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'Paradoxical pharmacology': therapeutic strategy used by the 'homeopathic pharmacology' for more than two centuries

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ABSTRACT

Using the empirical or phenomenological research method by observing the effects of drugs in the human physiology, Samuel Hahnemann proposed the homeopathic treatment. He synthesized modern pharmacodynamic in the 'primary action' of the drugs and in the consequent and opposite 'secondary action' or 'vital reaction' of the organism. Noting that drugs with 'contrary' primary action to the symptoms of the diseases caused worsening of the symptoms after its withdrawal, as a result of secondary action of the organism, Hahnemann proposed using this vital reaction (secondary action) in a curative way, administering to sick individuals the drugs that caused 'similar' symptoms in healthy individuals (therapeutic use of the similitude principle). According to the clinical and experimental pharmacology, this secondary action (vital reaction) of the organism is observed in the 'rebound effect' or 'paradoxical reaction' of several classes of drugs, which is the scientific basis of the 'homeopathic pharmacology'. In the last decade, exponents of modern pharmacology have suggested the therapeutic use of the paradoxical reaction ('paradoxical pharmacology'), proposing the use of drugs that cause an exacerbation of the disease in the short term to treat these same diseases in the long-term. In this review, we compare the various aspects between the 'homeopathic pharmacology' and the 'paradoxical pharmacology', reinforcing the validity of homeopathic assumptions and expanding the knowledge to optimize both proposals.

Keywords: Homeopathy; Pharmacology; Pharmacodynamic Action of Homeopathic Remedy; Secondary Effect; Rebound Effect; Paradoxical Reaction; Paradoxical Pharmacology.

Introduction

In the ancient Greece, Hippocrates recommended treatment of diseases by the principles of 'contraries' *(contraria contrariis curentur)* or 'similar' *(similia similibus curentur),* teaching that "whatever evil and from where come, you might want to always treat or by contrary or by similar" *(Liber de locis in homine).* Based on *Corpus Hippocraticus,* several exponents of the old medical schools spread these ways to treat [1].

The 'principle of contraries', which is applied to a large percentage of conventional modern therapeutic, employs medicines with contrary (enantiopathic, antipathetic, opposite or palliative) action to the signs and symptoms of the diseases, in order to minimize or neutralize their manifestations. On the other hand, the 'principle of similars' or 'principle of similitude', systematized by the homeopathic therapeutic, employs drugs that possess the property of exhibiting signs and symptoms similar to those manifested by diseases, in order to stimulate the organism to react against their own disturbances.

The homeopathic method of treatment is based on four pillars: 'principle of therapeutic similitude', 'proving of medicinal substances on healthy individuals', use of 'serially diluted and shaken (dynamized) medicines', and prescription of 'individualized medicines'. Although great importance was attributed to 'dynamized medicines' (infinitesimal or ultrahigh-diluted doses), which were introduced later in the homeopathic model to minimize the possible 'aggravation of the diseases' in the application of the similitude principle, the first two pillars are the proper foundation of the homeopathic epistemological model, remaining to 'individualized medicine' the essential condition for awakening the therapeutic response.

In the last decade, exponents of modern clinical and experimental pharmacology have suggested a therapeutic strategy similar to the one propagated by homeopathy for more than two centuries, called 'paradoxical pharmacology', proposing the use of conventional drugs that cause an exacerbation of the disease in the short-term to treat this same disease in the long-term.

In this review article, we propose identifying the conceptual and functional similarities between the 'homeopathic pharmacology' (therapeutic use of the similitude principle) and the 'paradoxical pharmacology' (therapeutic use of the paradoxical reaction), reinforcing the validity of homeopathic assumptions before the modern scientific rationality and expanding the knowledge to optimize both proposals.

Similitude in homeopathy – 'Law of similars'

During the development of the homeopathic methodology, Samuel Hahnemann maintained an experimental posture, using phenomenological research method to describing the effects of dozens of drugs in the human health and correlating his observations with evidences from medical literature.

In the work that inaugurated the homeopathy *(Essay on a new principle for ascertaining the curative power of drugs, 1796)* [2] and in the introduction of the *Organon of medicine* [3] he cited several reports of an opposite 'secondary action of the organism' after a 'primary action of the drug' described in your observations and in hundreds of bibliographical references. These descriptions were illustrated with 'examples of accidental homeopathic cure' reported by doctors of all times, supporting a scientific rationale for the principle of homeopathic cure:

"The seeds of the *poison tree (Strychnos nux vomica)* are very powerful; but the morbid symptoms it produces are not yet accurately known. The most I know concerning them is derived from my own observation. The primary action produce vertigo, anxiety, febrile rigour, and in their secondary action a certain immobility of all parts, at least of the limbs, and a spasmodic stretching, according to the size of the dose. Hence they are useful, not only, as is already known, in intermittent fever, but in cases of apoplexy. In their first direct action the muscular fiber has a peculiar mobility imparted to it, the sensitive system is morbidly exalted to a species of intoxication, accompanied by fearfulness and horror. Convulsions ensue. The irritability seems to exhaust it itself during this continued action on the muscular fiber, first in the animal, then in the vital functions. On passing into the indirect secondary action, there occurs a diminution of the irritability, first, in the vital functions (general perspiration), then in the animal, and lastly in the natural functions. In the latter, especially, this secondary action lasts several days. During the secondary action, there is a diminution of sensibility. Whether in the primary direct action the tonicity of the muscles is diminished, to be proportionately increased in the secondary action, cannot be accurately determined; this much, however, is certain, that the contractility of the fiber is as much diminished in the secondary action, as it was increased in the direct action". *(Essay on a new principle for ascertaining the curative power of drugs)*

