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"Similitude in Modern Pharmacology": two decades of studies contributing to the scientific basis of the homeopathic healing principle

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Dear Editors,

Homeopathy is based on the following four scientific pillars[1]: principle of cure by similars, proving of medicinal substances on healthy individuals, use of dynamized doses, and prescription of individualized medicines. Although great importance was attributed to dynamized doses (ultra-high dilutions), the first two pillars are the fundamental premises of the homeopathic epistemological model, remaining to individualized medicine the essential condition to awakening the therapeutic response.

In the systematization of the homeopathic method of treatment, Samuel Hahnemann based the "principle of cure by similars" (principle of therapeutic similitude) on the careful observation of the effects of medicines on human health. In the essay[2] that inaugurated homeopathy in 1796 and in paragraphs 59 and 65 of the *Organon of Medicine*[3], he describes the pharmacological effects of dozens of palliative drugs of his time, discriminating the "direct primary action of drug" and the consequent and opposite "indirect secondary action of the body," evidencing the new principle of cure proposed:

> [...] 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*, paragraph 65)[3]

In paragraph 63 of the *Organon of Medicine*[3], Hahnemann suggests a physiological explanation for the principle of therapeutic similitude (primary action of the drug followed by secondary and opposite action of the body), justifying its universal mechanism of action of drugs (biphasic action of drugs) on the automatic manifestation of "our life-preserving power" or "homeostasis" according to modern physiology:

> 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 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*, paragraph 63)[3]

Associating his empirical observations with hundreds of reports of involuntary homeopathic cures described in the literature and employing the inductive Aristotelian reasoning (*modus ponens*), Hahnemann enunciates the "principle of cure by similars" (*Organon of Medicine*, paragraphs 24-7)[3]: any medicine that cause, in their primary action, certain signs and symptoms in healthy individuals can be used, in their secondary action, to cure similar signs and symptoms in sick individuals (*similia similibus curentur*).

Therefore, the homeopathic method of treatment employs the secondary action or vital reaction of the body for therapeutic

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purposes by administering to ill individuals drugs that cause similar symptoms in healthy individuals in order to awaken a healing reaction of the body against their own disturbances or diseases.

By emphasizing that such secondary action of the body (vital reaction) is observed "in each and every instance with no exceptions" with ponderable or infinitesimal doses in both healthy and ill individuals, Hahnemann raised the principle of therapeutic similitude to the level of a "natural law of cure" (*Organon of Medicine*, paragraphs 58, 61, 110-2)[3].

In contrast, demonstrating the occurrence of evident worsening of disturbances or diseases after ceasing the palliative effect of drugs with contrary action to symptomatic manifestations ("principle of cure by contraries") (*Organon*, paragraphs 57-61)[3], Hahnemann reinforces the validity of homeopathic treatment according to the deductive Aristotelian reasoning (*modus tollens*) or "mode that affirms by denial":

> 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; […] - 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; [...] 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*, paragraph 59)[3]

According to the modern pharmacology, the "primary action" described by Hahnemann corresponds to the "therapeutic, adverse, and side effects" of conventional drugs, while the "secondary action" corresponds to the "rebound effect" or "paradoxical reaction" of the body, observed after discontinuation of several classes of drugs that act contrary (palliative or antipathic) to the signs and symptoms of diseases.

By definition, the term "rebound" is defined as the reversal of response upon withdrawal of a stimulus, while "rebound effect" means the production of increased negative symptoms when the drug ends or the patient no longer responds to it: if a drug produces a rebound effect, the condition it was used to treat may come back even stronger when the palliative drug is withdrawn (discontinued) or loses effectiveness (development of tolerance or tachyphylaxis).

The rebound effect manifests itself at different intervals (hours to weeks) after the end of the biological effect of the drug (pharmacological half-life), and its duration also varies. The rebound effect presents an intensity or frequency a few times higher than the corresponding baseline symptoms suppressed by the primary action of the antipathic drug. Although the rebound effect only occurs in a minority of susceptible individuals, it becomes an epidemiological concern when considering the exceedingly broad use of palliative treatments by the population.

