease, he justifies his choice of the homeopathic method.

Criticising the contrary method of the treatment of the diseases (*contraria contrariis curentur*), mentioned by Hippocrates and later Galen, Hahnemann cites several examples in which 'after such short antipathetic amelioration, aggravation follows in every case without exception' (paragraphs 58–59), inciting the ordinary physician to the progressive increase of the doses, causing 'another more serious disease or frequently incurability, even danger of life and death itself, but never a cure of a disease of considerable or of long standing' (paragraph 60).

He guides us to reflect on the adverse effects of the antagonistic employment of medicines, evidence of the validity of the opposite procedure, the homeopathic use of medicines according to similarity of symptoms:

'Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines,

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they had long since discovered the grand truth, *that the true radical healing art must be found in the exact opposite of such an antipathetic treatment of the symptoms of disease;* they would have become convinced, that as a medicinal action antagonistic to the symptoms of the disease is followed by only transient relief, and after that is passed, by invariable aggravation, the converse of that procedure, *the homoeopathic employment of medicines* according to similarity of symptoms, must effect a permanent and perfect cure [...]'. (paragraph 61).

In this paper I seek to demonstrate through serious or fatal iatrogenic events related to modern allopathic treatments, the validity of the principle of similitude.

Similitude and homeostasis

Observing the alterations that medicines cause to state of health, in the short and long term, Samuel Hahnemann describes the mechanism of action of the drugs in the organism, as an immediate 'primary action' of the medicine and a late 'secondary action or vital reaction' of the organism: 'Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action*. [...] To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or *counteraction*'. (*Organon*, paragraph 63).

He mentions several examples of the primary action and the consequent reaction of the vital force, which acts in an instinctive way in a sense to preserve the homeostasis or the balance of the internal environment ('life-preserving power'), producing intense and opposite symptoms to the those initially induced: '[...] Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee. After the profound stupefied sleep caused by opium, the following night will be all the more sleepless. After the constipation produced by opium (primary action), diarrhoea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues'. (*Organon*, paragraph 65)

Influenced by the vitalist thought of his time, Hahnemann uses the term 'reaction of the vital force' to explain the automatic phenomenon of organic self-regulation labelled in 1929 by the physiologist WB Cannon 'homeostasis': 'the ability or tendency of an organism or cell to maintain internal equilibrium by adjusting its physiological processes'. These physiological processes or homeostatic mechanisms are present in all of the levels of biological organisation, from the simple cellular to complex psychic and emotional functions.

Hahnemann stipulated the use of the 'totality of characteristic symptoms' to choose the ideal medicine, so that several levels of the biological organization were stimulated simultaneously. Initially he applied the similitude principle using substantial doses of substances, using ultra-dilution medicines only in subsequent phase of his clinical practice.

Similitude and modern pharmacology

In my studies of rebound effects and paradoxical reactions of the organism, described by modern pharmacology and physiology and corresponding to the secondary action or vital reaction of the homeopathic model, I found scientific validation of this phenomenon, usually after the interruption or discontinuation treatment, with many modern medicines of several classes.[2-4]

For example, drugs used for the treatment of angina pectoris (β-adrenoceptor blockers, calcium channel blockers, nitrates), whose primary effect is the improvement of angina. After suspension of the drug, a rebound effect occurs, consisting of exacerbated thoracic pain, in frequency as well as intensity. In some cases the pain is not responsive to any type of therapy. Drugs utilised to control arterial hypertension (central $\alpha 2$-adrenoceptor agonists, β-adrenoceptor blockers, hidralazine, ACE inhibitors, MAO inhibitors, nitrates, prostaglandin A_1, sodium nitroprusside) can provoke rebound arterial hypertension as a secondary reaction. Anti-arrhythmic medications (adenosine, amiodarone, β-adrenoceptor blockers, calcium channel blockers, disopyramide, encainide, digitalics, flecainide, lidocaine, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide) provoke, after the interruption of treatment, exacerbation of the initial arrhythmias. Anticoagulant drugs (argatroban, bezafibrate, heparin, salicylates, warfarin) whose primary effect is prophylaxis of thrombosis, cause thrombotic complications as a secondary or rebound effect. In the case of: anxiolytics (barbiturates, benzodiazepines, buspirone, meprobamate), sedatives-hypnotics (barbiturate, bendodiazepine, morphine, promethazine, tetrahydrocannabinol, zopiclone), CNS stimulants (amphetamine, caffeine, cocaine, mazindol, methylphenidate), antidepressants (MAO inhibitors, tricyclics, SSRIs), anti-psychotics (clozapine, phenothiazines, haloperidol, pimozide, thiethylperazine, thiothixene), a reaction of the organism trying to maintain homeostasis can be observed, with symptoms opposite to those expected in the primary therapeutic indication have been observed, further aggravating the initial condition. Drugs whose primary action is anti-inflammatory (ibuprofen, indomethacin, paracetamol, salicylates) induce a secondary response of the organ-

