Scientific basis of the homeopathic healing principle in modern pharmacology

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Abstract

Background: Homeopathy employs the so-called 'principle of similars' as therapeutic method - which consists in administering medicines that cause certain symptoms in healthy individuals to treat similar symptoms in sick individuals (*similia similibus curantur*) - to induce a secondary and healing reaction by the body against its own disorders. This secondary (vital, homeostatic or paradoxical) reaction of the body is based on the 'rebound effect' of modern drugs, a type of adverse event that occurs following discontinuation of several classes of drugs prescribed according to the 'principle of contraries' *(contraria contrariis curantur)*. Aim: The present review sought to scientifically substantiate the homeopathic healing principle vis-à-vis experimental and clinical pharmacology through a systematic study of the rebound effect of modern drugs or paradoxical reaction of the body. Methods: Employing as reference studies and revisions on the subject published since 1998, we updated the data adding recent studies included in database PubMed. Results: The rebound effect occurs after discontinuation of several classes of drugs with action contrary to the symptoms of diseases, exacerbating them to levels above the ones before treatment. Regardless of disease, drug, dose and duration of treatment, the rebound phenomenon manifests in a small proportion of susceptible individuals. Following the homeopathic premises, modern drugs might also be used according to the principle of therapeutic similitude, thus employing the rebound effect (paradoxical reaction) with curative intent. Conclusions: Evidenced by hundreds of studies that attest to the similarity of concepts and manifestations, the rebound effect of modern drugs scientifically substantiates the principle of homeopathic cure. Although the rebound phenomenon is an adverse event studied by modern pharmacology, it is not known by health care professionals, thus depriving doctors of knowledge indispensable for safe management of drugs.

Keywords

Homeopathy; Pharmacology; Physiological effects of drugs; Law of similars; Pharmacodynamic action of homeopathic remedies; Secondary action; Rebound effect

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Introduction

As early is in ancient Greece, Hippocrates, the 'Father of Medicine', taught that diseases could be treated according to the principle of contraries *(contraria contrariis curantur*) or of similars (*similia similibus curantur*). These recommendations were followed by later medical schools [1-3].

Currently, the principle of contraries is massively employed in conventional therapeutics. Medicines are used whose primary action is contrary ('anti') the signs or symptoms of diseases to neutralize or palliate their manifestations. In turn, the principle of similars is applied in homeopathic therapeutics. Medicines are used whose primary action is similar (*homeo*) to the signs and symptoms of diseases to trigger a reaction in the body against such manifestations, i.e., disease.

The homeopathic method of treatment is based on four pillars: 1) principle of therapeutic similitude, 2) testing of medicines on healthy individuals (homeopathic pathogenetic trials – HPT), 3) prescription of individualized medicines, and 4) use of serially diluted and agitated (potentized) medicines (high dilutions - HD). Although much relevance is attributed to HDs - introduced later into the homeopathic model initially to minimize possible worsening ('aggravation') of symptoms resulting from the application of the similitude principle - the first 2 pillars represent the proper foundation of the homeopathic epistemological model (hard core, in Lakatos' terms) [4]. In turn, medicines ought to be individualized (selected according to the all the characteristic signs and symptoms exhibited by patients) as indispensable condition for triggering a therapeutic response.

Given the epistemological relevance of therapeutic similitude vis-à-vis the remainder of homeopathic assumptions, in 1998 this author started a project aiming at providing scientific grounds for this principle through systematic study of the 'rebound effect' of modern drugs ('paradoxical reaction' of the body) [7-23]. The rebound effect consists in the appearance of a secondary reaction opposed to and after the end of the primary action of countless categories of conventional palliative drugs. This phenomenon is analogous to the one described in homeopathy, as is shown below.

Along the past decade, pharmacologists suggested a therapeutic strategy named 'paradoxical pharmacology'. Similar to the one applied in homeopathy for more than 2 centuries, it advocates the use of conventional drugs that cause a short-term exacerbation of disease to treat the very same disease in the long run [24-36]. Analogously, since the beginning of the research [7-9] we have been advocating the use of modern drugs according to the therapeutic similitude principle. In other words, using drugs which cause adverse events similar to the manifestations of disease to treat them homeopathically. This means employing the rebound effect (paradoxical reaction) with curative intention [37-46]; results are promising and indications countless. An example is provided by the use of potentized estrogen for treatment of endometriosis-related pelvic pain [44-46].

The present review of the rebound effect of modern drugs aims at providing scientific grounds to the homeopathic healing principle (therapeutic similitude) vis-à-vis clinical and experimental pharmacology by demonstrating the properties, particularities and similarities between both phenomena.

Materials and methods

Reference sources were studies and reviews on the rebound effect we published since 1998 [7-20,37-46]. The data were updated through a search of recent studies included in database PubMed using keywords 'rebound', 'withdrawal', 'paradoxical', 'acetylsalicylic acid', 'anti-inflammatory', 'bronchodilator', 'antidepressant', 'statin', 'proton pump inhibitor', 'bisphosphonate', 'biological therapy' and 'immunomodulatory drug'. We also describe suggestions for use of modern drugs according to the therapeutic similitude principle [24-36,37-46]. This is, by applying the rebound effect (paradoxical reaction) with curative intention; examples from present-day clinical practice are provided.

The similitude principle according to homeopathy

In the development of the homeopathic approach to treatment, Samuel Hahnemann (1755-1843) had resource to the phenomenological method of qualitative research to describe the effects of contemporary drugs on the human physiology and ground the therapeutic similitude principle. Hahnemann first noticed that medicines cause signs and symptoms in healthy individuals similar to the ones exhibited by patients cured with the same medicines. He then sought to confirm this empirical observation through analogy and enumeration. He surveyed the literature and found hundreds of clinical reports by doctors from all times and places, involving many different categories of drugs (strong argument) which confirmed his finding ["Examples of homeopathic cures performed unintentionally by physicians of the old school of medicine", 47]. With these evidences in hands and through the application of Aristotelian inductive reasoning (*modus ponens*), Hahnemann outlined the homeopathic healing principle: **for any medicine to cure symptoms in the sick, it must induce similar symptoms in the healthy**:

> And whence could arise that curative power which it [arsenic] exhibits in certain species of intermittent fevers (a virtue attested by so many thousands of examples, but in the practical application of which, sufficient precaution has not yet been observed, and which virtue was asserted centuries ago by Nicholas Myrepsus, and subsequently placed beyond a doubt by the testimony of Slevogt, Molitor, Jacobi, J.C. Bernhardt, Jüngken, Fauve, Brera, Darwin, May, Jackson and Fwler) if it did not proceed from **its peculiar faculty of exciting fever,** as almost every observer of the evils resulting from this substance has remarked, particularly Amatus Lusitanus, Degner, Buchholz, Heun and Knape. We may confidently believe E. Alexander, when he tells us that **arsenic** is a sovereign remedy in some cases of angina pectoris, since Tachenius, Guilbert, Preussius, Thilenius, and Pyl, gave seen it give rise to a strong **oppression of the chest**; Gresselius, to a **dyspnea approaching even to suffocation**; and Majault, in particular, saw it produce **sudden attacks of asthma excited by walking, attended with great prostration of the vital powers** (original emphasis) [47, p. 81-2].

It is traditionally asserted that homeopathy began with Hahnemann's publication of *Essay on a new principle to ascertaining the curative powers of drugs* [48], in 1796. In

this essay Hahnemann described the pharmacological effects of dozens of contemporary medicines, distinguishing between their 'primary actions' and the consequent and opposed 'secondary indirect actions' of the body, thus evidencing the new healing principle. Continuing with the example of arsenic:

> *Arsenic (Arsenicum album).*
>
> - *Direct primary action:* Tendency to excite spasm in the blood vessels and chills, with daily paroxysms; with continuous use in large doses, it gradually causes an almost constant feverish state; reduction of the muscle fiber tonus and of the nerve sensitivity (paralysis); it promotes cough (asthma); it causes some chronic skin diseases (desquamating).
> - *Secondary indirect action (healing principle):* Treatment for intermittent fever, with daily recurrence; useful for hectic and remittent fever; some kinds of paralysis; cough (asthma); similar skin diseases.

In § 63 to 65 of *Organon of medicine* [49], Hahnemann attempted a physiological explanation for such 'natural healing law'. He grounded the similitude principle on the primary action of drugs and the consequent and opposite secondary action, or vital reaction of the body:

> 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. Although a product of the medicinal and vital powers conjointly, it is principally due to the former power. To its action our vital force endeavors 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 of medicine,* § 63) [49].

As an example, Hahnemann described the primary actions of drugs in the various physiological systems and consequent secondary actions (reaction) of the body, characterized by effects opposite to the primary physiological changes. The latter lead the body back to the state previous to intervention (life-preserving power, i.e., modern homeostasis):

> [...] 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 (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed,

> there is actually such a thing, is produced in the secondary action by our vital force" (*Organon of medicine,* § 65) [49].

