

The mutual benefits of Science and Homeopathy: clarify, defend, improve

Paolo Bellavite,¹ Marta Marzotto,¹ Debora Olioso,¹ Clara Bonafini,¹ Beatrice Andreoli²

¹Department of Medicine, University of Verona

²Homeopathic Medicine School, Verona

Email of presenting author: paolo.bellavite@univr.it

ABSTRACT

Every medical approach comprises components that are "artistic", related to the practice, the skill, knowledge, intuition of the doctor, and components of "scientific" nature. Both are necessary. It is not always easy to distinguish these two dimensions of medical practice. What is classical Homeopathy is pretty clear, while there are considerable misunderstandings about the concept of Science. From this misconception often stem accusations of a lack of scientific basis, turned to this bicentennial medicine. Homeopathy lives of the progress of Science and promotes it. This happens basically because it activates a virtuous circle between Pharmacology (knowledge of remedies) and Pathology (knowledge of the mechanisms of disease): When a remedy "works", that means it is able to "target" the key causes and mechanisms of pathology and thus, at the same time, it can be considered as a probe that helps to clarify the pathology itself. The principles of Similarity (or the "Simile"), the effect of high dilutions and the systemic view of pathology are powerful "heuristic" stimuli for scientific research in medicine. On the other hand, the contribution of modern Science to the development of Homeopathy certainly should not be underestimated. The extraordinary development of the biomedicine can help to elucidate the mechanisms of action of homeopathic remedy down to the cellular and molecular details. Some recent examples of this evidence are from the physical, chemical, biological, immunological disciplines. These studies provide a solid foundation to the plausibility of the use of homeopathic drugs, thereby supporting their legality and their ethics. It remains open the question of how the understanding of the multiple cellular and

molecular mechanisms of a remedy can be useful in order to improve the practice of Homeopathy at the clinical level. To do this difficult task we will need to integrate knowledge from basic and simpler experimental models with “field” investigations – in humans, animals, plants - made by randomized clinical trials, comparative trials, prognostic factor research.

INTRODUCTION

Homeopathy, as all medical disciplines, contains features of Art and of Science. As in any medical approach, "artistic" components are related to practice, skill, knowledge, personal experience, intuition, and sometime luck. Components of "scientific" nature concern quantitative and rigorous evaluation of efficacy and, mostly, theories of the action mechanisms. Both are necessary. It is not always easy to distinguish these two dimensions of medical practice.

Not all the aspects of Homeopathy can be exploited scientifically. The medicine is not only Science but also "art", there is not only therapy but also "care" medicine of the person. This very important aspect deserves a whole discussion. Homeopathy is a complex method of diagnosis and of healing, which has various aspects dealing with peculiar traditional and philosophical background and other aspects dealing with the scientific and rational bases of medicine. These are exploited by rigorous scientific research, whose commitments may be divided in two main topics (see Figure 1): 1) clinical, veterinary and field research, trying to answer to the question: “does Homeopathy work?”, i.e. the problem of efficacy and effectiveness; 2) basic research, trying to answer to the question: “how does it work?”, i.e. the problem of the nature of the remedy and its putative action mechanisms. These great questions may be investigated utilizing different experimental models, made either of human subjects, of animals, of cells and of chemical solutions [1, 2].

Despite several progresses in the last twenty years, acceptance of Homeopathy into the mainstream medicine remains very difficult. A first difficulty is due to the structure of contemporary scientific thought inherited from positivism, characterized by three beliefs: a) everything is material and body is a machine (mechanism), b) everything object can be reduced to its single parts (reductionism), c) direct linear relations cause-effect and dose-effect. Clearly, this intellectual position, which is dominant in the so called “conventional medical system” makes difficult to appreciate the very nature of Homeopathy which is an approach based on different standpoints expressed since the time of Hahnemann.

A second problem is that there are different “opinions” on the evidence of clinical efficacy, about what is the grade of evidence, which is the sufficient evidence. The detractors of Homeopathy believe that the evidence is “lacking” and that the quality of evidence is “not sufficient”. Of course

this is an “opinion”, based on mostly subjective parameters and on “consensus” of self-defined experts. And “experts” are people who are - again - opinion leaders in a given subgroup of doctors or scientists. In other words, expertise is a concept strictly linked to a given paradigm and to its power of self-imposing in a given society and historic times.