ism, increasing inflammation and the plasma concentration of mediators of inflammation. Drugs whose primary effect is analgesic (caffeine, calcium channel blockers, clonidine, ergotamine, methysergide, opioids, salicylates) may provoke, as a paradoxical reaction, hyperalgesia. Diuretics (furosemide, torasemide, triamterene) used to decrease blood volume cause a rebound retention of sodium and potassium, increasing blood volume. Anti-dyspeptics (antacids, H_2 receptor antagonists, misoprostol, sucralfate) for the treatment of gastritis and gastroduodenal ulcers, cause, after an initial decline in acidity, a rebound increase in acidity.

The intensity of the paradoxical or rebound symptom is sometimes greater than the primarily suppressed symptom, expressing itself in variable period (hours to weeks) after the interruption or discontinuation of the medicine and variable duration (hours to weeks), according to the individual susceptibility (idiosyncrasy).

The principle of cure through similitude has started to interest in non-homeopathic researchers, who describe the same phenomena described by homeopathy plagiarizing the model and claiming exclusivity on a phenomenon described since the prehistory of Medicine.[5]

Material and methods

After studying the rebound or paradoxical effect of the organism as described by modern pharmacology,[2-4] I searched Medline (keywords: rebound effect and paradoxical reaction) and the internet (keywords: fatal or serious adverse drug reaction, rebound effect and paradoxical reaction), prioritising the sites of universities and governmental health agencies, selecting the best evidence of serious or fatal iatrogenic events caused by the rebound effect of drugs.

Similitude and aspirin

Acetylsalicylic acid (ASA) is a non-steroidal anti-inflammatory drug (NSAID) a non-selective inhibitor of the of the enzyme cycloxygenase (COX), which catalyses the conversion of arachidonic acid into prostaglandins (COX-2) and thromboxane (COX-1). When applied according to the principle of contraries, ASA has a primary action of inhibiting the development of thrombus, by inhibiting cycloxygenase 1 and hence blood platelet aggregation. Experimental studies, in vitro and in vivo, show that after the interruption or discontinuation of ASA or other drugs for prophylaxis of thromboembolism, the organism reacts by a secondary action or vital reaction that stimulates the COX-1 production and the blood platelet activity to values much higher than baseline, increasing the development of thrombus and the probability of a embolic event [acute myocardial infarction (AMI), cerebral vascular accident (CVA), etc] in susceptible individuals, both in substantial,[6-15] and infinitesimal doses.[16,17] Other experiments showed the effect of substantial[18] or ultra low[19-23] doses of aspirin in prophylaxis or reduction of haemorrhagic risks (reducing the bleeding time or the anti-thrombotic effect), neutralising the side effect of previously administered aspirin.

In a retrospective study, a total of 1236 patients hospitalised for acute coronary syndrome (ACS) were questioned in order to determine whether prophylactic aspirin intake had been interrupted: 51 of these ACSs occurred within 1 month after aspirin withdrawal. This represents 4.1% of all coronary events and 13.3% of recurrences. Among the patients who relapsed, the incidence of ST-segment elevation ACS was higher in those who stopped aspirin compared to the 332 patients who did not stop aspirin (39% vs 18%; $P = 0.001$). Mean delay between aspirin withdrawal and the acute coronary event was 10 ± 1.9 days. The results support the hypothesis that aspirin withdrawal in coronary patients may represent a risk for the occurrence of a new coronary event.[24,25]

Emile Ferrari, co-author of the study,[26] said that although the 'benefits of aspirin therapy in coronary patients are well known, the effects that aspirin withdrawal has on this group of patients are just now being studied'. As this study showed that 'aspirin therapy cannot be safely stopped in any case, but especially in patients with a history of coronary disease', it 'serves as a reminder for all medical professionals who treat coronary patients that aspirin withdrawal should not be advised, and that alternative recommendations should be considered'. In the same interview, Richard S Irwin, President of The American College of Chest Physicians, concludes that 'this study not only reinforces the importance of compliance with aspirin therapy in coronary patients, but it sends a message to all medical professionals that the decision to discontinue aspirin therapy should not be taken lightly'.