Pointing to the unpleasant results of indiscriminate use of medicines with action contrary to the signs and symptoms of disease (*Organon of medicine,* § 59-61) [49], Hahnemann called the attention to the fact that the secondary action (vital reaction) of the body might cause undesirable effects ("a relapse – indeed, a palpable aggravation of the malady"). Therefore, upon denying the efficacy of palliative or antipathic treatment (principle of contraries) for treatment of chronic diseases, Hahnemann sought to validate homeopathic treatment (similitude principle) through resource to Aristotelian inductive reasoning (*modus tollens*, affirmation through negation, indirect demonstration, i.e., the null hypothesis of modern biostatistics):

> Important symptoms of persistent diseases have never yet been treated with such palliative, antagonistic remedies, without the opposite state, a relapse - indeed, a palpable aggravation of the malady - occurring a few hours afterwards. For a persistent tendency to sleepiness during the day the physician prescribed coffee, whose primary action is to enliven; and when it had exhausted its action the day - somnolence increased; - for frequent waking at night he gave in the evening, without heeding the other symptoms of the disease, opium, which by virtue of its primary action produced the same night (stupefied, dull) sleep, but the subsequent nights were still more sleepless than before; - to chronic diarrheas he opposed, without regarding the other morbid signs, the same opium, whose primary action is to constipate the bowels, and after a transient stoppage of the diarrhea it subsequently became all the worse; - violent and frequently recurring pains of all kinds he could suppress with opium for but a short time; they then always returned in greater, often intolerable severity, or some much worse affection came in their stead. […] weakness of the bladder, with consequent retention of urine, was sought to be conquered by the antipathic work of cantharides to stimulate the urinary passages whereby evacuation of the urine was certainly at first effected but thereafter the bladder becomes less capable of stimulation and less able to contract, and paralysis of the bladder is imminent; - with large doses of purgative drugs and laxative salts, which excite the bowels to frequent evacuation, it was sought to remove a chronic tendency to constipation, but in the secondary action the bowels became still more confined; […] severely burnt parts feel instantaneous alleviation from the application of cold water, but the burning pain afterwards increases to an incredible degree, and the inflammation spreads and rises to a still greater height […] How often, in one word, the disease is aggravated, or something even worse is effected by the secondary action of such antagonistic (antipathic) remedies, the old school with its false theories does not perceive, but experience teaches it in a terrible manner (*Organon of medicine,* § 59) [49].

Since the secondary reaction of the body (opposed to the primary action of the drug) could occur with any category of drugs independently from the dose (ponderable or highly diluted), Hahnemann raised the similitude principle to the status of "natural phenomenon" (*Organon of medicine,* § 58, 61, 110-112) [49].

Through administration to the sick of the very medicines that induce similar symptoms in the healthy on HPT (similar to our phase I clinical trials) [50,51], the aim of therapeutic similitude is to trigger a curative homeostatic reaction by making the body react against its own disorders. It should be noticed that terms 'secondary action/reaction', 'vital reaction' and 'homeostatic reaction' designate one and the same phenomenon, i.e., the ability of living beings to maintain the internal environment constant (homeostasis) through automatic self-adjustment of the physiological processes, ranging from simple cell mechanisms to complex mental functions.

Similitude principle in modern pharmacology

In modern scientific terms, Hahnemann's 'primary action' corresponds to the 'therapeutic, adverse and side effects' of conventional drugs. In turn, the homeopathic 'secondary action' or 'vital reaction' corresponds to the 'rebound effect' or 'paradoxical reaction' of the body that follows discontinuation of countless categories of drugs that work in a manner opposed (palliative, antagonistic or enantiopathic) to the signs and symptoms of disease.

By definition, 'rebound effect' consists in the production of increased negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it was used to treat may come back even stronger when the drug is discontinued or loses effectiveness [52]. Analogously, 'paradoxical reaction' is a response opposed to the foreseen effect of a drug. Briefly, we might understand rebound effect as an automatic and instinctive manifestation of the homeostatic mechanisms aiming at reestablishing the original state, altered by the primary action of drugs, resulting in an effect opposed and contrary to the expected one.

According to reviews on this subject [53-55], the rebound effect appears following interruption or discontinuation of drugs, causing manifestations with stronger intensity and/or more frequent than the ones originally suppressed (which distinguish it from relapse of the original disease following the end of the primary action of drugs). These manifestations appear at variable intervals and also have variable duration. As a feature intrinsic to the phenomenon, one should consider a minimum interval of time to have a sound notion of the true magnitude of the phenomenon; this minimum interval corresponds to the full metabolism of drugs or absence of therapeutic effect (biological half-life). While discontinuation is a requisite for the rebound effect to manifest – since the primary action continues as long as receptors are bounded to the drug – some studies showed that it might also occur along the course of treatment, in cases of therapeutic failure or development of tolerance, tachyphylaxis or receptor desensitization. In turn, drug tapering avoids abrupt discontinuation, and thus minimizes the occurrence of the rebound effect.

The following examples with various categories of drugs illustrate the universal nature of the rebound effect [7-23].

Drugs classically used for treatment of **angina pectoris** (β-blockers, calcium channel blockers, nitrates, and others) with beneficial effects through their primary action might trigger a paradoxical increase of the frequency and intensity of chest pain after discontinuation. Drugs used for **arterial hypertension** (α-2 agonists, β-blockers, ACE inhibitors, MAO inhibitors, nitrates, sodium nitroprusside, hydralazine, and others) might produce rebound arterial hypertension once the primary biological effect ends. **Antiarrhythmic** drugs (adenosine, amiodarone, β-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine and procainamide, among others) may trigger rebound exacerbation of basal ventricular arrhythmias. **Antithrombotic** drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, clopidogrel, and others), might promote thrombotic complications as result of the rebound effect. Drugs with primary **pleiotropic or vasoprotective** effect (statins) might cause rebound endothelial dysfunction, resulting in predisposition to paradoxical vascular accidents.

Analogously, discontinuation of **anxiolytics** (barbiturates, benzodiazepines, carbamates, and others), **sedative-hypnotics** (barbiturates, benzodiazepines, morphine, promethazine, zopiclone, and others), **stimulants of the central nervous system** (amphetamines, caffeine, cocaine, mazindol, methylphenidate, and others), **antidepressants** (tricyclic, MAO inhibitors, selective serotonin reuptake inhibitors, and others) or **antipsychotics** (clozapine, phenothiazines, haloperidol, pimozide, and others) might cause rebound aggravation of the original condition after the end of their primary therapeutic effect.

Anti-inflammatory agents (steroids, ibuprofen, indomethacin, paracetamol, salicylates, and others) might trigger paradoxical increase of inflammation and rebound thrombosis (ibuprofen, indomethacin, diclofenac, salicylates, rofecoxib, and celecoxib, among others) as a function of their primary platelet anti-aggregation action.

Analgesics (caffeine, calcium channels blockers, clonidine, ergotamine, methysergide, opiates, salicylates, and others) might trigger rebound hyperalgesia. **Diuretics** (furosemide, torasemide, triamterene, and others) might cause rebound sodium and potassium retention, with consequent increase of the plasma volume and the blood pressure. **Bronchodilators** (short- and long-acting ß-adrenergic agonists, sodium cromoglycate, epinephrine, ipratropium and nedocromil, among others) might promote rebound bronchoconstriction as paradoxical reaction to discontinuation.

Anti-dyspeptic (antacids, H_2 antagonists, misoprostol, sucralfate, protons pump inhibitors, and others) might trigger rebound increase of hydrochloric acid and gastrin production, with worsening of the original condition. **Antiresorptive** drugs used for treatment of osteoporosis (bisphosphonates, denosumab, odanacatib and others) might cause paradoxical atypical fractures due to rebound osteoclast activity increase.

Discontinuation of drugs for treatment of **multiple sclerosis** (glucocorticoids, interferon, glatiramer acetate, natalizumab, fingolimod, and others) might cause rebound increase of inflammation, with attending exacerbation of clinical symptoms and increase of demyelination lesions. **Immunomodulatory** agents (recombinant monoclonal antibodies, tumor necrosis factor inhibitors, among others) indicated for treatment of psoriasis might trigger rebound psoriasis after discontinuation. The list of examples is much longer.

These clinical and experimental pharmacological evidences [7-23] show that the characteristics of the rebound effect are similar to the homeopathic secondary action or reaction (*Organon of medicine,* § 59, 64, 69) [49]: 1) it induces a body reaction opposed to and of greater intensity compared to the primary action of drugs; 2) it takes place after the end of the primary action of the drug, and as automatic manifestation of the body; 3) it does not depend on the type of drug, dose, treatment duration or category of symptoms (disease); 4) its magnitude is proportional to the primary action of the drug; and 5) it appears in susceptible individuals only (idiosyncrasy).

Despite the idiosyncratic nature of the rebound effect – which appears in a small proportion of individuals – scientific evidences point to the occurrence of severe and fatal events as result of the paradoxical reaction of the body following discontinuation of different categories of drugs. This corroborates the magnitude of the phenomenon, the need to be duly known by health care providers and the benefits of its therapeutic application according to the similitude principle.

Rebound effect promotes severe and fatal events [16,17,20,21]

Rebound effect of platelet anti-aggregation drugs [10,11]

Acetylsalicylic acid (ASA)

ASA belongs to non-steroidal anti-inflammatory drugs (NSAID) that are non-selective cyclooxygenase (COX) inhibitors; COX catalyses the conversion of arachidonic acid into prostaglandins (COX-2) and thromboxanes (COX-1). Largely used for prevention of thromboembolic events, ASA is able to avoid thrombus formation through inhibition of COX-1 (mediator of platelet activity by the thromboxane A2 (TXA_2) synthesis) and platelet aggregation.

Experimental studies [56-63] showed that following discontinuation of platelet anti-aggregation drugs for thromboembolism prevention, a rebound or paradoxical reaction might occur, resulting in increase of COX-1 production and platelet activity (TXA_2) to values higher than the ones before treatment. With this the odds for thromboembolic events (unstable angina (UA), acute myocardial infarction (AMI), stroke, and others) increase among susceptible individuals.