"*Arsenic,* whose effects are so powerful upon the human economy that we cannot decide whether it is more hurtful in the hands of the fool-hardy than it is salutary in those of the wise, - arsenic could never have effected so many remarkable cures of cancer in the face, as witnessed by numerous physicians, among whom I

will only cite *Fallopius, Bernhardt,* and *Roennow,* if this metallic oxide did not possess the homeopathic power of producing, in healthy persons, *very painful tubercles, which are cured with difficulty,* as witnessed by *Amatus Lusitanus*; very deep and *malignant ulcerations,* according to the testimony of *Heinreich* and *Knape;* and *cancerous ulcers,* as testified by *Heinze.* The ancients would not have been unanimous in the praise which they bestowed on the magnetic arsenical plaster of *Angelus Sala* against pestilential buboes and carbuncles, if arsenic did not, according to the report of Degner and *Pfann,* give rise to inflammatory tumours which *quickly turn to gangrene,* and to carbuncles or malignant pustules, as observed by *Verzascha* and *Pfann.* And whence could arise that curative power which it 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, Jiingken, Fauve, Brera, Darwin, May, Jackson,* and *Fowler*) if it did not proceed from *its peculiar faculty of excit ingfever,* 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,* have seen it give rise to very 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 depression of the vital powers*". (*Organon of medicine,* "Examples of accidental homeopathic cure")

With these several evidences, Hahnemann gathered 'strong arguments' that enabled him to induce a physiological mechanism to explain this 'biphasic' or 'bidirectional' action of drugs on the organism:

"Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action.* […] To its action our vital force 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 *counter-action".* (*Organon of medicine,* paragraph 63)

He exemplifies this biphasic action (primary action of the drug followed by a secondary and opposite action of the organism) in the non-pharmacological interventions and in the pharmacological effects of antipathic treatments used at that time:

"[…] A hand bathed in hot water is at first much warmer than the other hand that has not been so treated (primary action); but when it is withdrawn from the hot water and again thoroughly dried, it becomes in a short time cold, and at length much colder than the other (secondary action). A person heated by violent exercise (primary action) is afterwards affected with chilliness and shivering (secondary action). To one who was yesterday heated by drinking much wine (primary action), today every breath of air feels too cold (counteraction of the organism, secondary action). An arm that has been kept long in very cold water is at first much paler and colder (primary action) than the other; but removed from the cold water and dried, it subsequently becomes not only warmer than the other, but even hot, red and inflamed (secondary action, reaction of the vital force). 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)

Describing the sad results of the indiscriminate palliative (antipathic, enantiopathic) employment of medicines (*Organon of medicine,* paragraphs 56-61), Hahnemann alerts to the risks of this undesirable secondary action (vital reaction) of the organism that can produce "more serious disease or frequently even danger to life and death itself". This way, negating the efficacy of the conventional or palliative treatment (principle of contraries), Hahnemann validates the homeopathic treatment (principle of similitude) through the hypothetical syllogism or classical deductive logic "modus tollens" ('mode that affirms through negation' or 'indirect proof'). Through various examples, he concludes that "after such short antipathic amelioration, aggravation follows in every case without exception" (*Organon of medicine,* paragraph 58), i.e., after a primary action of palliative medicines occurs a secondary action of the organism, with worsening of symptoms:

"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 diarrhoea 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. For nocturnal cough of long standing the ordinary physician knew no better than to administer opium, whose primary action is to suppress every irritation; the cough would then perhaps cease the first night, but during the subsequent nights it would be still more severe, and if it were again and again suppressed by this palliative in increased doses, fever and nocturnal perspiration were added to the disease; - 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; - the ordinary physician seeks to remove chronic debility by the administration of wine, which, however, stimulates only in its primary action, and hence the forces sink all the lower in the secondary its primary action, and hence the forces sink all the lower in the secondary action; - by bitter substances and heating condiments he tries to strengthen and warm the chronically weak and cold stomach, but in the secondary action of these palliatives, which are stimulating in their primary action only, the stomach becomes yet more inactive; - long standing deficiency of vital heat and chilly disposition ought surely to yield to prescriptions of warm baths, but still more weak, cold, and chilly do the patients subsequently become; - 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; - by means of the sternutatory remedies that provoke a secretion of mucus, coryza with stoppage of the nose of long standing is sought to be removed, but it escapes observation that the disease is aggravated all the more by these antagonistic remedies (in their secondary action), and the nose becomes still more stopped; - by electricity and galvanism, with in their primary action greatly stimulate muscular action, chronically weak and almost paralytic limbs were soon excited to more active movements, but the consequence (the secondary action) was complete deadening of all muscular irritability and complete paralysis; - by venesections it was attempted to remove chronic determination of blood to the head, but they were always followed by greater congestion; - ordinary medical practitioners know nothing better with which to treat the paralytic torpor of the corporeal and mental organs, conjoined with unconsciousness, which prevails in many kinds of typhus, than with large

doses of valerian, because this is one of the most powerful medicinal agents for causing animation and increasing the motor faculty; in their ignorance, however, they knew not that this action is only a primary action, and that the organism, after that is passed, most certainly falls back, in the secondary (antagonistic) action, into still greater stupor and immobility, that is to say, into paralysis of the mental and corporeal organs (and death); they did not see, that the very diseases they supplied most plentifully with valerian, which is in such cases an oppositely acting, antipathic remedy, most infallibly terminated fatally. The old school physician rejoices that he is able to reduce for several hours the velocity of the small rapid pulse in cachectic patients with the very first dose of uncombined purple foxglove (which in its primary action makes the pulse slower); its rapidity, however, soon returns; repeated, and now increased doses effect an ever smaller diminution of its rapidity, and at length none at all - indeed - in the secondary action the pulse becomes uncountable; sleep, appetite and strength depart, and a speedy death is invariably the result, or else insanity ensues. How often, in one word, the disease is aggravated, or something even worse is affected 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)

Despite this secondary action of the organism be clearly observed after the primary action of the medicines in moderate-large doses (*Organon of medicine,* paragraphs 65, 112), as an instinctive and automatic mechanism of self-regulation of the internal environment (homeostasis), in homeopathic (small) doses, as result of weak primary action of the medicine, is not perceived an "obvious antagonistic secondary action" (*Organon of medicine,* paragraphs 66, 68, 112). In this situation, the organism "employs against it only so much reaction (secondary action) as is necessary for the restoration of the normal condition", and may be curative or not if the therapeutic similitude principle is observed. In this case, it is worth mentioning that although little significant (non "obvious", "reacts only so much as is requisite", "so much reaction as is necessary", "any more considerable reaction than will suffice", "little effort is required"), the secondary action (vital reaction) of the organism manifests itself and is perceived through their curative effects:

"[...] 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)

"In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but towards the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action (§ 63) or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action (§ 62-67), of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homoeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state". (*Organon of medicine,* paragraph 112)

"An obvious antagonistic secondary action, however, is, as may readily be conceived, not to be noticed from the action of quite minute homoeopathic doses of the deranging agents on the healthy body. A small dose of every one of them certainly produces a primary action that is perceptible to a sufficiently attentive; but the living organism employs against it only so much reaction (secondary action) as is necessary for the restoration of the normal condition". (*Organon of medicine,* paragraph 66)

"In homoeopathic cures they show us that from the uncommonly small doses of medicine (§ 275-287) required in this method of treatment, which are just sufficient, by the similarity of their symptoms, to overpower and remove from the sensation of the life principle the similar natural disease there certainly remains, after the destruction of the latter, at first a certain amount of medicinal disease alone in the organism, but, on account

of the extraordinary minuteness of the dose, it is so transient, so slight, and disappears so rapidly of its own accord, that the vital force has no need to employ, against this small artificial derangement of its health, any more considerable reaction than will suffice to elevate its present state of health up to the healthy point - that is, than will suffice to effect complete recovery, for which after the extinction of the previous morbid derangement but little effort is required (§ 64, B)". (*Organon of medicine,* paragraph 68)

Proposing to apply such 'secondary action' in a curative way (curative secondary action or effect), awakening a 'vital reaction' of the organism against its own disorders, Hahnemann suggested employing medicines that in their 'primary action' produce symptoms similar to the ones of natural disease, thus widening the notion of the 'curative similitude' (homeopathic method of treatment): every substance capable of provoking certain symptoms in healthy individuals (due to the primary action of the drug), can be used to cure similar symptoms in the sick (through the curative secondary action of the organism), according to the therapeutic similitude principle. (*Organon of medicine,* paragraphs 24-28)

In summary, in the exemplification of the harmful effects of the use of moderate-large doses in accordance with the antipathic treatment, Hahnemann reports that such secondary action (vital reaction) of the organism (opposed in character to the primary action of the drug) is evidently observed (*Organon of medicine,* paragraphs 58-61, 112). In the homeopathic treatment (minimal doses), Hahnemann reports that the curative secondary action of the organism reacts to the primary action of the homeopathic doses "only so much as is requisite to raise the health again to the normal healthy state" (*Organon of medicine,* paragraphs 66, 68, 112). As will be shown below, Hahnemann also employed the principle of therapeutic similitude with massive (ponderable) doses of medicines, awakening a curative secondary action of the organism to conduct a complete recovery. Thus, noting its manifestation in the most diverse situations, Hahnemann raises the principle of therapeutic similitude (an opposite curative secondary action of the organism after the primary action of the medicine) to the level of "natural law of cure" or "law of similars" (*Organon of medicine,* paragraphs 26-28, 50-53), **regardless of the doses,** since the symptomatic individualization is respected:

"The curative power of medicines, therefore, depends on their symptoms, similar to the disease but superior to it in strength (§ 12-26), so that each individual case of disease is most surely, radically, rapidly and permanently annihilated and removed only by a medicine capable of producing (in the human system) in the most similar and complete manner the totality of its symptoms, which at the same time are stronger than the disease". (*Organon of medicine,* paragraph 27)

"As this natural law of cure manifests itself in every pure experiment and every true observation in the world, the fact is consequently established; it matters little what may be scientific explanation of how it takes place; and I do not attach much importance to the attempts made to explain it. But the following view seems to commend itself as the most probable one, as it is founded on premises derived from experience". (*Organon of medicine,* paragraph 28)

As mentioned previously, although Hahnemann used in the early stage of the homeopathic therapy ponderable (massive) doses of drugs in accordance with the therapeutic principle of similitude, the infinitesimal or ultrahigh-diluted doses have emerged in order to allow the organism to react to the primary stimulus of the drugs without the possible toxicological disorders, observing later that they awakened and healed different symptoms of the substantial doses, enlarging the therapeutic approach.

Similitude in modern pharmacology – 'Homeopathic pharmacology'

Building a bridge between the principle of similitude and the modern pharmacology ('homeopathic pharmacology'), one can find countless reports in pharmacological compendia and clinical and experimental trials published in the scientific media describing the *secondary reaction of the organism opposed to the*

primary action of the drug, which confirm Hahnemann's theory. Such secondary action of the organism to preserve organic homeostasis is known as 'rebound effect' by modern pharmacology [4-15].

According to Webster's New World Medical Dictionary [16], 'rebound effect' means "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". Also named by the term 'paradoxical reaction' of the organism, one of the ironies of this phenomenon is that it makes the patients experience the very same effects they had hoped to make disappear by using palliative drugs, thus deconstructing the main pillar of modern pharmacological therapy, i.e., the treatment by principle of contraries. Although its exact mechanism remains unclear, the main hypothesis to explain the rebound (paradoxical) effect is that it might be caused by increased responsiveness (up-regulation) of the receptors of the involved drug.

In general terms, rebound effect is the result of the attempts of the organism to bring itself back into balance (homeostasis) after a drug is taken in order to neutralize the disease symptoms. Described in 1860 by Sorbonne professor Claude Bernard as "fixité du milieu intérieur", the term 'homeostasis' was minted in 1929 by Harvard physiologist Walter Bradford Cannon to name the tendency or ability of living beings to keep their internal environment constant through self-adjustment of their physiological processes. Such physiological processes or homeostatic mechanisms are present at all levels of the biological organization from the simplest of cells to the most complex mental and emotional functions.