Investigating the discontinuation of aspirin therapy as a risk factor for ischaemic stroke (IS), Maulaz *et al* conducted a case–control study on 309 patients with IS or transient ischaemic attack (TIA) undergoing long-term aspirin treatment before their index event and 309 controls who had not had an IS in the previous 6 months, comparing the frequency of aspirin therapy discontinuation in the 4 weeks before an ischaemic cerebral event in patients and the 4 weeks before interview in controls. Stopping aspirin therapy was associated with an odds ratio of 3.4 for IS or TIA (95% CI, 1.08–10.63; $P<0.005$), in other words, a risk 3.4 times greater of developing ischaemic accidents in patients who interrupted the treatment.[27]

Similarly, other classes of non-selective NSAID increase the risk of AMI after interruption of treatment, reflecting the results of experimental studies in which NSAIDs stimulated the platelet adhesion and thrombin activity.[28,29] A large case–control analysis on the British General Practice Research Database, with

8688 cases and 33,923 controls, studied the risk of AMI during NSAID exposure and after the cessation of NSAID therapy, finding that the risk of AMI was 1.52 (95% CI 1.33–1.74) for subjects who stopped taking NSAIDs 1–29 days prior to the index date, compared with non-users. These results suggest that the risk of AMI is increased during several weeks after the cessation of NSAID therapy.[30] Studying the frequency of stroke occurring after discontinuation of anti-platelet drugs (APD), Sibon *et al* found that only 4.49% of strokes were related to a recent APD discontinuation, but all cases occurred between 6 and 10 days after drug discontinuation ($P<0.0001$).[31]

In view of the known importance of the use of aspirin to prevent thromboembolic accidents, whose benefits surpass the risks,[32] physicians and patients should be alerted to the danger of the abrupt suspension of the medication, in order to minimise serious iatrogenic thromboembolic accidents.[33]

Similitude and COX-2 inhibitors

In September 2004, the selective anti-COX2 NSAID Rofecoxib (Vioxx) was immediately withdrawn due to a study which showed increased risk of heart attacks in patients who used it in high dosages and for a long period.

This retrospective cohort incision study,[34] sponsored by Food and Drug Administration (FDA), analysed the medical history of 1.4 million of patients from 1999 to 2001. From this total, 8.199 patients (0.58%) suffered a heart attack while taking rofecoxib. According to David Graham, coordinator of the study, the FDA would have to decide if the increasing risk of a heart attack, up to three times, compensated to the benefits of the medicine. Other studies had also demonstrated that the chronic consumption of rofecoxib in high doses (>50 mg/day) could elevate the risk of serious cardiovascular problems.[35–37]

Previous observational studies observed a particularly high risk of AMI for new users of rofecoxib,[38,39] with events occurring in short time after the suspension of low doses of the therapy, likely due to a rebound effect. Using data collected in a previous population-based cohort study,[40] a recent case-control study evaluated the temporal association of the risk of a first AMI with the use of rofecoxib and celecoxib, observing that the risk of AMI was higher following first-time use of rofecoxib (RR 1.67, 95% CI 1.21–2.30), with events occurring within a median of 9 (6–13) days after therapy had started. Treatment duration was not associated with increasing risk, and the risk remained elevated for the first 7 days after rofecoxib was discontinued (RR 1.23, 95% CI 1.05–1.44) but appeared to return to baseline between day 8 and 30 (RR 0.82, 95% CI 0.61–1.09).[41]

A recent meta-analysis of the effects of selective cyclo-oxygenase-2 (COX-2) inhibitors and traditional NSAIDs on the risk of serious vascular events (defined as myocardial infarction, stroke, or vascular death), for a period of at least 4 weeks duration. In placebo comparisons, allocation to a selective COX-2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events (1.2%/year vs 0.9%/year; rate ratio 1.42, 95% CI 1.13–1.78; $P = 0.003$), with no significant heterogeneity among the different selective COX-2 inhibitors. This was chiefly attributable to an increased risk of myocardial infarction (0.6%/year vs 0.3%/year; rate ratio 1.86, 95% CI 1.33–2.59; $P = 0.0003$), with little difference in other vascular outcomes. Overall, the incidence of serious vascular events was similar between a selective COX-2 inhibitor and any traditional NSAID (1.0%/year vs 0.9%/year; rate ratio 1.16, 95% CI 0.97–1.38; $P = 0.1$). The summary rate ratio for vascular events, compared with placebo, was 0.92 (0.67–1.26) for naproxen, 1.51 (0.96–2.37) for ibuprofen, and 1.63 (1.12–2.37) for diclofenac.[42]

Similitude and antidepressants

"Rebound phenomena" have also been demonstrated with antidepressants: an increase of 100% in the incidence rate of suicidal thoughts and behaviours among young patients with depression, taking selective serotonin reuptake inhibitors or SSRIs, when compared to patients treated with placebo has been observed.[43–49] The FDA Public Health Advisory published in October 2004 an alert on 'Suicidality in children and adolescents being treated with antidepressant medications'.[50] 'The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to 4 months) placebo-controlled trials of nine antidepressant drugs, including the SSRIs and others, in children and adolescents with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders. A total of 24 trials involving over 4400 patients were included. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%'.