In a retrospective study [64] 1,236 patients hospitalized for acute coronary syndrome (ACS) were inquired as to discontinuation of prophylactic ASA. 51 cases of ACS occurred within 1 month after withdrawal, representing 4.1% of all coronary events and 13.3% of cases of relapse. Among the patients who relapsed, the incidence of ACS with ST- elevation was higher among the ones who had discontinued ASA compared to the 332 patients who had not (39% vs. 18%; p= 0.001). The average interval between ASA withdrawal and acute coronary event was 10±1.9 days. These findings support the hypothesis that ASA withdrawal in coronary patients might represent a real risk for occurrence of a new thromboembolic event.

To investigate ASA discontinuation as risk factor for ischemic stroke (IS), Maulaz et al. [65] conducted a case-control study with 309 patients with IS or transient ischemic attack (TIA) subjected to long-term ASA treatment before the index event and 309 controls who had not had IS in the previous 6 months. The authors compared frequency of ASA discontinuation 4 weeks before an ischemic cerebral event among patients and before interview among controls. ASA discontinuance exhibited odds ratio (OR) 3.4 (95% confidence interval – 95%CI: 1.08-10.63; p< 0.005) for IS or TIA, i.e., 3.4 times higher risk for ischemic events among the patients who had discontinued treatment. These findings stress the relevance of adhering to ASA treatment, and provide an estimate of the risk associated with ASA discontinuation among patients at high risk for IS.

A meta-analysis [66] was performed with 50,279 patients (6 studies) at high risk for coronary artery disease (CAD) to assess the risk of discontinuation of or non-adherence to ASA. One study (31,750 patients) assessed adherence to ASA for secondary prevention of CAD, 2 studies (2,594 patients) the influence of ASA discontinuation on acute CAD, 2 studies (13,706 patients) adherence to ASA before or shortly after coronary artery bypass surgery, and 1 study (2,229 patients) ASA discontinuation among patients subjected to drug-eluting stent. Overall, ASA non-adherence/withdrawal was associated with 3-fold higher risk of major adverse cardiac events (OR = 3.14; 95%CI 1.75-5.61; p= 0.0001).

To assess the risk of AMI and death by CAD after discontinuation of aspirin low-dose in patients with history of cardiovascular events, a recent case-control study was conducted in the United Kingdom with 39,513 individuals who received a first prescription for ASA (75-300 mg/day) for secondary prevention of cardiovascular outcomes. The participants were followed up for 3.2 years, on average, to detect cases of non-fatal AMI or death by CAD. There were 876 cases of non-fatal AMI and 346 deaths by CAD. Compared to current users, the patients who had recently discontinued ASA exhibited significantly higher risk of non-fatal AMI or death by CAD combined (relative risk – RR: 1.43; 95%CI: 1.12-1.84) and of non-fatal AMI alone (RR: 1.63; 95%CI: 1.23-2.14). There was no significant association between recent discontinuation of low dose ASA and risk of death by CAD (RR: 1.07; 95%CI: 0.67-1.69). For every 1,000 patients-years there were about 4 more cases of non-fatal AMI among patients who discontinued low dose ASA (recent discontinuers) compared to patients who continued treatment [67,68].

In a recent review, Gerstein et al. [69] called the attention to rebound platelet aggregation associated with ASA discontinuation in the perioperative period, which might trigger significant ischemic events among patients with established cardiovascular disease. In many surgical procedures, the risk of bleeding due to intraoperative ASA is minimal compared to the risk for thromboembolism concomitant to discontinuation [70-73].

Studying the frequency of stroke occurring after antiplatelet drugs (APD) discontinuation, Sibon & Orgogozo [74] found that only 4.49% of strokes were related to recent APD discontinuation, but all cases occurred between 6 and 10 days after withdrawal (p< 0.0001).

Countless evidences confirm rebound platelet aggregation to be a natural and universal (independent from the drug used) phenomenon; all categories of APD (salicylates, heparin,

warfarin, clopidogrel, and others) cause rebound thromboembolism after discontinuation, and might cause severe and fatal cardiovascular accidents [75-79].

Non-steroidal anti-inflammatory drugs (NSAID)

The mechanisms by which NSAID, including COX-2 inhibitors, increase cardiovascular risk are several: reduced prostacyclin production in the vascular endothelium, suppression of nitric oxide synthesis, reduced neovascularization, abolition of adrenomedullin activity, and increased free-radical production, among others. These mechanisms also influence the platelet activity, which plays a crucial role in the development of events.

Just as ASA, also other classes of non-selective COX inhibitor NSAID increase the risk of AMI after discontinuance. One case-control study performed in the United Kingdom [80] with 8,688 cases and 33,923 controls assessed risk for AMI during and after exposure to diclofenac. The results showed that risk for AMI was 1.52 (95%CI 1.33-1.74) times higher among the individuals who had stopped treatment 1 to 29 days prior to the index event compared to non-users. These results suggest that rebound effect might occur several weeks after NSAID discontinuation. Also ibuprofen discontinuation triggers rebound platelet aggregation with increased thrombus formation and cardiovascular events (AMI) [81]. Use of NSAID is independently associated with increased risk for cerebrovascular events in patients with stable atherothrombosis [82].

To assess the cardiovascular risks of selective COX-2 inhibitors, a retrospective cohort study analyzed the medical records of 1.4 million users (1999-2001) [83]. The results showed that 8,199 patients (0.58%) suffered a heart attack during use of rofecoxib. Previous studies had demonstrated that chronic use of rofecoxib in high dose (> 50 mg/day) might increase the risk for severe cardiovascular problems [84-87].

Linking the rebound effect to platelet activity and considering that antiplatelet therapy with ASA is associated with reduced vascular mortality, Serebruany et al. [88] sought to establish the effect of use and withdrawal of NSAID on platelet activity. The authors concluded that drug discontinuation was associated with rebound platelet activation, which might result in higher risk for vascular events. Also *in vitro* experiments demonstrated that same thrombogenic mechanism for rofecoxib [89].

Confirming this hypothesis, observational studies detected high risk for AMI among new rofecoxib users [90,91]. Events occurred soon after discontinuation of rofecoxib in low dose, similar to the rebound effect dynamics. Using data collected in a previous cohort study [92], a case-control study [93] assessed the temporal nature of risk for first AMI associated with use of rofecoxib and celecoxib. The results showed that risk for AMI was higher following use of rofecoxib (RR: 1.67; 95%CI: 1.21-2.30); events occurred 9 (6-13) days after onset of treatment, on average. Treatment duration was not associated with increased risk, which remained high along the first 7 days after rofecoxib discontinuation (RR: 1.23; 95%CI: 1.05-1.44) to return to baseline between days 8 and 30 (RR: 0.82; 95%CI 0.61-1.09), thus characterizing the rebound phenomenon.

In a large systematic review of the effects of NSAID (both selective and non-selective COX-2 inhibitors) on cardiovascular events, 23 observational studies (17 case-control and 6 cohort studies) were analyzed, to a total of 1.6 million patients [94]. Rofecoxib was associated with patent dose-related risk, RR 1.33 (95%CI: 1.00-1.79) with ≤ 25 mg/day and RR 2.19 (95%CI: 1.64-2.91) with > 25 mg/day. Relative to the older, non-selective drugs, diclofenac exhibited RR 1.40 (95% CI: 1.16-1.70; 9 studies), meloxicam RR 1.25 (95%CI: 1.00-1.55; 3 studies) and indomethacin RR 1.30 (95%CI: 1.07-1.60; 6 studies). The data showed that risk was higher at the onset of treatment (first 30 days) consisting of first cardiovascular events.

In a nationwide case-control study conducted in Finland (33,309 cases; 138,949 controls) on risk for hospital admission with AMI under NSAID use [95] the estimated RR was: rofecoxib, 1.36 (95%CI: 1.18-1.58; 12 studies); diclofenac, 1.40 (95%CI: 1.19-1.65; 10 studies); meloxicam, 1.24 (95%CI: 1.06-1.45; 4 studies); and indomethacin, 1.36 (95%CI: 1.15-1.61; 7 studies). In another meta-analysis [96] Kearney et al. assessed the effects of selective and nonselective NSAID on risk for severe vascular events along 4 weeks at least (145,373 participants). The authors reviewed data from 138 randomized trials and obtained RR 1.42 (95%CI: 1.13-1.78) for rofecoxib and 1.63 (95%CI: 1.12-2.37) for diclofenac.

Reinforcing the causal role of the rebound effect, several studies conducted in the past decade reported similar results [97-101] calling the attention to the occurrence of fatal vascular events after NSAID discontinuation. A recent meta-analysis published in the *British Medical Journal* [102] analyzed a cohort of 446,763 individuals, including 61,460 who exhibited AMI during use of all classes of NSAID. The results indicated increased risk for AMI independently from drug class, dose and length of use. Use along 1-7 days was associated with higher risk (OR: 1.24; 95%CI: 0.91-1.82) for celecoxib, (OR: 1.48; 95%CI: 1.00-2.26) for ibuprofen, (OR: 1.50; 95%CI: 1.06-2.04) for diclofenac, (OR: 1.53; 95%CI: 1.07-2.33) for naproxen and (OR: 1.58; 95%CI: 1.07-2.17) for rofecoxib.