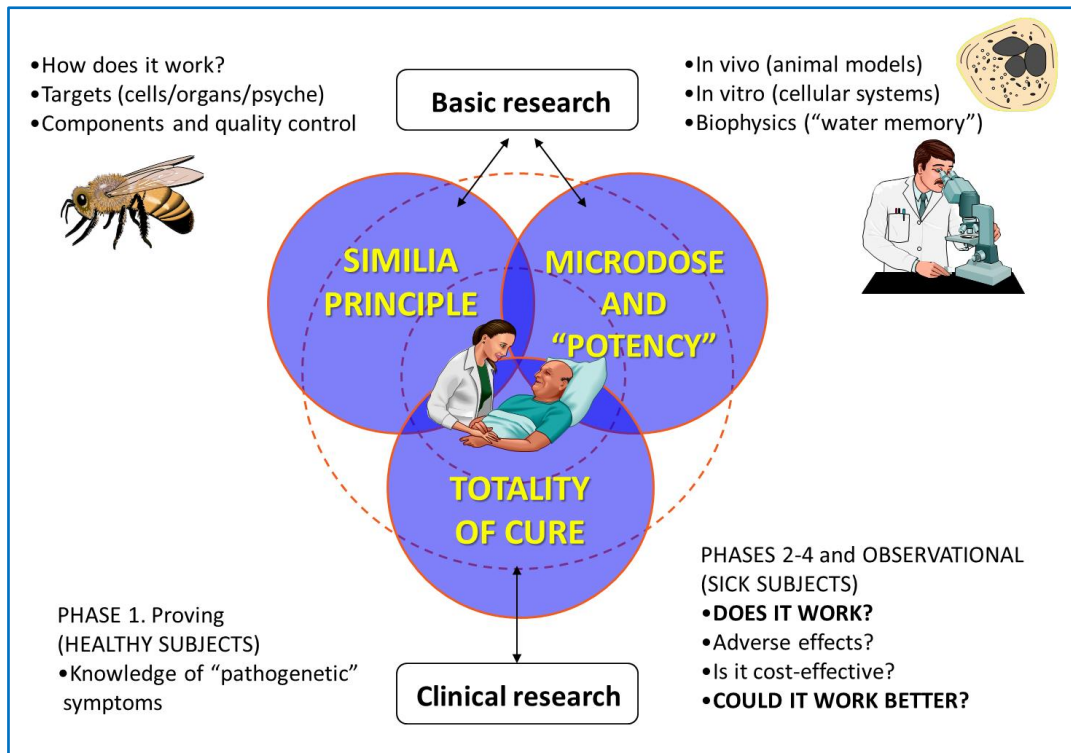


Figure 1. Objects of the scientific research in Homeopathy

Related with this discrepancy of opinions is the problem of suitable methods to prove Homeopathy. As is well known, the so called Evidence-Based-Medicine trusts only in rigorous double-blind clinical trials and on meta-analyses, but interrogations have been raised if this method may alter the normal clinical setting of homeopathic cure, particularly in chronic cases. Moreover, the criteria of evidence are often based on parameters that do not comply with the clinical approach which is typical of homeopathic approach. Recently it has been argued by bioethicists that we need a more sophisticated approach to evidence in medicine, recognizing that “*what constitutes evidence can be defined and measured in different ways by different people or groups and that judgements about competing epistemes are ultimately about the value of particular data or outcomes*” [3]

Finally, there are different opinions on the “plausibility” of Homeopathy concerning its action mechanisms that are claimed as in contrast with current pharmacological theories. In this case, the detractors of Homeopathy maintain that the theories are incompatible with current scientific

knowledge. This is a serious objection, but it can be shown that is wrong and misleading and we will see why.

In this presentation we will consider especially on the latter point, trying to clarify how Homeopathic claims are in the same line of recent Science innovations. But it interesting to start expressing some quick idea concerning the first point, the philosophical basis of medicine and Science.

What is “Science”? What is “scientific”?

What is classical Homeopathy is pretty clear, while paradoxically in the Western world there are still considerable misunderstandings about the concept of Science. From this misconception often stem accusations of a lack of scientific basis, turned to this bicentennial medicine.