This had been attributed to the 'syndrome of activation', where the antidepressant produces psychomotor improvement prior to mood improvement, but this hypothesis does not apply to all studies, because the suicidal tendency was observed throughout treatment, principally when the dose is changed. Relating the paradoxical symptoms to the alteration of the dose, the FDA reinforces the hypothesis of rebound phenomenon: 'Paediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers

and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose'.[50]

On July 1st, 2005, the FDA advised: 'Several recent scientific publications suggest the possibility of an increased risk for suicidal behaviour in adults who are being treated with antidepressant medications. Even before these reports became available, the FDA began a complete review of all available data to determine whether there is an increased risk of suicidality (suicidal thinking or behaviour) in adults being treated with antidepressant medications. It is expected that this review will take a year or longer to complete. In the meantime, FDA is highlighting that adults being treated with antidepressant medications, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behaviour. Close watching may be especially important early in treatment, or when the dose is changed, either increased or decreased'.[51]

On May 12, 2006, GlaxoSmithKline and the FDA warned that a re-analysis of clinical trials involving nearly 15,000 adults (8958 receiving Paroxetine and 5953 Placebo) showed that patients, aged 18–64, taking Paroxetine had six times greater incidence of suicidal behaviour with higher incidence in young adults (ages 18–30): "The FDA stressed that all patients, especially young adults and those who are improving, should be carefully monitored when treated with Paxoretine".[52]

Like other anxiolytic sedatives[53–55] and antidepressants,[56–65] SSRIs[64–68] can provoke, after their interruption or discontinuation or when the dose is changed, as a *secondary action* or *vital reaction*, an exacerbation of the suppressed symptoms by the primary action of the drug (depression, anxiety, mania, panic, somnolence etc).

Similitude and bronchodilators

Over the last decades, several studies have confirmed that "rebound bronchoconstriction" occurs after interruption or discontinuation of bronchodilators, with aggravation of asthma and increased of bronchial reactivity.[69–85] In November 2005, the FDA warned that the long-acting β-2 agonists (salmeterol and formoterol), including when combined with the steroid fluticasone, "may increase the chance of severe asthma episodes, and death when those episodes occur",[86] and ordered a "black box" warning on the packaging, alerting doctors to the fact that the medicine could have potentially fatal side-effects.

At the request of the FDA, due to reports of serious paradoxical bronchospasm associated with the use of salmeterol and the previous epidemics of asthma-related deaths in patients taking other long-acting β agonists, GlaxoSmithKline initiated, in 1996, a randomised trial compared salmeterol to placebo (Salmeterol Multicenter Asthma Research Trial—SMART), that was prematurely halted in September 2002 after an interim analysis suggested an increased risk of asthma-related death in patients who use the drug as compared to a placebo.[87–89] Emphasising the commercial interests at stake, Wolfe and Lurie, in their critical analysis in The Lancet, conclude:[90] 'It is now approaching 3 years since the SMART study was terminated. The results have still not found their way into print and the drugs' labels have still not been finalised. Instead, the company, seemingly under little pressure from the FDA, has succeeded in drawing out the process and initially misleading the agency, physicians, and patients with not-per-protocol analyses that diminished the drug's apparent risks. In the absence of the transparency associated with Advisory Committee meetings, these deceptions would never have come to public attention. In 2001, however, only 21% of new drug approvals were preceded by Advisory Committee meetings, allowing most drugs to avoid similar public scrutiny'.

Discussion

Homeostasis promotes organic reactions to restore the balance of the internal environment altered by medicines, external stimuli and emotional factors. The secondary action or vital reaction of the homeopathic model is confirmed by studies about the rebound effect or paradoxical reaction of hundreds of modern medicines, utilised according to the contrary principle. The development of tolerance to a repeatedly administered drug is the result of a same regulated adaptive process.

The intensity and the severity of the paradoxical reactions are in conformity with the pharmacological conceptualisation of rebound effect, in which the rebound phenomenon sometimes is of greater intensity than the similar phenomenon initially suppressed. Although rebound effects manifest in a small proportion of the individuals, in view of their idiosyncratic nature, these serious or fatal paradoxical events assume epidemiological importance when we consider the enormous current consumption of allopathic drugs. In the controlled studies, compared to placebo, the risk of ischaemic events is 3.4 times larger after aspirin withdrawal, 1.52 times larger after NSAID withdrawal and 1.67 times larger after rofecoxib withdrawal: the risk of suicidal behaviour 6 times larger after SSRI antidepressant withdrawal. An "inconclusive" but important risk of fatal paradoxical bronchospasm after long-acting β agonists, withdrawal has also been reported.

After the suspension of the therapy, the time of appearance of the serious paradoxical reaction does not vary greatly between drugs: average of 10 days for aspirin, 2 weeks for the NSAIDs and 9 days for rofecoxib. The duration of the rebound effect was

mentioned only in the study with the rofecoxib, persisting for 30 days at the maximum. In this same study, the duration of the treatment, before the interruption of the drug, did not show association with the risk of awakening the serious paradoxical event.