Rebound effect of bronchodilators *(ß-adrenergic agonists)* [10,12]

Several studies performed along the past decades confirmed clinical and experimental observations showing that 'rebound bronchoconstriction' might occur after partial or complete discontinuation of bronchodilators, with 'worsening of asthma' and increase of 'bronchial reactivity' [103-108].

As consequence of reports of severe paradoxical bronchospasm associated with use of the long-acting ß2 agonist salmeterol and previous epidemics of asthma-related deaths in patients using other long-acting ß agonists (LABA) the US Food and Drug Administration (FDA) requested GlaxoSmithKline to conduct a randomized trial comparing salmeterol to placebo. The study (Salmeterol Multicenter Asthma Research Trial - SMART) was started in 1996, to be prematurely interrupted in September/2002 after an interim analysis suggested increased risk for asthma-related death among the participants who used the drug compared to the placebo group [12].

In 2005, the FDA Public Health Advisory began warning about the higher risk of severe asthma and death by asthma associated with use of LABA (salmeterol and formoterol), even when combined to steroid fluticasone. On those grounds FDA demanded GlaxoSmithKline to add a warning on labels for doctors and users to be aware of the potentially fatal side effects of these drugs [109].

Following countless complaints from the scientific community [110] aroused by GlaxoSmithKline hiding SMART results, the data corresponding to the overall analysis of the 26,355 randomized participants were finally published in 2006 [111]. Following a review of the interim analysis, exploratory analysis of each outcome in the various subpopulations was performed. The results showed significant increase in respiratory event-related deaths (RR: 2.16; 95%CI: 1.06-4.41), asthma-related deaths (RR: 4.37; 95%CI: 1.25-15.34), and asthma-related deaths and life-threatening experiences combined (RR: 1.71; 95%CI: 1.01-2.89) among the subjects receiving salmeterol versus placebo. Such increase was greater among African Americans compared to whites.

In 2006 Salpeter et al. [112] published a meta-analysis of 19 placebo-controlled trials involving 33,826 participants with asthma corresponding to 16,848 patient-years (mean trial duration 6 months). Only 15% of the participants were African-American. The tested LABA were salmeterol, formoterol and eformoterol. About 53% of the participants from both groups concomitantly used inhaled steroids. The aim of the study was to assess the effects of LABA on severe asthma exacerbations demanding hospital admission, life-threatening asthma attacks, and asthma-related deaths. Subgroup analysis was performed to compare the results for salmeterol and formoterol in children and adults. For group LABA, hospital admission exhibited OR 2.6 (95%CI: 1.6-4.3) and life-threatening exacerbations OR 2.1 (95%CI: 1.5-3.0). Risk for hospital admission was increased for salmeterol (OR: 1.7; 95%CI: 1.1-2.7), formoterol (OR: 3.2; 95%CI: 1.7-6.0), children (OR: 3.9; 95%CI: 1.7-8.8) and adults (OR: 2.0; 95%CI: 1.0-3.9). Fatal asthma attacks associated with LABA had OR 1.8 (95%CI: 1.1-2.9) without significant difference between salmeterol and formoterol or between children and adults. OR of asthma-related deaths was obtained from SMART (OR: 3.5; 95%CI: 1.3-9.3; p= 0.013). Compared to group placebo, the risk of severe exacerbations and asthma-related deaths doubled (from 2 to 4 times). In spite of the well-known protector effect of inhaled steroids, the authors analyzed separately studies in which more than 75% of the participants concomitantly used these drugs; risk of hospital admission had OR 2.1 (95%CI: 1.34-3.4) which reveals the magnitude of the rebound effect [112].

In the physiological explanation of the findings, the authors correlated ß-agonist regular use (combined or not to inhaled steroids) with tolerance to drug effects and poorer disease control [113-116]. Tolerance is due to a negative feedback mechanism in the ß-adrenergic system that represents an adaptive response to receptor stimulation. Stimulation results in receptor uncoupling and internalization (desensitization) followed by decrease of the receptor density and downregulation of receptor gene expression [117]. The maintenance of some degree of bronchodilation notwithstanding, regular use of ß-agonists increases bronchial hyperreactivity. These effects, together with reduction of the response to subsequent ß-agonist rescue, might impair the control of asthma without the warning represented by increase of symptoms [116,118]. As indicated in older studies [103-108],

'bronchial hyperreactivity' is the same as 'rebound hyperreactivity' or 'rebound bronchoconstriction' [119].

A recent retrospective cohort study analyzed risk for severe asthma exacerbation among 940,449 asthma patients. The results evidenced significant association between hospital admission and intubation and use of LABA by comparison to short-acting ß-agonists [120]. Diverging from a previous meta-analysis [121] which found reduction of the risk for death by asthma with combination of salmeterol and inhaled steroids, a later meta-analysis [122] evidenced higher risk of severe adverse events with both formoterol alone or combined with inhaled steroids.

Several other studies [123-125] confirmed the occurrence of severe rebound bronchoconstriction following LABA discontinuation, resulting in severe and fatal events.

Rebound effect of antidepressants *(tricyclic and serotonin reuptake inhibitors)* [10,13]

Just as other classes of palliative drugs, also antidepressants are associated with rebound increase of depression symptoms following discontinuation (or dose reduction among more susceptible individuals) attended by patent changes in the involved receptors and/or mediators. In a review on this subject, Wolfe [54] observed that antidepressants might cause a variety of withdrawal reactions beginning few days after discontinuation and lasting several weeks. Both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI) cause a similar syndrome, commonly characterized by gastrointestinal or somatic distress, sleep disorders, mood changes and motion problems, among others. Treatment consists in restarting the drug, prevention in tapering.

In another review [126], Lader broadened the comprehension of this 'withdrawal syndrome' (rebound effect) of antidepressants through further data and studies:

> The phenomenon has been postulated to be associated with rebound symptoms such as return of depression following abrupt discontinuation. Discontinuation symptoms are now known to be associated with most classes of antidepressants, if medication is stopped without appropriate down-tapering of dose and/or dose frequency. The phenomena associated with stopping almost all antidepressants including the SSRIs are believed to result not from true dependence but from a reduction in intra-synaptic serotonin (5-HT) levels following receptor down-regulation [126].

This syndrome is characterized by 'time-locked emergence of new' or time-point (biological half-life) and is clearly defined by measurable signs and symptoms that appear following reduction or discontinuation of an antidepressant along a few weeks [127]. Typically, patients describe transient symptoms that begin and peak within 1 week since treatment interruption, are mild in severity and run a limited course, usually lasting up to 3 weeks [128]. Although data in the literature indicate that these mild, self-limited rebound symptoms appear in a small proportion of individuals [128,129] some studies show that severe and disabling withdrawal syndrome might occur in up to 5% of patients, thus requiring changes in therapeutic strategy for such idiosyncratic individuals [130]. The

literature indicates that paroxetine is associated with a significantly greater proportion of withdrawal reactions (around 5%) than other SSRI (fluoxetine, for example), with deterioration of various aspects of health and functioning [128,131-134]. The most likely explanation for this difference is the long half-life of the main metabolite of fluoxetine, which thus acts as natural buffer [135].

As with other categories of drugs, rebound or withdrawal reactions are not specific for the clinical conditions (disease) for which a drug is used. The antidepressant discontinuation syndrome is similar (incidence, nature and extent) in depression, panic disorder, generalized anxiety disorder, social anxiety disorder and obsessive-compulsive disorder. Analogously, duration of treatment does not influence withdrawal reactions [136].

In a review of neurobiological mechanisms underlying the antidepressant withdrawal syndrome, Harvey et al. [137] suggested a preliminary molecular perspective and a hypothesis on the neuronal implications of drug discontinuation. They described evidences that support possible association between the rebound effect of antidepressants and abnormalities in the brain glutamate activity, nitric oxide and γ-amino butyric acid.

The symptoms that appear following antidepressant discontinuation (withdrawal syndrome) include dizziness, nausea, gastrointestinal distress, headache, gait instability, lethargy, paresthesia, anxiety, irritability, vivid dreams and depressed mood, among others. While cholinergic overdrive may account for some of the symptoms that appear after withdrawal of tricyclic antidepressants, others suggest increased excitability of serotonergic neurons. Just as chronic antidepressant treatment results in desensitization of post- and presynaptic serotonin ($5\text{-}HT_{1A}$) receptors, abrupt interruption of 5-HT reuptake inhibition causes transient deficit of the intra-synaptic 5-HT availability due to loss of the inhibition of the $5\text{-}HT_{1A}$ receptor-mediated postsynaptic control, resulting in paradoxical increase of the circulating 5-HT [137-139].

Countless studies conducted in recent years call the attention to an increased risk for suicidal ideation, attempts or behaviors (suicidality) associated with use of antidepressants. In the most comprehensive meta-analysis of placebo-controlled studies that sought to analyze the relationship between antidepressants and suicidality among pediatric patients, Hammad et al. [140] included all the studies submitted to FDA. The analyzed data corresponded to 4,582 patients in 24 clinical trials. 16 trials studied patients with major depressive disorder (MDD), 4 obsessive-compulsive disorder (OCD), and 4 non-obsessive-compulsive anxiety disorder (non-OCD anxiety). Only 20 trials were included in the analysis of the relationship with risk of suicidality. The multicenter trial (TADS) [141] was the only individual study that showed statistically significant relative risk (RR: 4.62; 95% CI 1.02-20.92). The overall RR for SSRI in the depression studies was 1.66 (95%CI: 1.02-2.68). For all drugs and all indications, RR was 1.95 (95%CI: 1.28-2.98). The overall risk difference (RD) for all drugs and all indications was 0.02 (95%CI: 0.01-0.03). FDA concluded that these medications were associated with twice higher risk of causing suicidality.