Science is not the research of “truth”, nor is the sure and only trustable source of knowledge. Science is the concerted human effort to describe and understand some features of the nature, through observation of natural phenomena, followed by construction of theories that can be verified/falsified through experimentation. This is an unceasing dynamic process of trial and error. As maintained by Max Born (1882-1970), Nobel Prize-winning physicist, *“There is no philosophical high-road in Science, with epistemological signposts. No, we are in a jungle and find our way by trial and error, building our roads behind us as we proceed.”* It is not a tool for certainty, but a manner to reduce uncertainty on the natural reality, or even to estimate it in terms of probability (statistics). Science is based on the continuous questioning of current knowledge on the basis of new observations and more and more advanced hypotheses. Sometimes someone destroys the previous theories, sometimes theories are strengthened, but we can’t say a priori and we can’t say forever. No true scientist has the definite truth in his pockets.

Sir Karl Raimund Popper (1902-1994) was an Austrian-British philosopher and professor. He is generally regarded as one of the greatest philosophers of Science of the 20th century. He wrote: *“We must not look upon Science as a “body of knowledge”, but rather as a system of hypotheses, or as a system of guesses or anticipations that in principle cannot be justified, but with which we work as long as they stand up to tests. . .”* [4] In conclusion, a theory should be considered scientific if, and only if, it provides good hypotheses to be tested and so proved as true or false.

Hahnemann was highly cultured and curious man and fed the Science of his time, thorough knowledge of chemistry and botany, the experiment on humans, the criticism of current knowledge. Perhaps the latter "transgressive" attitude, that has created so much trouble in life, is what characterizes best, in Popper's sense, the mentality of a scientist.

Scientific language is mainly quantitative (numbers) and his method is the experiment. Science has no dogma or constituted authorities. Science is for all, universal, although its technological applications can undoubtedly be used by rich or powerful groups.

Homeopathy as a Science

Contrary to what is gratuitously believed, most of the traditional concepts proposed by Homeopathy (the principle of "Similarity", drug experimentation on healthy people, the individualization of prescription, the use of very low doses of medicines) are germane to scientific criteria [5]. Homeopathy has always been (also) a Science. It was the first example of systematic testing of medicines on the healthy people. This happened at least one hundred years before the introduction of the studies in Phase 1 of the modern pharmacology. Only one example: pharmacologic properties of nitroglycerin were experienced and described by homeopaths in 1849, three decades before the allopathic one [6]. Early attempts to investigate homeopathy utilizing the tools of modern medical science were carried out especially in Germany and United States in the 19th century and are carefully described in a seminal book dated 1936 by Linn John Boyd, Professor of Medicine at the New York Homeopathic Medical College [7]. Unfortunately, those efforts were mostly ignored or dismissed by both "orthodox" homeopaths and academia.

In any case, the major and undisputable contribution of Hahnemann and his followers to Science are the new "unconventional" and highly inspiring hypotheses: The "Simile" and the "Minimum dose". For this very reason, Homeopathy is a Science. Hahnemann expressed the pharmacological bases of the major principle of Homeopathy in these terms: *"The majority of substances have more than one action; the first is a direct action, which gradually changes into the second, which I call its indirect secondary action. The second is generally the opposite of the first"* [8]. This principle can actually be verified or falsified, so is the object of scientific investigation.

The other more controversial principle is that of dilution: *"A medicine whose selection has been accurately homoeopathic must be all the more salutary the more its dose is reduced to the degree of minuteness appropriate for a gentle remedial effect..."* (Organon par. 277) Also this fundamental observation can be checked experimentally in a number of systems: today we call this phenomenon "non-linearity" or "hormesis" and we know its applications in immunology and neurobiology. To be precise, we also know that this is not a "law" that applies always, but is a principle that applies often and in several experimental conditions, when the target system is endowed with proper sensitivity and responsiveness.

Looking at the history of medicine without prejudicial opinions, these two principles can be regarded as two major working hypotheses. So they are the object of scientific investigation. They can be formulated in another modern language:

- a) The same substance or similar substances can have opposite (inverse) effects in different conditions as different doses of drug or as different sensitivity of the target system
- b) Pharmacological power of the original substance is retained (or even enhanced?) in serial dilutions with succussion, in non-linear way.