The observation that there is no association between the dose of the substance and the paradoxical reaction, expressed by Hahnemann in paragraph 121 of the *Organon*, has been confirmed in two lines of research investigating the effect of antithrombotic drugs on thromboembolism and haemorrhage induced by aspirin. The first experimental model showed paradoxical or secondary thromboembolism after the administration of substantial[6,15] or ultra low[16,17] doses of antithrombotic agents (rebound effect). The second model showed the effect of substantial[18] or ultra low[19-23] doses of aspirin in prophylaxis or reduction of hemorrhagic risks (reducing the bleeding time or the antithrombotic effect), neutralising the side effect of aspirin previously administration in high doses (identity principle or curative rebound effect).

A mathematical model has been proposed to study the rebound effect and the tolerance of the organism. The oral detection and analysis of exogenous substances are proposed to be the primary stimulus for these mechanisms: the model reproduces the gradual decrease in drug effect when tolerance develops, the high sensitivity to small changes in dose, the rebound phenomenon and the large reactions following withdrawal in dependence. The model verifies the proposed theory and provides a basis for the implementation of mathematical models of specific physiological processes. In addition, it establishes a relation between the drug dose at any moment, and the resulting drug effect and relates the magnitude of the reactions following withdrawal to the rate of tolerance and rebound effect.[91,92]

Using inductive thought and pure observation, Hahnemann was ahead of the scientific thought of his time, developing guidelines for the treatment of the diseases that remain effective to the present, although they are not recognised by contemporary science. "These incontrovertible truths, which spontaneously offer themselves to our notice in nature and experience, explain to us the beneficial action that takes place under homoeopathic treatment; whilst, on the other hand, they demonstrate the perversity of the antipathetic and palliative treatment of diseases with antagonistically acting medicines". (*Organon*, paragraph 67)

References

1 Hahnemann S. *Organon of Medicine*, 6th Edn. (Translated by William Boericke). New Delhi: B Jain Publishers, 1991.

2 Teixeira MZ. *Semelhante cura semelhante: o princípio de cura homeopático fundamentado pela racionalidade médica e científica [Similar cures similar: the homoeopathic cure principle based by the medical and scientific rationality]*. São Paulo: Editorial Petrus, 1998.

3 Teixeira MZ. Similitude in modern pharmacology. *Homeopathy* 1999; **88**: 112–120.

4 Teixeira MZ. Homeopathic use of modern medicines: utilisation of the curative rebound effect. *Med Hypotheses* 2003; **60**: 276–283.

5 Teixeira MZ. Paradoxical strategy for treating chronic diseases: a therapeutic model used in homeopathy for more than two centuries. *Homeopathy* 2005; **94**: 265–266.

6 Ardelt W, Pasold K, Hillemanns HG. Side effects of drug for thromboembolism prophylaxis. Results from the University Women's Clinic Freiburg/Br. *Fortschr Med* 1979; **97**: 471–474.

7 Terashita Z, Imura Y, Tanabe M, *et al.* CV-4151—a potent, selective thromboxane A2 synthetase inhibitor. *Thromb Res* 1986; **41**: 223–237.

8 Averkov OV, Zateishchikov DA, Gratsianskii NA, Logutov IuA, Iavelov IS, Ianus V. Unstable angina: effect of aspirin and heparin on treatment outcome in hospital patients (a double-blind, placebo-controlled study). *Kardiologiia* 1993; **33**: 4–9.

9 Mousa SA, Forsythe MS, Bozarth JM, Reilly TM. Effect of single oral dose of aspirin on human platelet functions and plasma plasminogen activator inhibitor-1. *Cardiology* 1993; **83**: 367–373.

10 Beving H, Eksborg S, Malmgren RS, Nordlander R, Ryden L, Olsson P. Inter-individual variations of the effect of low dose aspirin regime on platelet cyclooxygenase activity. *Thromb Res* 1994; **74**: 39–51.

11 Raskob GE, Durica SS, Morrissey JH, Owen WL, Comp PC. Effect of treatment with low-dose warfarin aspirin on activated factor VII. *Blood* 1995; **85**: 3034–3039.

12 Col J. Current point of view on medical treatment of unstable angina. *Arch Mal Coeur Vaiss* 1996; **Spec (5)**: 15–18.

13 Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, *et al.* Effects of integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. *Circulation* 1996; **94**: 2083–2089.

14 Aguejouf O, Belougne-Malfati E, Doutremepuich F, Belon P, Doutremepuich C. Tromboembolic complications several days after a single-dose administration of aspirin. *Thromb Res* 1998; **89**: 123–127.

15 Main C, Palmer S, Griffin S, *et al.* Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation. *Health Technol Assess* 2004; **8**: 1–156.