According to the aforementioned considerations, the most plausible hypothesis for this relationship is that antidepressant (partial or full) discontinuation might trigger significant worsening of depression symptoms that are initially suppressed (suicidality, for instance),

as a result of rebound phenomenon [132,142-145]. However, the adverse events assessed in randomized trials (meta-analyses) are only the ones that occur during or immediately after treatment, while drugs with long half-life (as e.g. fluoxetine) are not considered. Such agents require longer follow up so that the rebound effect might manifest, different from antidepressants with short half-life (paroxetine, sertraline, venlafaxine, among others) [146-148]. As mentioned above, not taking the biological half-life of drugs into account is a relevant source of bias in the study of the rebound effect.

Several other studies that assessed risk of suicide among antidepressant users reported similar findings [149-155]. This fact should call the attention of doctors and patients as to the care needed in the discontinuation of these drugs.

Rebound effect of lipid-lowering drugs *(statins)* [14]

Statins are the most widely prescribed cholesterol-lowering drugs, and are considered to be the first choice for prevention of CAD and atherosclerosis (i.e., the main cause of death in developed countries). Statins act by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, namely, the rate-limiting enzyme in endogenous cholesterol biosynthesis. This enzyme catalyzes reduction of HMG-CoA to mevalonic acid. Enzyme inhibition is effective to lower the plasma total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglyceride levels in humans and thus might be useful to treat atherosclerosis and dyslipidemia [14].

The clinical benefits of statins seem to extend beyond their lipid-lowering effects. In addition to reducing the cholesterol biosynthesis, mevalonate inhibition by statins also reduces the synthesis of significant intermediates, such as isoprenoids (farnesyl pyrophosphate, geranylgeranyl pyrophosphate, coenzyme Q10, dolichol, isopentenyladenosine, and others). These intermediates participate in posttranslational prenylation of several proteins (e.g., Ras, Rho, Rac) which modulate a wide variety of cellular processes including cellular signaling, differentiation and proliferation. Given the central role of these isoprenylated proteins in the endothelial function, atherosclerotic plaque stability, platelet activity, coagulation, oxidation and inflammatory and immune responses, the primary effects of these compounds are extremely beneficial for a broad spectrum of disorders (cardiovascular disease, osteoporosis, Alzheimer's disease and related vascular dementia, viral and bacterial infections, among others). These cholesterol-lowering-independent effects of statins are termed 'pleiotropic effects', and involve vasoprotective actions, including improvement of the endothelial function, increased nitric oxide (NO) bioavailability with antioxidant effects, inhibition of inflammatory-thrombogenic responses, immunomodulatory actions, progenitor cell regulation, and atherosclerotic plaque stabilization [156-158].

Independently from rebound increase of cholesterol biosynthesis, scientific evidences suggest that discontinuation of statins leads to rebound impairment of the vascular function (pleiotropic effects) with consequent increase of morbidity and mortality among patients with vascular disease. Statin withdrawal increases the activation of heterotrimeric G-proteins Rho and Rac, which trigger reactive oxygen species (ROS) production and

suppression of NO bioavailability. In humans, statin discontinuation results in a pro-oxidant, proinflammatory and pro-thrombotic state, with deterioration of the endothelium function. Epidemiological studies indicate that statin discontinuation in patients with AMI and ischemic stroke significantly increases the odds of early cardiological and neurological deterioration, attended by poor outcomes. Shortly, statin withdrawal results in rapid return to endothelial dysfunction and amplification of oxidative and inflammatory processes, which may increase the vascular risk [159-162].

Clinical studies found that statin discontinuation, especially after acute vascular events (AMI or stroke), has a harmful effect on cardiovascular parameters and mortality (rebound effect). Patients who discontinued statins exhibited poorer outcomes compared to the ones never prescribed these drugs. Observational studies [163-168] showed that statin withdrawal resulted in increased mortality risk (by fatal vascular events) compared to drug maintenance (2.3 to 7.5-fold) and no treatment (1.25 to 1.69-fold). Interventional studies reported that statin interruption led to significantly increase of the mortality risk compared to treatment maintenance (4.66-fold) [169] in addition to significantly increased risk of fatal vascular events compared to treatment maintenance (2.27 to 8.67-fold) and no treatment (19.01-fold) [169,170]. Statin discontinuation was also considered an independent predictor of all-cause 1-year mortality [171].

In an analysis of data from 2,466 Canadian patients with brain hemorrhage (2003-2008), Dowlatshahi et al. [172] described the relationship of statin use and discontinuation with IS incidence through assessment of event severity and 30-day mortality. Overall, 537 patients (21.7%) used statins and exhibited less propension for severe IS on admission (54.7% vs. 67%) although the rates of unfavorable outcomes (70% vs. 67%) and 30-day mortality (36% vs. 37%) were similar compared to non-users. 158 among those 537 patients had statins interrupted on admission; this group was more prone to exhibit severe IS (65% vs. 27%; $p< 0.01$), unfavorable outcomes (90% vs. 62%; $p<0.01$) and higher 30-day mortality (71% vs. 21%; $p< 0.01$). Following adjustment for IS severity, statin discontinuation remained associated with unfavorable outcomes (adjusted OR: 2.4; 95%CI: 1.13-4.56) and high mortality (adjusted OR: 2.0; 95%CI: 1.30-3.04). The authors concluded that statin discontinuation is a factor for poorer outcome and a marker of poor prognosis, as mentioned above. Upon analyzing the data from 12,689 patients with IS admitted to 17 hospitals in Northern California, USA (2000-2007), Flint et al. [173] found similar results. The patients who discontinued statins on admission exhibited significantly higher risk of death (RR: 2.5; 95%CI: 2.1-2.9; $p< 0.001$).

Contributing to broaden the scope of research, later studies [174-179] reinforced the previous findings that statin discontinuation might induce rebound deterioration of the vascular function and subsequent vascular accidents.

Rebound effect of gastric acid suppressants *(antacids, H_2 antagonists, proton pump inhibitors)* [15]

According to FDA [180], rebound acid hypersecretion is defined as increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels following discontinuation of antisecretory agents. Initially reported in association with use of H_2 antagonists, rebound

acid hypersecretion is related to elevation of the serum gastrin and/or upregulation of the H_2-receptors. Elevated gastrin levels or hypergastrinemia is a secondary effect of chronic inhibition of the gastric acid secretion, with occurs in long-term antisecretory treatment. Increased plasma gastrin stimulates histamine production and release by enterochromaffin-like (ECL) cells, which induces gastric acid production by the parietal cells. In addition, increase of the parietal cell mass might occur together with chronic use of antisecretory agents, this being an additional mechanism that accounts for the increase in acid secretion that occurs after treatment discontinuation. Another possible cause of rebound acid secretion is increased sensitivity to histamine [181].

While neutralization of the gastric acidity by antacids (aluminum/magnesium hydroxide or calcium carbonate) does not have antisecretory effect, it also causes rebound acid hypersecretion following treatment discontinuation. Clinical trials confirmed this hypothesis upon detecting occurrence of rebound effect 1 hour after administration of the standard antacid dose to healthy individuals [182,183].

Analogously, H_2 antagonists (cimetidine, famotidine, nizatidine and ranitidine) cause rebound acid hypersecretion after drug withdrawal. Although the exact mechanism remains unclear, the main hypotheses are that the rebound effect is related to greater responsiveness of the H_2-receptor to stimulation by histamine after chronic competitive inhibition and impairment of the inhibitory branch of gastrin-dependent acid secretion [184]. Studies with patients and healthy individuals showed that rebound acid hypersecretion occurred 2-3 days after 4-week treatment and lasted 10 days [185-190].

Proton pump inhibitors - PPI (esomeprazole, lansoprazole, omeprazole and pantoprazole) block the final step of acid secretion, resulting in intense and persistent reduction of gastric acid, with concomitant increase of gastrin release. This rebound hypergastrinemia results in continuous stimulation of ECL cells and consequent hyperhistaminemia, without increase of the gastric acid secretion, since the proton pump is effectively blocked. In addition, stimulation of ECL cell proliferation increases the ECL cell mass, which persists longer than the effect of PPI when the drug is discontinued. As any rebound effect manifestation, rebound acid hypersecretion is evident at a given time-point after treatment withdrawal, as a function of the half-life of drugs (absence of biological effects). Following sufficient time of treatment with PPI, rebound acid hypersecretion occurs from the second week (half-life of PPI) to the normalization of the ECL cell mass (about 2 months), i.e., 2-3 months after treatment discontinuation. This phenomenon lasts long, at least two months longer than the duration of treatment, being attended by persistent and significantly elevated acid hypersecretion [191-197].

Gastrin has trophic action in many tissues and stimulates the *in vitro* growth of a large number of tumor cell lines, including colon cancer cells. While some authors associate hypergastrinemia to increased risk for colon cancer, 2 population-based case-control studies conducted in the United Kingdom (1987-2002) and Denmark (1989-2005) did not find any evidence of such increase among regular PPI users [198,199]. However, it should be noticed that rebound hypergastrinemia occurs some time after treatment discontinuation (half-life) which fact was not considered in these studies (assessment bias).