Illustrating these assertions, drugs classically used in the treatment of *angina pectoris* (ß-blockers, calcium channel blockers, nitrates, and others) with beneficial effects in their primary effect (anti-angina), might awaken a paradoxical increase of the frequency and intensity of chest pain after discontinuation or irregular use of doses, which sometimes does not respond to any therapeutic means. Drugs used for the control of *arterial hypertension* (α-2 agonists, ß-blockers, ACE inhibitors, MAO inhibitors, nitrates, sodium nitroprusside, hydralazine, and others) might produce rebound arterial hypertension as a paradoxical reaction of the organism to the primary stimulus; *antiarrhythmic* drugs (adenosine, amiodarone, ß-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine, procainamide, quinidine, digital, and others) may awaken a rebound exacerbation of basal ventricular arrhythmias, when the treatment is interrupted. *Hypolipidemic* drugs (clofibrate, colestipol, colestiramine, nicotinic acid, fluvastatin, lovastatin, pravastatin, and others), used in its primary action to treat hyperlipidemia, promote increased rebound of lipid after their interruption. *Antithrombotic* drugs (argatroban, heparin, salicylates, warfarin, clopidogrel, and others), employed due to their primary effect in the prophylaxis of thrombosis, can promote thrombotic complications as paradoxical reaction of the organism.

In the use of psychiatric drugs such as *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) it can be observed a paradoxical reaction of the organism, which seeking to keep organic homeostasis, promote the appearance of symptoms contrary to the ones expected from their primary therapeutic use, consequently worsening the initial clinical picture. Drugs with *anti-inflammatory* primary action (corticosteroids, ibuprofen, indometacin, paracetamol, salicylates, and others) might trigger paradoxical reactions of the organism that increase inflammation together with the serum concentration of its mediators. Drugs with *analgesic* primary action (caffeine, calcium channels blockers, clonidine, ergotamine, methysergide, opiates, salicylates, and others) can exhibit significant hyperalgesia as a rebound effect. *Diuretics* (furosemide, torasemide, triamterene, and others) enantiopathically used to diminish the volume of plasma (edema, arterial hypertension, congestive heart

failure, and others) may cause rebound retention of sodium and potassium thus increasing the basal volume of plasma.

Drugs primarily used as *anti-dyspeptic* (antacids, H_2 antagonists, misoprostol, sucralfate, protons pump inhibitors, and others) in the treatment of gastritis and gastro-duodenal ulcers might promote, after the primary decrease of acidity, rebound increase of the production of hydrochloric acid by the stomach eventually causing perforation of chronic gastro-duodenal ulcers. *Bronchodilators* (adrenergic drugs, sodium chromoglycate, epinephrine, ipratropium, nedocromil, formoterol, salmeterol, and others) used in the treatment of bronchial asthma can worsen bronchial constriction as paradoxical response of the organism to the interruption or discontinuation of treatment. *Antiresorptive drugs* (bisphosphonates, denosumab, and others), given to treat osteoporosis, can cause paradoxical atypical fractures after their biological effect (half-life), as a result of rebound increased of the osteoclastic activity. *Immunomodulatory drugs* (natalizumab, fingolimod, and others) used in the treatment of multiple sclerosis, can cause immune reconstitution inflammatory syndrome (IRIS) with rebound worsening of disease, after treatment withdrawal, among others [4-15].

Despite such phenomena appearing in a minority of individuals in view of their idiosyncratic nature, contemporary scientific evidences point to the occurrence of *severe and fatal iatrogenic events* as a function of the rebound effect or paradoxical reaction of the organism following the discontinuance of many classes of modern enantiopathic drugs [6]. As a result of primary anticoagulant action, all types of non-steroidal anti-inflammatory drugs awaken thrombogenic paradoxical reactions after discontinuation, leading to a significant increase to the incidence of thrombosis and causing acute myocardial infarction (AMI) and encephalic vascular accidents (EVA) [7,17,18].

Analogously, long-acting ß-agonist bronchodilators after their primary bronchodilator action can cause significant irreversible and fatal paradoxical bronchospasm [8,19,20]. Antidepressant agents, inhibiting the recapture of serotonin (SSRIs), promote a rebound exacerbation of suicidality after an initial improvement of this same symptom [9,21,22]. After a primary increase of their pleiotropic effects (vascular protective), statins cause paradoxical and fatal vascular events (AMI, EVA) [10,23,24]. Proton-pump inhibitors (PPIs) cause rebound hypergastrinemia and acid hypersecretion after an initial decrease of acidity, thus exacerbating gastritis and ulcers, gastric cancer and carcinoid tumor [11,25,26]. In addition to severe paradoxical atypical fractures after denosumab withdrawal [13,27] and severe relapses of multiple sclerosis after natalizumab withdrawal [14,28,29], recent studies warn of fatal risks inherent to the rebound effect of others drugs of modern biological therapy [30,31].

According to this evidence of the modern pharmacology, *rebound effect* or *paradoxical reaction of the organism* has an intensity higher than the one of the symptoms originally suppressed: in controlled studies, in relation to the placebo, a risk of ischemic accidents was 3.4 times larger after salicylates withdrawal, 1.52 times larger after non-steroidal anti-inflammatory drugs withdrawal, 1.67 times larger after rofecoxib withdrawal, and 1.69 times larger after statins withdrawal; a risk of suicidal behaviours 6 times larger after SSRI antidepressants withdrawal, and a risk of fatal paradoxical bronchospasm 4 times larger after long-acting beta agonists withdrawal.

With similar estimates to the rebound effect of other drugs, long-acting beta agonists cause approximately 1 rebound bronchospasm followed by death every 1,000 patients-year-use, corresponding to 4,000-5,000 deaths/year in 2004 in the USA alone (40,000-50,000 worldwide) [8,32]. SSRI antidepressants cause approximately 5 rebound suicidality events every 1,000 teenagers patients-year-use, corresponding to 16,500 suicidal behavior or thoughts in 2007 only in USA [9]. Salicylates cause approximately 4 rebound acute myocardial infarction every 1,000 patients-year-use [33,34]. Studies described the increased incidence of gastric carcinoids in last decades (400% in men and 900% in women) in view of the growing consumption of

the PPIs [11]. Bisphosphonates cause 1-3 severe paradoxical atypical fractures every 1,000 patients-year-use [13]. Natalizumab awakens rebound worsening of multiple sclerosis around 10% of patients who discontinued treatment [14].

The rebound effect appears some time (hours to weeks) after the decrease or discontinuation of the treatment ('withdrawal syndrome') according to the pharmacokinetic properties of the involved drug and the idiosyncratic peculiarities of the individuals: average of 10 days for salicylates, 14 days for the non-steroidal anti-inflammatory drugs, 9 days for the rofecoxib, 7 days for the SSRI antidepressants, 7 days for the statins, and 7-14 days for the PPIs. The duration of the rebound effect is also variable: remaining for 30 days with rofecoxib, 21 days with SSRI antidepressants, and 30 days with PPIs. The duration of the treatment did not show association with the risk of awakening the paradoxical events.