These concepts are the object of hundreds of studies published in major scientific literature, concerning either clinical evidence and basic research. The evidence that the homeopathic principles are working is very strong. Of course, when we translate these hypotheses into experimental work, not all evidence was positive but this is normal in every field of Science and especially in Medicine. In any case, the science of Homeopathy is growing, especially in the last twenty years [9], and a number of fields and disciplines are involved (see Figure 2).

CLARIFY

The controversy surrounding homeopathic treatments stems in part from the seeming lack of a plausible mechanism for the purported therapeutic effects of ultra-low dose or high dilution remedies[10, 11]. In fact, the scientific validity of a therapeutic method does not depend so much on its success rate as on the fact that the clinical results should be consistent with a pathophysiological, biochemical, and pharmacological theory or rationale. However, it must point out that in Science the "plausibility" is not a good criterion to judge the reality of the phenomena, but only a criterion for assessing the adherence of a theory to the dominant thought. A theory may be wrong even if it is plausible, while a phenomenon can be real even if it is not plausible. The history of Science, since the days of Copernicus and Galileo Galilei shows that theories must fit the facts, and not vice versa.

Homeopathy is a living paradox for pharmacology and toxicology, but also a powerful stimulus to research, if the pharmacologist has an open mind to what is new and challenging. That a toxic substance acts better and more positively in low doses or high dilutions, or that a substance acts in the opposite way on the sick compared to the healthy, is suggested both by homeopaths and by several laboratory studies from the late nineteenth century. Today, these experiences are rediscovered following the models of hormesis [12-15] and paradoxical pharmacology [16-18].

Homeopathy has always gone in search of the "explanation" of his claims, though often in vain. This explanation is not in the philosophy, but in biology, toxicology, immunology, physics and chemistry (Figure 2). Current research in laboratory animals, plants, cell models and biophysics

is building this rationale platform, even if many aspects are still obscure or controversial (as in any new field of science).

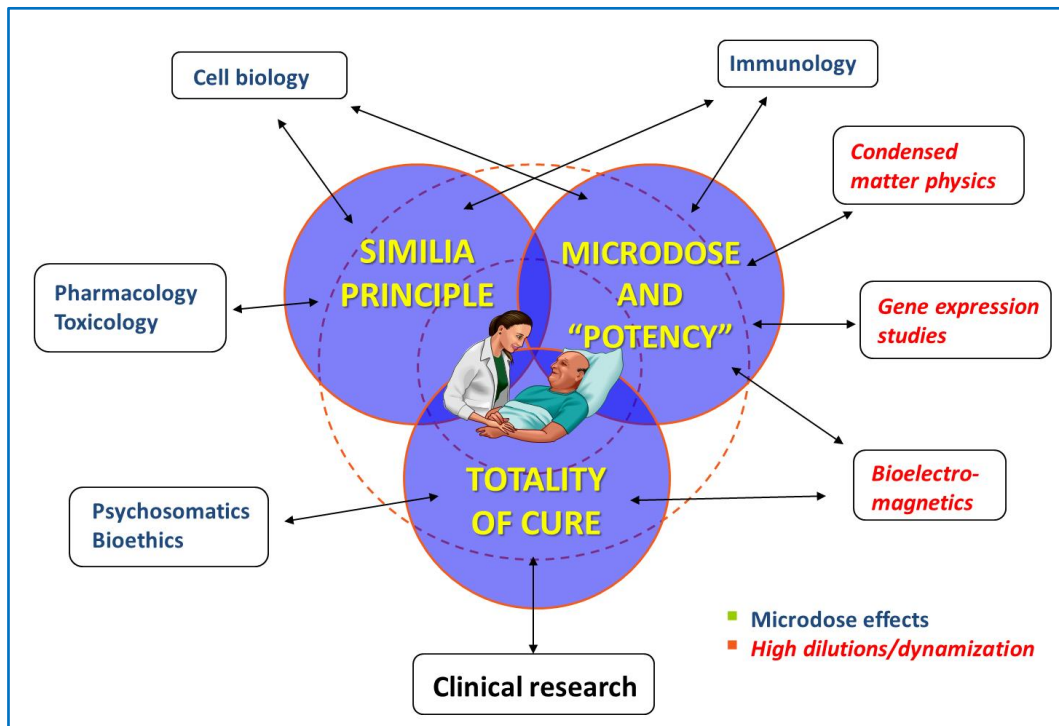


Figure 2. Science fields involved in the investigation of the three major homeopathic principles.