Some studies suggest that the increase in the frequency of gastroesophageal reflux disease (GERD) in the past decades might be due to excessive use of PPI for treatment of unspecific symptoms. For this same reason, hypergastrinemia might play a role in the progression of Barrett's esophagus into cancer, considering the noteworthy rise in the incidence of adenocarcinoma of the cardioesophageal junction along the past 2 decades and that acid-suppressive therapy for GERD considerably increased along this same period [200-203].

A population-based cohort study conducted in Denmark (1990-2003) found direct relationship between increased incidence of gastric cancer and increased number of prescriptions or length of treatment with PPI compared with users and non-users of H_2 antagonists. According to the authors, these data suggest that hypergastrinemia might be a risk factor for development of gastric cancer, as consequence of excessive PPI use [204].

Carcinoid tumors have long been acknowledged to be a consequence of hypergastrinemia in Zollinger-Ellison syndrome and atrophic gastritis [205]. Analogously to esophageal cancer, the increase in the incidence of gastric carcinoids along the past 3 decades (400% among men and 900% among women) might also be associated with the widespread selling of PPI [206-208]. According to McCarthy [203] the scientific basis to correlate chronic use of PPI with the rise in carcinoid tumors is quite strong and should be taken into consideration. Hypergastrinemia might also stimulate the development of carcinoid tumors in other sites.

To assess the occurrence and clinical relevance of rebound acid hypersecretion following discontinuation of PPI, Hunfeld et al. [209] performed a systematic review that included 8 studies. 5 studies (including 4 randomized trials) did not find any evidence for rebound acid hypersecretion (RAHS) following PPI withdrawal. From the 3 remaining uncontrolled trials, 2 suggested that RAHS might occur in *H. pylori*-negative patients after 8 weeks of treatment with PPI. The authors concluded that there is no strong evidence for clinically relevant increase of acid production following PPI withdrawal. Fossmark and Waldum [210] criticized the selection of studies for the just mentioned review, since it did not consider a treatment duration sufficient for development of significant hyperplasia of the ECL cells and subsequent RAHS. These authors stressed that it is not possible to assess RAHS after one single dose of PPI or less than 25 days of treatment, even though the studies were randomized trials: "these five studies merely show that PPI must be used more than 1-25 days to induce RAHS ".

Clinical evidences for RAHS after PPI withdrawal were provided by recent interventional studies [211-215]. Upon investigating whether RAHS also occurs in patients without GERD, some studies found worsening of symptoms in about 70% of long-term PPI users following discontinuation of treatment [211,214].

PPI are commonly used, and represent a considerable onus for the health system in many countries for being prescribed for a wide variety of acid-dependent gastrointestinal symptoms [216-220]. In Denmark, use of PPI increased 7 times from 1993 to 2007, in addition to substantial increase from 20 to 33 daily doses per 1,000 individuals from 2003 to 2007. In 2006, about 7% of Danish population was treated with PPI [221-223]. In Australia, use of PPI increased 1,318%, while the one of H_2 antagonists decreased by 72% [224]. In USA, use of PPI continuously increased from 1999 to 2004, while the one of H_2

antagonists decreased. In 2007, esomeprazole, lansoprazole and pantoprazole ranked 4th, 8th and 13th among the most sold drugs in US, corresponding to 26.4, 20.4, and 16.1 million prescriptions, respectively. Comparatively, ranitidine and famotidine ranked 47th and 120th among generic drugs, corresponding to 13 and 3 million prescriptions, respectively [225].

While such liberal use of PPI is recommended recent protocols for dyspepsia [226,227], a large proportion of PPI users do not exhibit acid-dependent symptoms or precise indication for this treatment [219,221,228-231]. Some studies indicate that up to 33% of patients who start PPI refill the prescription with no indication whatsoever for maintenance treatment [219,232]. As a function of the development of RAHS, such empirical behavior might complicate PPI withdrawal, causing relapse of acid-dependent symptoms (heartburn, acid regurgitation and dyspepsia) and consequent resumption of treatment [211,212,233].

Other studies [234-237] stress the relevance of RAHS following PPI discontinuation, calling the attention of doctors to the risks associated with and care required by this treatment.

Rebound effect of bone resorption inhibitors *(bisphosphonates and denosumab)* [18]

Osteoporosis is characterized by bone mass reduction and increased bone fragility. It affects 10 million people in USA and more than 75 million worldwide (20-30% of postmenopausal women). Antiresorptive drugs, such as bisphosphonates (BP), are considered the first-choice to reduce the risk of osteoporotic fractures. By inhibiting bone resorption through osteoclast activity reduction, BP (alendronate, risedronate, ibandronate and zoledronic acid, among others) increase the bone mineral density (BMD), thus reducing the risk of fractures. In USA, more than 150 million prescriptions of BP were filled for outpatients from 2005 to 2009 [238].

BP exhibit specific pharmacological properties that distinguish them from other bone resorption inhibitors, including skeletal retention (bone matrix) and long-term persistence of effects after discontinuation [239]. These characteristics result in a long half-life, which hinders the definition of the duration of the biological activity of BP, and consequent investigation of rebound effect, as is shown next.

In spite of the confirmed usefulness of BP to reduce the frequency of 'typical' fractures among patients with osteoporosis, the number of reports of 'atypical' subtrochanteric or diaphyseal femur fractures in patients using BP after no or low-energy trauma increased in in recent years. In 2010, the American Society for Bone and Mineral Research (ASBMR) published the report by a task force that investigated several issues related with this disorder [240]. Systematic reviews discussed clinical and experimental evidences for the occurrence of this adverse event secondary to use of BP seeking to understand its pathogenesis [241-245].

Atypical femur fractures associated with BP exhibit specific radiological characteristics (transverse or oblique direction, no comminution, cortical thickening, stress fracture or stress reaction on the affected and/or the contralateral side) and exclusive clinical

manifestations (long prodrome with pain, bilaterality, slow consolidation). The fact such fractures occur without previous history of trauma suggests a systemic pathogenesis like the rebound phenomenon, since this type of fracture is commonly associated with significant trauma (traffic accidents, for instance) in which the energy conveyed to the bone results in the propagation of several fracture lines, resulting in comminution. Although their incidence is low, this type of fracture exhibits high morbidity.

A case series [244] and epidemiological studies [246-250] evidenced the relationship between BP use for variable periods (3 months to 9 years) and occurrence of atypical fractures; association with cumulative medication use was ruled out. As mentioned above, such variable interval of time for the phenomenon to manifest is a consequence of the long half-life of BP (up to 5 years after 1-year treatment). This is a peculiar feature of 'deposit drugs', retained for years in the body (in the bones, in this case), which does not allow for immediate manifestation of rebound effect after discontinuation. Tolerance, tachyphylaxis and receptor desensitization account for the occurrence of rebound effect also during long-term treatment with BP.

The earliest hypothesis to explain the occurrence of atypical fractures suggest that the long duration of the action of BP, suppressing bone remodeling, might result in hypermineralization and micro-damage accumulation, with resulting impairment of the bone integrity. However, histomorphometric analysis of samples of biopsy of affected bones showed no hypermineralization or abnormalities in hydroxyapatite crystals. These findings are indicative of greater bone mineral maturity with no change whatsoever in the crystallization indices after treatment [244,251-254].

As in the case of other categories of drugs, experimental studies demonstrated rebound (paradoxical) increase of osteoclast activity following BP discontinuation [245,251,255]. Such 'biphasic anti-osteolytic effect' was evidenced by rebound increase of bone remodeling markers (collagen type 1 C-telopeptide), eroded surfaces (3 times higher than at baseline) and of the number of active osteoclasts (6 times higher than at baseline) after initial decrease caused by the direct action of BP. The magnitude of the rebound phenomenon accounts for the occurrence of complete fractures, in the absence of trauma, affecting one of the stronger areas of the femur, as well as their slow consolidation. These aspects reinforce the hypothesis that rebound effect is the main systemic pathogenic mechanism of atypical femur fractures. Other studies reported rebound bone resorption following discontinuation of other antiresorptive agents (hormone replacement therapy and monoclonal antibodies) [245].

While the incidence of hip fractures decreased since the introduction of BP in USA, subtrochanteric or femoral diaphyseal fractures increased along the same period. Although they represent a small subset (5-10%) of all femur and hip fractures, the subtrochanteric ones have considerable influence on morbidity and mortality, the results being similar to the ones of hip fractures [256,257]. In a prospective 2-year study of 87 patients with subtrochanteric fractures the mortality rate was 8% after 4 months, 14% after 12 months and 25% after 24 months. Revision surgery was required in 8% of the cases. By the end of the follow-up period, only 46% of the patients regained their walking ability and 71% had living conditions similar to those before the fracture [258].

Rebound bone resorption attended by increase of bone remodeling markers, osteoclast activity and propension for atypical fractures was described also after discontinuation of other categories of antiresorptive agents, such as hormone replacement therapy, human monoclonal antibodies (denosumab) and selective cathepsin K inhibitors (odanacatib), among others [245,259-262].

Other recent studies corroborate the occurrence of atypical femur fractures during treatment with BP and denosumab [263-266], therefore supporting the increasing calls warning doctors and patients about this serious adverse event.

Rebound effect of immunomodulating agents for treatment of multiple sclerosis (*natalizumab and fingolimod*) [19]

According to current hypotheses, the main event in the pathogenesis of multiple sclerosis (MS) is activation of peripheral autoreactive T lymphocytes. Following proliferation and crossing through the blood-brain barrier, these cells trigger a cascade of inflammatory events, which culminates in demyelination and axonal damage. Lymphocyte migration through the blood-brain barrier requires interaction of adhesion molecules expressed on the cell surface, such as selectins and integrins via their endothelial receptors [19].