Despite the fact that the drug withdrawal ('half-life' time) is a prerequisite for the manifestation of the paradoxical reaction of the organism or rebound effect, because the primary effect of the drug lasts as long as the receptors are stimulated, studies show that the rebound effect can occur even during drug use, occurrence which can be explained by the phenomenon of 'tolerance' (adaptation of the organism to the drug with the loss of pharmacological effect). On the other hand, the slow and gradual decrease of the doses, avoiding an abrupt discontinuation, is a procedure to minimize the manifestation of the rebound effect.

As evidenced by clinical and experimental pharmacology [4-15], the common properties of the rebound effect or paradoxical reaction of the organism are the same as the ones of the homeopathic secondary action described by Hahnemann (*Organon of medicine,* paragraphs 59, 64, 69): (i) it appears only in susceptible individuals, who present in their constitution symptoms similar to the pathogenetic effects of the drug; (ii) it does not depend on the drug, repetition (magnitude) of doses or type of symptoms (disease); (iii) it appears after the primary action of the drug (discontinuation or decrease of the doses), as an automatic manifestation of the organism; (iv) it induces an organic state (symptoms) opposite and greater in intensity and/or frequency than the primary action of the drug; (v) the magnitude of its effect is proportional to the intensity of the primary action of the drug.

Use of modern drugs according to the principle of similitude – 'New homeopathic medicines'

In order to learn the healing properties of drugs to allow for the application of the principle of therapeutic similitude, homeopathy employs the 'proving of medicinal substances on healthy individuals' or 'homeopathic pathogenetic trials' (HPTs) as its model of pharmacological clinical research. HPTs can be compared to the modern 'phase I studies' which takes into account all types of primary or direct actions, the so-called pathogenetic effects or symptoms (mental, general or physical), awakened by drugs on the state of human health. These very same pathogenetic effects are called by modern pharmacology as *therapeutic, adverse or side effects* of the drugs.

Although Hahnemann laid down the ideal stipulations to carry out HPTs (*Organon of medicine*, paragraphs 105-145), the Homeopathic Materia Medica (compendium which brings together the primary or pathogenetic effects of substances) is actually composed by a compilation of the signs and symptoms recorded along the testing of thousands of drugs in both healthy and ill individuals, in ponderable (substances in raw state) and diluted (dynamized medicines) doses. In this way, it comprises the pictures of artificial states of the disease needed to apply the homeopathic therapeutic method.

To substantiate the validity of pathogenetic trials with ponderable doses and/or on ill individuals, Hahnemann observed that the effects of experiments described by previous authors carried out with "large doses of medicinal substances" on healthy (poisonings) and ill (therapeutic overdoses) individuals were very

similar to his observations while testing the very same substances on himself and other healthy individuals (*Organon of medicine,* paragraphs 110-112).

"I saw, moreover, that the morbid lesions which previous authors had observed to result from medicinal substances when taken into the stomach of healthy persons, either in large doses given by mistake or in order to produce death in themselves or others, or under other circumstances, accorded very much with my own observations when experimenting with the same substances on myself and other healthy individuals. These authors give details of what occurred as histories of poisoning and as proofs of the pernicious effects of these powerful substances, chiefly in order to warn others from their use; partly also for the sake of exalting their own skill, when, under the use of the remedies they employed to combat these dangerous accidents, health gradually returned; but partly also, when the persons so affected died under their treatment, in order to seek their own justification in the dangerous character of these substances, which they then termed poisons. None of these observers ever dreamed that the symptoms they recorded merely as proofs of the noxious and poisonous character of these substances were sure revelations of the power of these drugs to extinguish curatively similar symptoms occurring in natural disease, that these their pathogenetic phenomena were intimations of their homoeopathic curative action, and that the only possible way to ascertain their medicinal powers is to observe those changes of health medicines are capable of producing in the healthy organism; for the pure, peculiar powers of medicines available for the cure of disease are to be learned neither by any ingenious a priori speculations, nor by the smell, taste or appearance of the drugs, nor by their chemical analysis, nor yet by the employment of several of them at one time in a mixture (prescription) in diseases; it was never suspected that these histories of medicinal diseases would one day furnish the first rudiments of the true, pure materia medica, which from the earliest times until now has consisted solely of false conjectures and fictions of the imagination - that is to say, did not exist at all." (*Organon of medicine,* paragraph 110)

"The agreement of my observations on the pure effects of medicines with these older ones - although they were recorded without reference to any therapeutic object, - and the very concordance of these accounts with others of the same kind by different authors must easily convince us that medicinal substances act in the morbid changes they produce in the healthy human body according to fixed, eternal laws of nature, and by virtue of these are enabled to produce certain, reliable disease symptoms each according to its own peculiar character". (*Organon of medicine,* paragraph 111)

In this regard, it is worth observing that the historical revisions carried out by Robert Ellis Dudgeon [35] and Richard Hughes [36] show that most of the symptoms listed in the works of homeopathic materia medica written by Hahnemann *(Fragmenta de Viribus Medicamentorum Positivis, Materia Medica Pura and The Chronic Diseases)* arise from the use of medicines in ponderable (moderate-large) doses and on ill individuals.