16 Doutremepuich C, Aguejouf O, Pintigny D, Sertillanges MN, De Seze O. Thrombogenic properties of ultra-low-dose of acetylsalicylic acid in a vessel model of laser-induced thrombus formation. *Thromb Res* 1994; **76**: 225–229.

17 Doutremepuich CH, Aguejouf O, Belon P. Effects of ultra-low dose aspirin on embolization in a model of laser-induced thrombus formation. *Semin Thromb Hemost* 1996; **22**(Suppl 1): 67–70.

18 Aguejouf O, Malfatti E, Belon P, Doutremepuich C. Effects of acetyl salicylic acid therapy on an experimental thrombosis induced by laser beam. *Thromb Res* 2000; **99**: 595–602.

19 Belougne-Malfatti E, Aguejouf O, Doutremepuich F, Belon P, Doutremepuich C. Combination of two doses of acetyl salicylic acid: experimental study of arterial thrombosis. *Thromb Res* 1998; **90**: 215–221.

20 Doutremepuich C, Aguejouf O, Malfatti E, Belon P. Time related neutralization of two doses acetyl salicylic acid. *Thromb Res* 2000; **100**: 317–323.

21 Doutremepuich C, Pailley D, Anne MC, De Seze O, Paccalin J, Quilichini R. Template bleeding time after ingestion of ultra-low doses of acetylsalicylic acid in healthy subjects. Preliminary study. *Thromb Res* 1987; **48**: 501–504.

22 Doutremepuich C, De Seze O, Le Roy D, Lalanne MC, Anne MC. Aspirin at very ultra low dosage in healthy volunteers: effects on bleeding time, platelet aggregation and coagulation. *Haemostasis* 1990; **20**: 99–105.

23 Lalanne MC, Doutremepuich C, de Seze O, Belon P. What is the effect of acetylsalicylic acid at ultra low dose on the interaction platelets/vessel wall? *Thromb Res* 1990; **60**: 231–236.

24 Ferrari E, Benhamou M, Cerboni P, Baudouy M. Coronary syndromes following aspirin withdrawal. 69a Annual International Scientific Assembly of The American College of Chest Physicians, Orlando, EUA. 2003. *CHEST* 2003; **124**: 148S.

25 Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol* 2005; **45**: 456–459.

26 Aetna InteliHealth, Harvard Medical School. Health News: Aspirin withdrawal may pose risk to coronary patients. Available on: ⟨http://www.intelihealth.com/IH/ihtIH/WSAZR000/333/341/371250.html⟩.

27 Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discountinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol* 2005; **62**: 1217–1220.

28 Andrioli G, Lussignoli S, Ortolani R, Minuz P, Vella F, Bellavite P. Dual effects of diclofenac on human platelet adhesion in vitro. *Blood Coagul Fibrinolysis* 1996; **7**: 153–156.

29 Andrioli G, Lussignoli S, Gaino S, Benoni G, Bellavite P. Study on paradoxical effects of NSAIDs on platelet activation. *Inflammation* 1997; **21**: 519–530.

30 Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR. Discontinuation of nonsteroidal anti-inflammatory drugs is associated with an increased risk of acute myocardial infarction. *Arch Intern Med* 2004; **164**: 2472–2476.

31 Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. *Neurology* 2004; **62**: 1187–1189.

32 Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged > or = 70. *BMJ* 2005; **330**: 1306.

33 Pijak MR. Rebound inflammation and the risk of ischemic stroke after discontinuation of aspirin therapy. *Arch Neurol* 2006; **63**: 300–301.

34 Griffin MR, Stein CM, Graham DJ, Daugherty JR, Arbogast PG, Ray WA. High frequency of use of rofecoxib at greater than recommended doses: cause for concern. *Pharmacoepidemiol Drug Saf* 2004; **13**: 339–343.

35 Bombardier C, Laine L, Reicin A, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; **343**: 1520–1528.

36 Graham DJ, Campen D, Hui R, *et al.* Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case control study. *Lancet* 2005; **365**: 475–481.

37 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case control analysis. *BMJ* 2005; **330**: 1366.

38 Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002; **360**: 1071–1073.

39 Johnsen SP, Larsson H, Tarone RE, *et al.* Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case–control study. *Arch Intern Med* 2005; **165**: 978–984.

40 Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005; **142**: 481–489.

41 Levesque LE, Brophy JM, Zhang B. Time variations in the risk of myocardial infarction among elderly users of COX-2 inhibitors. *CMAJ* 2006; **174**: 1563–1569.

42 Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; **332**: 1302–1308.

43 Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. *BMJ* 2004; **328**: 879–883.

44 Culpepper L, Davidson JR, Dietrich AJ, Goodman WK, Kroenke K, Schwenk TL. Suicidality as a possible side effect of antidepressant treatment. *J Clin Psychiatry* 2004; **65**: 742–749.

45 Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004; **292**: 338–343.