Natalizumab (NTZ), a humanized monoclonal antibody, is a selective inhibitor of the aforementioned adhesion molecules, thus it hinders lymphocyte migration to the central nervous system (CNS), consequently reducing the frequency of acute exacerbations, number of brain lesions and progression of disease [19]. Fingolimod (FGD) is a modulator (functional antagonist) of the sphingosine-1-phosphate receptor on lymphocytes, able to reduce the ability of these cells to migrate from lymph nodes to CNS, thus minimizing neuronal inflammation and consequent demyelination [19].

The beneficial primary effect of treatment notwithstanding, observational studies [267-275] evidenced worsening of disease activity following NTZ discontinuation (rebound effect or immune reconstitution inflammatory syndrome - IRIS - without progressive multifocal leukoencephalopathy) [276-278]. This condition is attended by intense exacerbation of symptoms, increase of the number and/or size of demyelination lesions and disease progression.

In addition to NTZ, also other immunomodulating drugs or biological response modifiers, such as FGD [279] and tumor necrosis factor alpha antagonists - anti-TNFα (infliximab, adalimumab, etanercept) [280] might cause rebound demyelination disorders.

Recent studies [281-286] corroborate the occurrence of severe rebound demyelination (IRIS) following discontinuation of immunomodulating drugs (NTZ and FGD) used for treatment of MS, attended by cognitive disorders, neurodegeneration and fatal outcomes.

Rebound effect of immunomodulating agents for treatment of psoriasis (*efalizumab and anti-TNFα*) [23]

Psoriasis is an autoimmune inflammatory disease modulated by Th1 lymphocytes. Following contact with an unknown antigen, a subset of T lymphocytes converts into CD4+ and CD8+ memory T cells. The latter proliferate and migrate from lymph nodes to the skin, where they trigger an inflammatory reaction, with production of proinflammatory mediators (the number of T cells infiltrating the skin is correlated with disease activity). Advances in the understanding of the pathophysiology of psoriasis along the past decades, including the role of T cells and cytokines, were crucial for the development of biological therapy with immunomodulating drugs [23].

Term 'biological' alludes to the use of agents synthesized from living body products, which modulate the immune system through stimulating or inhibitory actions on specific sites. In the case of psoriasis, biologic drugs selectively inhibit the activation and maturation of antigen-presenting cells, thus blocking cytokine secretion and inhibiting the activation and proliferation of T cells, their migration to the skin, effector function and reactivation. While the safety profile of these drugs is considered more favorable compared to the conventional systemic immunosuppressant agents, since they do not cause generalized immunosuppression, the initial enthusiasm was soon replaced by a cautious attitude resulting from the accumulated experience and occurrence of severe adverse effects. Biological drugs for psoriasis fall into 2 main categories: T cell modulators (efalizumab and alefacept) and anti-TNFα (infliximab, adalimumab and etanercept) [23].

Efalizumab, the main agent for treatment of psoriasis, is a human monoclonal IgG1 antibody, which binds to leukocyte function-associated antigen (LFA)-1 alpha-chain, blocking the interaction between LFA-1 and intercellular adhesion molecule (ICAM)-1. The results are reduced T cell activation, inhibition of the migration and recruitment of T cells to the dermis/epidermis and reduced cell T reactivation in various steps of the pathophysiology of psoriasis [23].

In spite of the beneficial primary effects of this palliative (enantiopathic, contrary) treatment, some studies reported worsening of disease activity following discontinuation of the aforementioned immunomodulating agents (rebound psoriasis) [287-290]. This condition is attended by exacerbation of signs and symptoms (increase of the size or greater severity of skin lesions, worsening of arthritis, etc.).

Randomized placebo-controlled trials [287,291-297] evidenced occurrence of rebound psoriasis following discontinuation of efalizumab (≥125% worse compared to baseline, Psoriasis Area and Severity Index – PASI) in about 15% of patients. Observational studies [298-308] reported even greater estimates, of up to 30% of patients.

In some cases, rebound effect might result in fatal disease progression (IRIS) [276,309-312], just as in the case of NTZ for treatment of MS. This adverse event led the European Medicines Agency (EMA) to recommend withdrawing the marketing authorization for efalizumab on February 2009 [312].

Analogously, several studies showed that discontinuation of other immunomodulating drugs used for treatment of psoriasis trigger rebound effect: alefacept [313,314], etanercept [298,306,315] and infliximab [316,317]. Many authors do not characterize worsening of psoriasis 'during' treatment with anti-TNFα as rebound psoriasis (since according to the classic definition, rebound effect occurs after discontinuation of drugs). Yet several studies [318-322] found exacerbation of psoriasis with shift in its morphology (toward the pustular, erythrodermic or guttate forms) during treatment with anti-TNFα (etanercept, adalimumab and infliximab, among others), which might be considered as probable rebound effect (development of tolerance) as mentioned above.

Epidemiology of the rebound effect of modern drugs

Rebound effect appears after a variable interval (hours to weeks) following the end of the biological effect (half-life) of drugs; also its duration is variable. The interval between drug discontinuation and appearance of rebound effect is similar for drugs with short half-life: 10 days for salicylates, 14 days for diclofenac and 9 days for rofecoxib [10,11], 7 days for statins [14], 7-14 days for SSRI antidepressants [10,13] and PPI [15], on average. In the case of deposit drugs (bisphosphonates) [18] this time is longer. The duration of the rebound effect remains for 30 days for rofecoxib [10,11], 22 days for SSRI [10,13] and 30 days for IBP [15]. There is no relationship between treatment duration and manifestation of rebound effect.

In randomized placebo-controlled studies, the average risk of thrombotic events was 3.4 times higher following discontinuation of salicylates, 1.52 higher after NSAID, 1.67 higher after rofecoxib [10,11] and 1.69 higher after statin [14] withdrawal. Analogously, the risk of suicidality was 6 times higher after SSRI discontinuation [13] and the one of rebound bronchospasm 4 times higher following LABA withdrawal [10,12].

Illustrating the frequency and magnitude of the rebound effect, which might cause severe and fatal adverse events, epidemiological studies evidenced that LABA cause about 1 rebound episode of bronchospasm followed by death per 1,000 patient-years; this corresponded to 4,000-5,000 deaths in USA in 2004 (and 40,000-50,000 deaths worldwide) [10,12]. SSRI cause 5 rebound suicidal behaviors per 1,000 adolescent-years, which corresponded to 16,500 events in USA in 2007 [10,13]. Salicylates cause about 4 episodes of rebound AMI per 1,000 patient-years [10,11]. Some studies reported that the incidence of gastric carcinoid tumors increased in the past decades (100% among men and 900% among women) in association with increasing use of PPI, in relation to rebound hypergastrinemia [15]. Bisphosphonates cause 1-3 paradoxical severe atypical fractures per 1,000 patient-years (0.1-0.3%) [18]. Natalizumab causes rebound exacerbation of MS in about 10% of patients, attended by severe demyelination (IRIS) in some cases [19]. Efalizumab causes rebound psoriasis in 15-30% of patients, and might also induce IRIS [23].

Paradoxical pharmacology [24-36]

A therapeutic approach developed by Richard A. Bond in 2001 [24], 'paradoxical pharmacology' suggests employing the paradoxical effects of drugs (secondary reaction of the body opposed to the primary effects of drugs) with curative intention. Universal in nature, according to Bond, such paradoxical, bidirectional or compensatory effects are proper to various categories of drugs, independently from the dose used, and appear in a variable proportion of susceptible individuals. Although not fully elucidated, the paradoxical effect manifests at various levels of the autoregulation biological systems, making the functioning of the full body extremely complex, from the subcellular level (channels, enzymes, receptors, transporters, organelles, etc.) to cells, tissues and organs [25-29].

Affecting all physiological systems, these paradoxical and bidirectional effects have variable mechanisms: different actions in one same receptor due to time-related effects (e.g., ß-blockers with intrinsic sympathomimetic activity); stereochemical effects (e.g., salbutamol); multiple receptor targets with or without associated time-related effects (e.g., procainamide); antibody-mediated reactions (e.g., heparin-induced thromboembolism); pharmacokinetic effects of competing compartments (e.g., bicarbonate); interruption of and non-linear effects in systems (e.g., dopaminergic agents); systemic overcompensation (e.g., antiretroviral therapy and IRIS); other higher-level feedback mechanisms (e.g., acne fulminans associated with isotretinoin), among others [29].