According to Hughes [36], in 1805, Hahnemann published the pathogenetic studies of 27 remedies in *Fragmenta de Viribus Medicamentorum Positivis* [37], which thus represents the first homeopathic materia medica that he used in his clinical practice. The sources of the pathogenetic symptoms listed were his own observations (of poisonings, therapeutic overdoses, self-experimentation and tests on other healthy individuals) as well as the ones 'by others' and reported in the literature. In this context, 'observations by others' (namely, reports of poisonings in healthy individuals and therapeutic overdoses in the ill) represent a large fraction of most pathogenetic studies published in the six volumes of *Materia Medica Pura* [38], in which only 13 of the 61 remedies do not present such kind of data. Still in Köthen, Hahnemann published between 1828-1830 the 4 volumes of the first edition of *The Chronic Diseases* [39], which introduced 17 new and 5 extended pathogenetic studies of remedies already published in *Materia Medica Pura*. With the only exception of *Kalium carbonicum* and *Natrum muriaticum* - which were tested in potentiated doses (30cH) and in (2 and 3, respectively) healthy individuals - the remainder of medicines were tested in diversified potencies (e.g. 'small portions of a grain', 2nd and 3rd trituration, 6th and 30th potency) and on individuals suffering from

chronic diseases. The second edition of *The Chronic Diseases*, published between 1830-1835, added 25 pathogenetic studies (13 new and 12 already published in *Materia Medica Pura* and extended) to the 22 listed in the first edition. In both editions, the pathogenetic manifestations listed are adverse and side effects of drugs prescribed to patients suffering from chronic diseases. Referring to the written "Examination of the sources of the common materia medica", cited as preamble to the second volume of the *Materia Medica Pura,* Hughes stated explicitly: "Hahnemann's own additions to the second issue of his work must be of the same character as his contributions to the first, *i.e.,* they must be collateral effects of the drugs observed on the patients to whom he gave them" [36].

Analogously, homeopathic treatment was also accomplished with ponderable (moderate-large) doses on the grounds of the pathogenetic manifestations observed after the intake of ponderable doses by healthy (poisonings) and ill (therapeutic overdoses) individuals. In work that inaugurates the homeopathy [2], Hahnemann mentions the use of drugs of his time in the homeopathic treatment of numerous diseases and epidemics (uterine colic with *Matricaria chamomilla;* autumnal dysentery with *Arnica montana*; painful indurations of the lymph nodes with *Conium maculatum*; paralytic and spasmodic affections with *Solanum dulcamara*; chronic hemorrhages, mania and seizures with *Hyosciamus niger*; tremors, fasciculations, cramps and intermittent fevers with *Ignatia amara;* amaurosis, cataracts and opacities of the cornea with *Anemona pratensis*, etc.), applying them according to the principle of similitude ('adverse/side effects' mentioned in literature) and substantial doses. In *The Lesser Writings* [40], Hahnemann describes similar applications in other epidemic diseases (remittent and scarlet fevers, typhus, cholera, etc). In 1799, during an epidemic of scarlet fever [41] Hahnemann used for the first time diluted and agitated doses in order to decrease the pathogenetic power of doses and thus avoid aggravation [42]. In 1814, during the treatment of typhus or hospital fever [43], Hahnemann outlined the pharmacotechnique of potentization (serial dilutions and strong agitation). The "theory of potentization" strictly speaking only appeared in 1827 [44], when Hahnemann incorporated the processes of trituration and succussion in order to develop and exalt the "dynamic medicinal powers of natural substances".

In addition to the examples of classical homeopathic medicines that were derived in the past from conventional drugs (*Ammonium, Arsenic, Borax, Camphora, Chamomilla, Digitalis, Hydrastis, Mercurius, Nux vomica, Opium, Sulphur, Valeriana,* among others), some modern studies have used conventional drugs in accordance with the curative rebound effect: contraceptive drugs used as inducers of rebound ovulation and consequent pregnancy [45]; central nervous system stimulants used with beneficial effect on attention deficit hyperactivity disorder (ADHD) [46]; among others.

Retracing classic homeopathy steps to conclude this research [47-52], we systematized the use of modern conventional drugs according to the principle of therapeutic similitude. This proposal suggests stimulating the curative rebound effect (paradoxical reaction) by employing conventional drugs that caused similar symptoms (primary actions or pathogenetic effects) in healthy or ill individuals.

To make this proposal operative a *Homeopathic Materia Medica of Modern Drugs* **grouping together all primary (therapeutic, adverse and side) effects of drugs** (described in *The United States Pharmacopeia Dispensing Information* [53]) **according to the traditional chapter scheme of the homeopathic materia medica was needed.** To facilitate the effective *selection of an individualized medicine,* which is the basic premise for successful homeopathic treatment, the second stage involved the elaboration of a *Homeopathic Repertory of Modern Drugs,* where symptoms (primary or direct effects) and their corresponding remedies are arranged as in the classical homeopathic repertories [49].

This research project is entitled "*New Homeopathic Medicines: use of modern drugs according to the principle of similitude"* and can be found in free online version at http://www.newhomeopathicmedicines.com.

Paradoxical pharmacology

Therapeutic approach suggested by Richard A. Bond in 2001 [54,55], the 'paradoxical pharmacology' proposes a strategy to treat chronic diseases using the *paradoxical drug reactions,* where the therapeutic effect is derived from compensatory response, rather than the primary or direct drug effect. These *paradoxical* or *bidirectional* drug reactions produce an outcome that is opposite to the outcome that would be expected from the drug's known effects. Such bidirectional reactions arise in a wide variety of drug classes, to a greater or lesser frequency, in the same or different individuals **and not related to the doses used.** Although incompletely understood, the clinical paradoxical effect occurs when conflicts arise at different levels in self-regulating biological systems, as complexity increases from subcellular components (channels, enzymes, receptors, transporters, organelles, etc.) to cells, tissues, organs, and the whole individual [56-60].

As a possible general hypothesis to explain the functioning of the paradoxical pharmacology is the "difference between the chronic versus the acute effect of drugs". Reiterating that the acute and chronic responses to drugs often differ substantially and, indeed, are often opposite in nature, Bond [54] warns that most contraindications for drugs are predicted on the basis of the false assumption that the chronic effect will be simply a more prolonged version of the acute effect, in view of the fact that experiments that analyze chronic effects are not performed, in part, because we cannot see how to get by the initial contraindications. Certain drugs also lose effectiveness with time (tolerance, tachyphylaxis or desensitization) as is the case of the analgesic effects of opioids that wane with repeated administration for weeks or months.

Occurring at any physiological system, with various drug classes and without changing doses, the mechanisms of such paradoxical and bidirectional effects include different actions at the same receptor, owing to changes with time and downstream effects (e.g., ß-blockers with intrinsic sympathomimetic activity); stereochemical effects (e.g., salbutamol); multiple receptor targets with or without associated temporal effects (e.g., procainamide); antibody-mediated reactions (e.g., heparin-induced thromboembolism); pharmacokinetic competing compartment effects (e.g., bicarbonate); disruption and non-linear effects in oscillating systems (e.g., dopaminergic agents), systemic overcompensation (e.g., antiretroviral therapy and immune reconstitution inflammatory syndrome), and other higher-level feedback mechanisms (e.g., digoxin) and feedback response loops at multiple levels (e.g., isotretinoin-associated acne fulminans), among others [60].