46 Leon AC, Marzuk PM, Tardiff K, Teres JJ. Paroxetine, other antidepressants, and youth suicide in New York City: 1993 through 1998. *J Clin Psychiatry* 2004; **65**: 915–918.

47 Gunnell D, Ashby D. Antidepressants and suicide: what is the balance of benefit and harm. *BMJ* 2004; **329**: 34–38.

48 Lenzer J. Secret US report surfaces on antidepressants in children. *BMJ* 2004; **329**: 307.

49 Nelson R. Antidepressant use in children – safe or not? Hiding unfavorable data makes it hard to know. *Am J Nurs* 2004; **104**: 25–26.

50 US Food and Drug Administration. FDA Public Health Advisory (October 15, 2004): "Suicidality in children and adolescents being treated with antidepressant medications". Available on: ⟨http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm⟩.

51 US Food and Drug Administration. FDA Public Health Advisory (June 30, 2005): 'Suicidality in adults being treated with antidepressant Medications'. Available on: ⟨http://www.fda.gov/cder/drug/advisory/SSRI200507.htm⟩.

52 Aetna InteliHealth, Harvard Medical School. Health News: FDA warns of suicide risk for Paxil. Available on: ⟨http://www.intelihealth.com/IH/ihtIH/EMIHC000/333/8014/466054.html⟩.

53 Spencer TJ, Biederman J, Wilens TE, Faraone SV. Novel treatments for attention-deficit/hyperactivity disorder in children. *J Clin Psychiatry* 2002; **63**(Suppl 12): 16–22.

54 Hesse LM, Von Moltke LL, Greenblatt DJ. Clinically important drug interactions with zopiclone, zolpidem and zaleplon. *CNS Drugs* 2003; **17**: 513–532.

55 Wichniak A, Brunner H, Ising M, Pedrosa Gil F, Holsboer F, Friess E. Impaired hypothalamic pituitary–adrenocortical (HPA) system is related to severity of benzodiazepine withdrawal in patients with depression. *Psychoneuroendocrinology* 2004; **29**: 1101–1108.

56 Verdoux H, Bourgeois M. Short-term sequelae of lithium discontinuation. *Encephale* 1993; **19**: 645–650.

57 Steiger A, Benkert O, Holsboer F. Effects of long-term treatment with the MAO-A inhibitor moclobemide on sleep EEG and nocturnal hormonal secretion in normal men. *Neuropsychobiology* 1994; **30**: 101–105.

58 Feige B, Voderholzer U, Riemann D, Dittmann R, Hohagen F, Berger M. Fluoxetine and sleep EEG: effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. *Neuropsychopharmacology* 2002; **26**: 246–258.

59 D'Aquila PS, Peana AT, Panin F, Grixoni C, Cossu M, Serra G. Reversal of antidepressant-induced dopaminergic behavioural supersensitivity after long-term chronic imipramine withdrawal. *Eur J Pharmacol* 2003; **458**: 129–134.

60 D'Aquila PS, Panin F, Serra G. Long-term imipramine withdrawal induces a depressive-like behaviour in the forced swimming test. *Eur J Pharmacol* 2004; **492**: 61–63.

61 Verster JC, Volkerts ER. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. *CNS Drug Rev* 2004; **10**: 45–76.

62 Lerman C, Niaura R, Collins BN, *et al.* Effect of bupropion on depression symptoms in a smoking cessation clinical trial. *Psychol Addict Behav* 2004; **18**: 362–366.

63 Wolfe RM. Antidepressant withdrawal reactions. *Am Fam Physician* 1997; **56**: 455–462.

64 Feige B, Voderholzer U, Riemann D, Dittmann R, Hohagen F, Berger M. Fluoxetine and sleep EEG: effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. *Neuropsychopharmacology* 2002; **26**: 246–258.

65 Wolfe RM. Antidepressant withdrawal reactions. *Am Fam Physician* 1997; **56**: 455–462.

66 Pace-Schott EF, Gersh T, Silvestri R, Stickgold R, Salzman C, Hobson JA. SSRI treatment suppresses dream recall frequency but increases subjective dream intensity in normal subjects. *J Sleep Res* 2001; **10**: 129–142.

67 Gervasoni D, Panconi E, Henninot V, *et al.* Effect of chronic treatment with milnacipran on sleep architecture in rats compared with paroxetine and imipramine. *Pharmacol Biochem Behav* 2002; **73**: 557–563.

68 De Oliveira RA, Cunha GM, Borges KD, *et al.* The effect of venlafaxine on behaviour, body weight and striatal monoamine levels on sleep-deprived female rats. *Pharmacol Biochem Behav* 2004; **79**: 499–506.

69 Stolley PD. Why the United States was spared an epidemic of deaths due to asthma. *Am Rev Respir Dis* 1972; **105**: 883–890.