Just as this author found in his systematic study of the rebound effect, also pharmacologists describe several examples of paradoxical and bidirectional effects of drugs affecting various systems and involving different categories of drugs: immunomodulators (systemic glucocorticoids and anti-TNFα), anticancer drugs (chemotherapy, radiotherapy and arsenic), antiarrhythmic agents (procainamide and isoproterenol), antihypertensive drugs (methyldopa, clonidine, guanabenz, moxonidine and thiazides), vasodilators (nitrates), drugs for treatment of heart failure (ß-blockers, ACE inhibitors, angiotensin II receptor blockers and hydralazine), lipid modifying drugs (fibrates and ezetimibe), inotropes and chronotropic drugs (isoprenaline, epinephrine, β-blockers and calcium channel blockers), vasoconstrictors (ergot alkaloids, vasopressin), anesthetics (sevoflurane, ketamine, propofol), antiepileptic drugs (e.g., benzodiazepines, barbiturates, hydantoin), hypnosedatives (anticholinergics, antihistamines, antispasmodics, barbiturates, benzodiazepines, bromides, chloral hydrate, ethanol, opioids), psychotropic drugs (antidepressants, antipsychotics), drugs with action on the peripheral nervous system (acetylcholinesterase inhibitors, capsaicin), antidyskinetics (dopaminergic agents), acid-base agents (sodium lactate, bicarbonate), agents active on the bone metabolism (e.g., parathyroid hormone, bisphosphonates), electrolytes (hypertonic saline, magnesium hydroxide), glycemic agents (insulin, hypoglycemic agents), steroids (dexamethasone), thyroid agents (iodine, lithium), antihyperuricemic agents (xanthine oxidase and urate oxidase inhibitors), gastrointestinal drugs (opioids, cholecystokinin and ceruletide), agents active in the blood (erythropoietin, vitamin K antagonists, platelet adenosine diphosphate receptor antagonists), bronchodilators (e.g., short- and long-acting β_2-agonists), dermatological drugs (high-intensity long-wave ultraviolet light, 8-methoxypsoralen and histamine-receptor antagonists), among others [29].

According to Bond, a possible hypothesis to account for the working of paradoxical pharmacology is the difference between the acute and chronic effects of drugs [24]. Stressing that the acute and chronic responses to drugs might be substantially different, and often of opposite nature, that author suggests that "exacerbating a disease makes use of the body's compensatory and redundant mechanisms to achieve a beneficial long-term response". This phenomenon is particularly evident in receptor-mediated events; acute exposure to agonists might activate receptors and increase signaling, while chronic exposure might desensitize receptors, with consequent signaling decrease. The same applies to receptor antagonists.

Analogously to homeopathic treatment, which employs minimal doses (HD) to avoid possible initial worsening of disease, the advocates of paradoxical pharmacology suggest, as general rule, beginning treatment with very small doses to then increase them gradually over weeks [24].

As examples of the therapeutic use of paradoxical reactions, some authors list clinical conditions that might be thus treated. Congestive heart failure (CHF) is related to deficient cardiac contractility; acute use of ß-adrenergic agonists increases the heart contractility, improves hemodynamics and reduces the related symptoms. In turn, chronic use of such drugs results in higher mortality. Short-term use of ß-adrenergic antagonists (ß-blockers: carvedilol, metoprolol and bisoprolol, among others) reduces contractility and exacerbates CHF, with worsening of disease. In turn, long-term use of these drugs results in increased cardiac contractility and lower mortality [24,28,29,30]. The same occurs with calcium channel blockers [31].

Analogously, ß-adrenergic agonists are the most powerful bronchodilators and play a considerable role in all the stages of the management of asthma. However, as was mentioned above, chronic use of these drugs is associated with paradoxical irreversible and fatal bronchospasm. In turn, short-term use of ß-adrenergic antagonists causes bronchoconstriction and worsening of asthma, while long-term use causes bronchodilation and improvement of asthma management [24,28,32,33].

Additional examples are use of methylphenidate (CNS stimulant) for treatment of attention-deficit hyperactivity disorder (ADHD) and of 5-HT_{1A} receptor agonists (hyperalgesia mediators) to achieve analgesia [28]. It is long known that thiazides afford paradoxical antidiuretic benefits in the treatment of diabetes insipidus, with reduction of polyuria and elevation of the urine osmolality [34].

Arsenic trioxide (As_2O_3), a carcinogen, has been used in homeopathy for more than 2 centuries as adjuvant for treatment of various types of cancer. As a function of its biphasic effects, it is considered by paradoxical pharmacology as a promising anticancer agent [35,36,323-325]; its clinical efficacy was demonstrated for acute promyelocytic leukemia [326-329], small-cell lung cancer [330,331] and liver cancer [332,333], among other uses [29].

New homeopathic drugs: use of modern drugs according to the therapeutic similitude principle [37-46]

Once again, the basic assumption underlying the homeopathic healing principle is the use of drugs that cause pathogenetic manifestations (signs, symptoms, physiological or pathological effects, etc.) similar to the disorders to be cured. A similar use might be made of any type of drug (natural or synthetic) and in any dose (ponderable or infinitesimal) provided the therapeutic similitude principle is observed. Thus being, modern drugs might be used according to the homeopathic assumptions, provided they induce primary effects (therapeutic, adverse or side effects) similar to the full set of characteristic signs and symptoms exhibited by patients.

Since 2003 [37-46] this author advocates the use of the rebound effect of modern drugs with curative intent. For this purpose patients are given drugs, in HD, which caused a similar set of adverse events in phase I-IV pharmacological clinical trials aiming at stimulating the homeostatic reaction of the body against its own disorders.

To make this idea feasible, a *Homeopathic Materia Medica of Modern Drugs* [39] was prepared, in which all the primary or pathogenetic effects (therapeutic, adverse and side effects) of 1,250 modern drugs described in *The United States Pharmacopeia Dispensing Information (USPDI)* [334] are organized according to an anatomical-functional distribution following the format of the traditional homeopathic materia medica [335]. To facilitate the choice of the individualized medicine to be prescribed, according to the full set of similar symptoms (i.e., the *sine qua non* requirement for the success of homeopathic treatment) next a *Homeopathic Repertory of Modern Drugs* [39] was prepared. Here pathogenetic effects and the corresponding drugs are organized according to the format of the traditional homeopathic repertories, following the aforementioned anatomical-functional distribution [336].

The full project, entitled *New Homeopathic Medicines: use of modern drugs according to the therapeutic similitude principle*, is available as 3 digital volumes (*Scientific Basis of the Principle of Similitude in Modern Pharmacology*, *Homeopathic Materia Medica of Modern Drugs,* and *Homeopathic Repertory of Modern Drugs*) online, open-access (http://www.newhomeopathicmedicines.com) to all interested readers.

As example of off label use of countless categories of modern drugs according to the therapeutic similitude principle, dozens of drugs that increase the blood pressure as primary effect (adalimumab, cyclosporine, dopamine and anti-inflammatory agents, among others) might be homeopathically used for treatment of hypertension, **provided other primary or pathogenetic effects are similar to the full set of signs and symptoms exhibited by the patient**. When one complies with such **therapeutic individualization**, drugs that increase the blood sugar (amprenavir, corticotropin, diazoxide and estrogen, among others) might be homeopathically used for treatment of diabetes. Drugs that cause inflammation of the gastric mucosa (abacavir, anti-inflammatory agents, carbidopa and cilostazol, among others) might be homeopathically used for treatment of gastritis and gastric ulcer. Drugs that cause immunosuppression (cyclosporine, steroids and immunosuppressant agents, among others) might be used to stimulate the immune system of immunosuppressed patients, and so forth [39-43,46].

As a concrete application, we recently developed a clinical research protocol for use of potentized estrogen (17-ß estradiol) for treatment of endometriosis-associated pelvic pain, since estrogen causes endometrial hyperplasia or proliferation as adverse event [44]. Reporting significant improvement versus placebo in relation to pain, depression and quality of life [45], this study can be accessed in the present special dossier.

Conclusions

Upon describing the undesirable effects of indiscriminate use of drugs according to the contrary principle, Hahnemann called the attention to the risks derived from their secondary action (rebound effect or paradoxical reaction) resulting in "more serious disease or frequently even danger to life and death itself". In turn, he validated the therapeutic similitude principle through the Aristotelian *modus tollens*:

> If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or frequently even danger to life and death itself, but never a cure of a disease of considerable or of long standing (*Organon of medicine*, § 60) [49].

Bridging between the therapeutic similarity principle and modern scientific reason, hundreds of studies in the medical literature describe the occurrence of secondary reactions following and opposed to the primary actions of many categories drugs, thus corroborating the homeopathic assumption. Such secondary action or reaction, which occurs automatically and instinctively to maintain the system homeostasis, is described by contemporary pharmacology and physiology as rebound effect of drugs or paradoxical reaction of the body, respectively. Analogously, the primary action of drugs represents the therapeutic, adverse and side effects of modern drugs.

By definition, the intensity and/or frequency of the rebound effect are higher compared to the original symptoms, suppressed by the primary action of the drug. This characteristic distinguishes the rebound effect from the natural return of chronic symptoms after the end of treatment. While drug discontinuation is a requisite for occurrence of rebound effect, it might also appear during treatment, as a function of the development of tolerance or therapeutic failure.

In conventional therapeutics, a large number of iatrogenic events might be avoided were health care providers to pay attention to the possible occurrence of rebound effect [21]; worsening of diseases is minimized by tapering. While not conventionally described or included among the adverse effects of classical pharmacology, the effects of discontinuation are a part of the pharmacology of any drug [55] therefore they ought to be considered in the teaching of modern pharmacology.

By employing the rebound effect of conventional drugs with curative intent we might broaden the scope of therapeutic similitude through the addition of hundreds of 'new homeopathic drugs'. Such new drugs cover signs and symptoms absent in the classical homeopathic pathogenetic trials and will allow treating countless modern disorders, diseases and syndromes with homeopathy.

Just as homeopathic practitioners assert along more than 2 centuries [38,43] the advocates of paradoxical pharmacology [28] call investigators to approach the paradoxical phenomenon (rebound effect, therapeutic similitude) with no prejudice whatsoever, and to challenge the current dogmatic therapeutic paradigms through new approaches no matter how difficult is for our peers to accept new ideas.

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