Some examples of paradoxical and bidirectional drug effects are illustrated in different pharmaceutical or systems classes: immunomodulators (e.g., systemic glucocorticosteroids, TNFα antagonists), antineoplastic agents and carcinogens (e.g., chemotherapy, radiotherapy, arsenic), antidysrhythmic drugs (e.g., procainamide, isoprenaline), antihypertensive drugs (e.g., methyldopa, clonidine, guanabenz, moxonidine, thiazides), vasodilators (e.g., nitrates), drugs for congestive heart failure (e.g., ß-blockers, ACE inhibitors, angiotensin II receptor antagonists, hydralazine), lipid-modifying drugs (e.g., fibrates, ezetimibe), inotropes and chronotropes (e.g., isoprenaline, epinephrine, ß-blockers and calcium channel blockers), vasoconstrictors (e.g., ergot alkaloids, vasopressin), anaesthetics (e.g., sevoflurane, ketamine, propofol), antiepileptic drugs (e.g., benzodiazepines, barbiturates, hydantoins), hypnosedatives (e.g., anticholinergics, antihistamines, antispasmodics, barbiturates, benzodiazepines, bromides, chloral hydrate, ethanol, opioids), psychotropic drugs (e.g., antidepressants, antipsychotics), peripheral nervous system drugs (e.g., acetylcholinesterase inhibitors, capsaicin), antidyskinetic drugs (e.g., dopaminergic agents), acid-base agents (e.g., sodium lactate, bicarbonate), bone metabolism agents (e.g., parathyroid hormone, bisphosphonates), electrolytes (e.g., hypertonic saline, magnaesium hydroxide), glycaemic agents (e.g., insulin, antiglycaemics), steroid hormones (e.g., dexamethasone suppression), thyroid agents (e.g., iodine, lithium), antihyperuricaemics (e.g., xanthine oxidase inhibitors, urate oxidases), gastrointestinal agents (e.g., opioids, cholecystokinin or ceruletide), haematological agents (e.g., erythropoietin, vitamin K antagonists, platelet adenosine diphosphate receptor antagonists), respiratory agents (e.g., short- and long-acting $ß_2$-agonists, oxygen), skin agents (e.g., high-

intensity long-wave ultraviolet light and 8-methoxypsoralen, histamine$_1$-receptor antagonists), among others [60].

In terms of 'doses', Smith et al [60], claim that "clinical bidirectional and paradoxical effects are not necessarily of explicit dose responsiveness", and "do not necessarily occur at doses different from those producing anticipated effects": "they may occur at entirely appropriate doses or regardless of dose, in intended or unintended target systems", and "they may arise in the same patient at the same doses in different circumstances (known or unknown physiological or pathological states in time)". In view of these aspects **(no relationship with doses),** the authors ruled out the mechanism of *hormesis* (biphasic dose-response curve, with beneficial or stimulatory effects at low doses and adverse or inhibitory effects at high doses) [61] as an explanation for the phenomenon.

As in various physiological systems, in which an external primary stress can result in a secondary compensatory benefit, a 'pharmacologic stress' can be used therapeutically to gain long-term benefit: "exacerbating a disease (acute or short-term effect) can make use of the body's compensatory and redundant mechanisms to achieve a beneficial long-term response (chronic effect)". Like other authors [56], Bond warns that dosing will be a serious concern in this strategy, proposing as a general rule "start at a very low dose and increase the dose over a period of weeks" [54].

Some examples of prescription of drugs that cause similar effects to those which are to be treated are cited in the literature in which paradoxical and bidirectional responses may be harnessed for benefit. Congestive heart failure (CHF) is a disease of impaired cardiac contractility usually as a result of ischemic damage to the heart muscle, and the acute use of ß-adrenoceptor agonists, increasing cardiac contractility, improved hemodynamic and decreased symptoms of CHF.

However, their chronic use resulted in an increase in mortality. On the contrary, while the short-term use of ß-adrenoceptor antagonists (ß-blockers: carvedilol, metoprolol) exacerbate the CHF (worsening of disease), the long-term use results in an increase in cardiac contractility and a decrease in mortality [54,59,60,62]. The same is observed with calcium channel blockers [63].

Analogously, ß$_2$-adrenoceptor agonists are the most potent bronchodilators and play a major role in every stage of asthma management; however, as previously mentioned, their chronic use is associated with irreversible and fatal paradoxical bronchospasm (asthma-related deaths). On the other hand, while the short-term use of ß-adrenoceptor antagonists (ß-blockers) produces bronchoconstriction and worsening asthma, the long-term use produces bronchodilation and a positive outcome in asthmatics [54,59,64,65].

Additional examples include the use of methylphenidate (central nervous system stimulant) in the treatment of hyperactivity disorders, and the use of serotonin 5-HT$_{1A}$ receptor agonist (mediator of hyperalgesia) to produce analgesia [59]. Thiazides have long provided paradoxical antidiuretic benefit in the treatment of diabetes insipidus, reducing polyuria and increasing urine osmolality [66].

Arsenic trioxide (As_2O_3), a major carcinogenic agent that is employed by homeopathy for more than two centuries to treat various types of cancer (as initially described), have been used paradoxically as a promising anticancer agent (e.g., in acute promyelocytic leukemia) [67,68], among others [60].

Non-pharmacological examples of short-term detrimental behaviors (exercising, dieting, saving money, disciplining education, among others) for a long-term benefit are also described: exemplifying, exercises that expose the heart to brief episodes of ischemia protect the myocardium from cell death produced by subsequent prolonged ischemic episodes [54,59].

Discussion

Despite the different terminologies consequent to scientific knowledge of different times, descriptions and properties of 'secondary action' or 'vital reaction' of the homeopathic model present similar aspects to the 'rebound effect' or 'paradoxical reaction' of modern pharmacology, indicating they are the same phenomena.