Following the deductive Aristotelian reasoning employed by Hahnemann to validate the homeopathic healing principle, since 1998, we have been scientifically substantiating the "similitude in modern pharmacology" through the systematic study of the rebound effect (paradoxical reaction) of many classes of drugs[4-14], confirming the homeopathic postulate and the principle of similitude: a universal occurrence of strong secondary and opposite action of the body after ceasing the primary action of the drugs (Figure 1).

Illustrating the rebound phenomenon[4-14], it is observed that drugs classically used for the treatment of *angina pectoris* (e.g., β-blockers, calcium channel blockers, and nitrates) with beneficial effects through their primary action might trigger a paradoxical increase of the frequency and intensity of chest pain after its discontinuation. Drugs used for *arterial hypertension* (e.g., α-2 agonists, β-blockers, ACE inhibitors, MAO inhibitors, nitrates, sodium nitroprusside, and hydralazine) might produce rebound arterial hypertension after the end of the primary biological effect (half-life). *Antiarrhythmic* drugs (e.g., adenosine, amiodarone, β-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine, and procainamide) may trigger rebound exacerbation of basal ventricular arrhythmias. *Antithrombotic* drugs (e.g., argatroban,

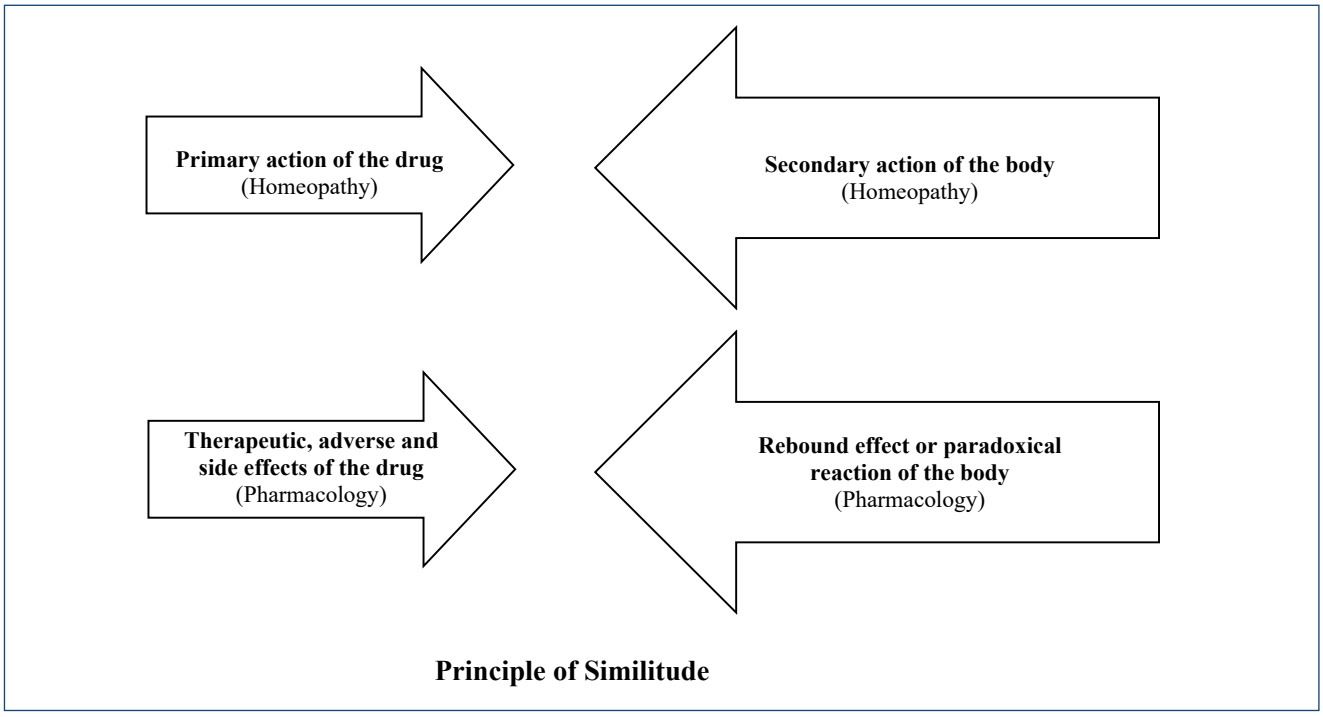

Figure 1. Universal mechanism of action of drugs (biphasic action of drugs): primary action of the drug followed by secondary and opposite action of the body (principle of similitude).