70 Aellig WH. Pindolol – a beta-adrenoceptor blocking drug with partial agonist activity: clinical pharmacological considerations. *Br J Clin Pharmacol* 1982; **13**(Suppl 2): 187S–192S.

71 Newcomb R, Tashkin DP, Hui KK, Conolly ME, Lee E, Dauphinee B. Rebound hyperresponsiveness to muscarinic stimulation after chronic therapy with an inhaled muscarinic antagonist. *Am Rev Respir Dis* 1985; **132**: 12–15.

72 Vathenen AS, Knox AJ, Higgins BG, Britton JR, Tattersfield AE. Rebound increase in bronchial responsiveness after treatment with inhaled terbutaline. *Lancet* 1988; **1**: 554–558.

73 Svedmyr N. Action of corticosteroids on beta-adrenergic receptors. Clinical aspects. *Am Rev Respir Dis* 1990; **141**(2, Part 2): S31–S38.

74 Cochrane GM. Bronchial asthma and the role of beta 2-agonists. *Lung* 1990; **168**(Suppl): 66–70.

75 Svedmyr N. The current place of beta 2-agonists in the management of asthma. *Lung* 1990; **168**(Suppl): 105–110.

76 Mintzer MJ. Asthma therapy: present trends and future prospects. *Compr Ther* 1990; **16**: 12–16.

77 Beach R, Young CL, Harkawat R, *et al.* Effect on airway responsiveness of six weeks treatment with salmeterol. *Pulm Pharmacol* 1993; **6**: 155–157.

78 Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung KF. Regular formoterol treatment in mild asthma. Effect on bronchial responsiveness during and after treatment. *Am J Respir Crit Care Med* 1995; **152**(4, Part 1): 1170–1174.

79 De Jong JW, van der Mark TW, Koeter GH, Postma DS. Rebound airway obstruction and responsiveness after cessation of terbutaline: effects of budesonide. *Am J Respir Crit Care Med* 1996; **153**: 70–75.

80 Kozlik-Feldmann R, von Berg A, Berdel D, Reinhardt D. Long-term effects of formoterol and salbutamol on bronchial hyperreactivity and beta-adrenoceptor density on lymphocytes in children with bronchial asthma. *Eur J Med Res* 1996; **1**: 465–470.

81 Wilding PJ, Clark MM, Oborne J, Bennett JA, Tattersfield AE. Effect of regular terbutaline on the airway response to inhaled budesonide. *Thorax* 1996; **51**: 989–992.

82 Bennett JA, Thompson Coon J, Pavord ID, Wilding PJ, Tattersfield AE. The airway effects of stopping regular oral theophylline in patients with asthma. *Br J Clin Pharmacol* 1998; **45**: 402–404.

83 Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. *Respir Med* 2000; **94**: 767–771.

84 Farmer P, Pugin J. Beta-adrenergic agonists exert their 'anti-inflammatory' effects in monocytic cells through the IkappaB/NF-kappaB pathway. *Am J Physiol Lung Cell Mol Physiol* 2000; **279**: L675–L682.

85 Van Schayck CP, Closterman SG, Bijl-Hofland ID, Van den Hoogen H, Folgering HT, Van Weel C. Is the increase in bronchial responsiveness or FEV1 shortly after cessation of beta2-agonists reflecting a real deterioration of the disease in allergic asthmatic patients? A comparison between short-acting and long-acting beta2-agonists. *Respir Med* 2002; **96**: 155–162.

86 US Food and Drug Administration. FDA Public Health Advisory: 'Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol inhalation powder), Foradil Aerolizer (formoterol fumarate inhalation powder)'. Available on: ⟨http://www.fda.gov/cder/drug/advisory/LABA.htm⟩.

87 Knobil K, Yancey S, Kral K, Rickard K. Salmeterol multicenter asthma research trial (SMART): results from an interim analysis. 69th Annual International Scientific Assembly of The American College of Chest Physicians, Orlando, EUA, 2003. *CHEST* 2003; **124**: 335S.

88 US Food and Drug Administration. The FDA Safety Information and Adverse Event Reporting Program: 2003 Safety Alert – Serevent (salmeterol xinafoate). Available on: ⟨http://www.fda.gov/medwatch/SAFETY/2003/serevent.htm⟩.

89 Health Canada. Advisory 2005-107, October 4, 2005: Safety information about a class of asthma drugs known as long-acting beta-2 agonists. Available on: ⟨http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_107_e.html⟩.

90 Lurie P, Wolfe SM. Misleading data analyses in salmeterol (SMART) study. *Lancet* 2005; **366**: 1261–1262 discussion 1262.

91 Peper A. A theory of drug tolerance and dependence I: a conceptual analysis. *J Theor Biol* 2004; **229**: 477–490.

92 Peper A. A theory of drug tolerance and dependence II: the mathematical model. *J Theor Biol* 2004; **229**: 491–500.