Both phenomena are manifestations of the secondary effects and opposite of the organism to the primary effects of the drugs, indicating a homeostatic response of the organism to return to initial balance modified by the inducing agent. Demonstrating its universal character, the rebound effect (paradoxical reaction) can occur with all classes of drugs with contrary (enantiopathic) action to the symptoms of diseases and in different individuals, although it manifests itself in a minority of individuals in view of its idiosyncratic character.

By definition, the manifestation of the rebound effect always reaches an intensity and/or frequency greater than the disturbance initially suppressed by the drug, causing a worsening of the natural disease. Described in detail in studies about the rebound effect, the 'magnitude' of this paradoxical phenomenon can cause serious and fatal iatrogenic diseases on users of various classes of modern drugs. In view of this magnitude, the curative use of the rebound effect (paradoxical reaction) has great therapeutic potential.

Despite not being valued in recent studies of 'paradoxical pharmacology', it is worth mentioning that this secondary action of the organism occurs in the absence of primary action of the drug. In studies on the rebound effect, this property is restricted to 'half life' time of each drug, which varies around 7-14 days after discontinuation of drugs with short-medium half-life; in drugs of deposit (bisphosphonates, for example) this time is longer. However, other aspects of extreme importance must also be observed: even during treatment, some studies show the manifestation of the rebound effect, which can be justified by the gradual decrease of dosage or temporary discontinuation (therapeutic failure). According to individual idiosyncrasy, small changes in drug serum concentration can trigger the paradoxical phenomenon. Still on this property, the phenomenon of 'tolerance' (tachyphylaxis or desensitization) should also be valued: as previously mentioned, even during the treatment the adaptation of the organism to the drug can occur with the loss of primary pharmacological action, allowing the manifestation of secondary or paradoxical reaction of the organism.

As described in paradoxical pharmacology [60], *the awakening of paradoxical reaction of the organism is independent of the doses of the drugs,* property also observed in the homeopathic model and in the studies on the rebound effect (unlike the hormetic mechanisms) [61,69-74]. However, if drugs that cause similar effects to those which are to be treated are prescribed, their strong doses can cause worsening of natural diseases, with disastrous consequences. As well as the homeopathic model uses ultrahigh-diluted doses of medicines to arouse the curative secondary action of the organism safely (avoiding the 'homeopathic aggravations'), Bond [54] proposes as a general rule "start at a very low dose and increase the dose over a period of weeks".

Unlike strong doses that awaken a curative paradoxical reaction in a lot of individuals (with the damages of the side effects and the initial aggravation of the diseases), ultrahigh-diluted or very low doses (although they are safe for your smaller pathogenetic power) arouse the curative secondary action only in individuals with idiosyncratic characteristics of the drug (importance of the 'individualized medicine' in accordance with the totality of characteristic symptoms). These are aspects that should be taken into consideration in the choice of the drug and the dose.

On the other hand, studying and describing the various physiological mechanisms involved in the manifestation of the rebound effect or paradoxical reaction of the organism, the 'paradoxical pharmacology' brings important subsidies to elucidate the *modus operandi* of the homeopathic vital reaction, general term used to describe the opposite and secondary action of the organism (after cease the primary action of the drug) in order to maintain the internal homeostasis ("life-preserving power", according to Hahnemann).

Conclusion

A great number of iatrogenic diseases could be avoided if the health professionals were elucidated about the homeostatic maintenance controlled through the rebound effect or paradoxical reaction of the organism, preventing the worsening of clinical functions with the slow and gradual discontinuation of the drugs used according to the principle of the contraries [12,15]. Although they are not included in the conventional adverse events for drugs, "drug discontinuation effects are part of the pharmacology of a drug" [65], and should be routinely incorporated into the teaching of modern pharmacology.

Describing the sad results of the indiscriminate antipathic or palliative employment of drugs (*Organon of medicine,* paragraphs 59-61), Hahnemann alerts to the possible risks produced by secondary action (rebound effect) of the organism, validating the principle of similitude through the deductive logic "modus tollens" or "indirect proof":

"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, paragraph 60)*

Since 1997, we have grounded scientifically the 'old', 'classic' or 'traditional' similia principle, that was founded by Hahnemann on 'symptom similarity' (*Organon,* paragraphs 22-70), confirming the principle of similitude as 'natural law' through the continuous study of modern reports of increased iatrogenic events after withdrawal of enantiopathic drugs and demonstrating the importance of the *rebound (paradoxical) symptoms* in promoting deep alterations in the organic balance, **although it was deemed 'unviable' and 'non-scientific' by other authors at the time:**

"The old principle of similarity was formulated as a general 'law' on the basis of empirical evidence and analogical reasoning, but this kind of formulation does not allow any progress in the search for the possible mechanism of the alleged therapeutic effects. […] The last question is whether these concepts can be extended to the 'classic' similia principle that was founded on 'symptom similarity'. This is the most controversial point because the analysis of symptoms does not appear to be as 'scientific' as the objective measurement of some physiological or biochemical parameter. The use of symptoms as the basis for the choice of remedy appears to be in contradiction with modern scientific medicine, which demands explanations at the biochemical and molecular level". [74]

Using these rebound symptoms in a curative way, the homeopathic (paradoxical) pharmacology stimulates the body to react against their own diseases.

As well as suggested by the spreaders of the principle of therapeutic similitude for more than two centuries [48], Bond and Giles encourage the scientists and researchers to examine the paradoxical phenomenon systematically, changing the dogma of current treatment and incorporating new approaches to the modern therapeutic arsenal:

"The identification of the phenomena of temporal differences in the effects of both agonists and antagonists in numerous drug classes has, at first observation, seemed extremely paradoxical. However, as scientists, our natural inclination is to ask the question 'why?'. Over the coming years the mechanistic basis for such behavior will undoubtedly be revealed, and the paradox will be no more. […] Nevertheless for those of us who have felt compelled to challenge dogma of current treatment paradigms because we observed paradoxical behavior, the path has been long and challenging. Seemingly 'simple' explanations of mechanism of action of a

particular drug class become turned on their head, and obtaining funding, and acceptance of paradigm-shifting ideas by peers, takes many years".[59]

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