bezafibrate, heparin, salicylates, warfarin, and clopidogrel) might promote thrombotic complications as a result of the rebound effect. Drugs with primary *pleiotropic* or *vasoprotective* action (statins) might cause rebound endothelial dysfunction, resulting in predisposition to paradoxical vascular accidents.

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

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

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

Anti-dyspeptic (e.g., antacids, H2 antagonists, misoprostol, sucralfate, and proton-pump inhibitors) might trigger rebound increase of hydrochloric acid production and gastrin, with worsening of the original condition. *Antiresorptive* drugs used for the treatment of osteoporosis (e.g., bisphosphonates, denosumab, and odanacatib) might cause paradoxical atypical fractures due to the rebound increase of osteoclast activity.

Discontinuation of drugs for the treatment of *multiple sclerosis* (e.g., glucocorticoids, interferon, glatiramer acetate, natalizumab, and fingolimod) might cause rebound increase of the inflammation with exacerbation of clinical symptoms and increase of demyelination lesions. *Immunomodulatory* agents (e.g., recombinant monoclonal antibodies and tumor necrosis factor inhibitors) indicated for the treatment of psoriasis might trigger rebound psoriasis after discontinuation. The list of examples is much longer[4-14].

According to these examples, the rebound effect, a universal and automatic physiological mechanism to maintain a constant

internal environment or homeostasis, is liable to be elicited by all types of palliative drugs. Due to the high intensity of primary action of drug, such paradoxical reaction might induce severe and eventually fatal adverse events.

Exemplifying these iatrogenic events, the long-acting β-adrenergic bronchodilators cause 1 episode of fatal rebound bronchospasm per 1,000 patient-years of use, corresponding to 4,000–5,000 deaths in 2004 in the United States alone, and 40,000–50,000 deaths worldwide[5,7]. Selective serotonin reuptake inhibitor antidepressants cause 5 rebound suicidal manifestations per 1,000 patient-years of use among adolescents, corresponding to 16,500 cases of suicidal ideation or behavior in 2007 in the United States alone[5,8]. Bisphosphonates cause 1–3 episodes of paradoxical atypical fractures per 1,000 patient-years of use[11].

Assuming that the principle of therapeutic similitude is a "natural law of cure," since 2003, we have been suggesting the homeopathic use of modern drugs employing the rebound effect in a therapeutic way[15-19], proposing to administer, in ultra-diluted doses, drugs that present, in their primary action, a set of signs and symptoms similar to the manifestations of sick individuals.

The proposal entitled "New Homeopathic Medicines: Use of modern drugs according to the principle of similitude" encompasses 1,250 modern drugs and has been available, since 2021, in three free-access digital books indexed in the Virtual Health Library (i.e., PAHO, WHO, and BIREME)[20]: "Scientific basis of the principle of similitude in modern pharmacology,"[21] "Homeopathic materia medica of modern drugs,"[22] and "Homeopathic repertory of modern drugs."[23]

To test the clinical and scientific validity of this proposal, we developed a randomized controlled trial employing potentized estrogen (17-β estradiol) for the treatment of endometriosis-associated pelvic pain[24], in view of the fact that estrogen causes as an adverse event a set of signs and symptoms similar to the endometriosis syndrome, observing significant improvement compared with placebo in relation to pain, depression, and quality of life[25].

We hope that these studies will be useful to all homeopathic doctors and researchers in the scientific validation of the therapeutic similitude and enable new applications for the homeopathic treatment.

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