Today the progress of chemistry and physics (bioelectromagnetism, water structure, etc.) biology (receptors, genome) and pathology mainly connected with the theory of dynamic systems and of chaos, have given impetus to the incredible homeopathic theories. Homeopathy future depends also on the advances of "conventional" sciences (ugly word but you get the idea).

The Simile

The principle of Similarity holds that a “pathogenic” substance administered in small doses may correct the physiologic imbalance of a diseased organism presenting symptoms similar to those that the substance causes when tested in healthy people. This process is comparable to desensitization of allergic people with small doses of allergens administered by sublingual way[19-21]. Likewise β -blockers that decrease the contractility of the normal heart may improve it in the presence of heart failure [16, 17]. The antidepressants that may relieve melancholy in a depressed individual may cause it in a normal subject.

Regarding the inspiring role of the “Simile” as inversion of effects on pharmacology, the long-lasting studies from the group of the hematologist Christian Doutremepuich deserve citation. Starting from the observation that acetylsalicylic acid (Aspirin) at very ultra-low dosage reduced the experimental bleeding time in volunteers having previously ingested aspirin [22], they extensively investigated the effects of ultra-low doses of acetylsalicylic acid in a rat model of thrombus formation [23, 24]. Compared to placebo, the administration of acetylsalicylic acid at ultra-low doses induced an increase in number of emboli and in the duration of embolization. These findings are highly paradoxical because the “conventional” pharmacological effect of acetylsalicylic acid is to inhibit platelet aggregation and thrombus formation (see Figure 3). These effects are probably attributable to compensatory host response rather than direct effects of the drugs.

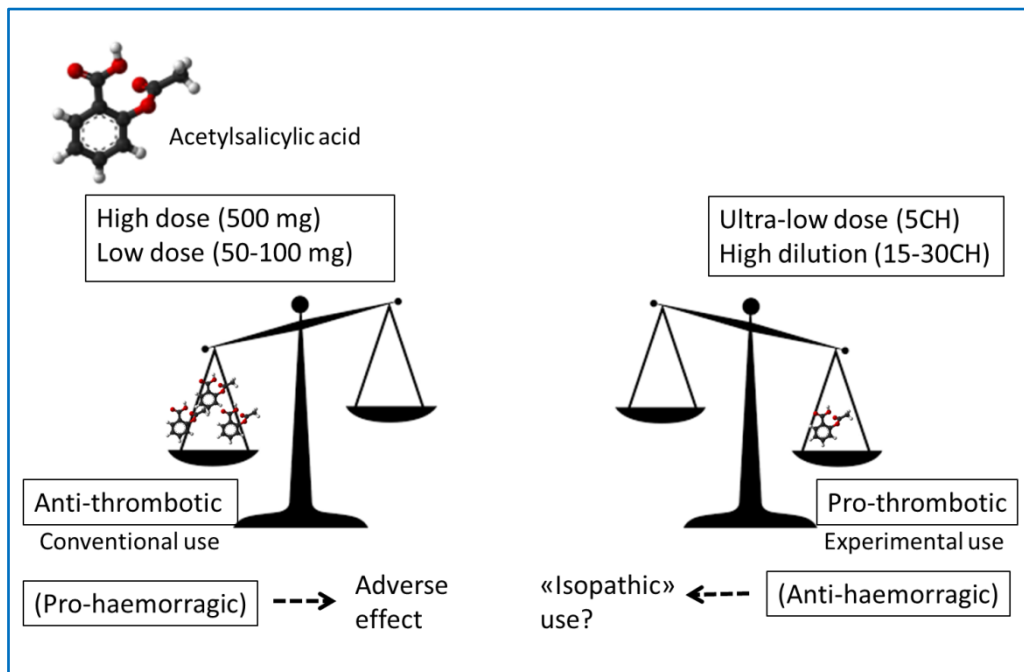


Figure 3. Inverse and paradoxical effects of Aspirin at conventional doses and at homeopathic doses according to the studies cited in the text.

From these studies the hypothesis emerged that ultra-low-dose aspirin could decrease the bleeding complications with possible beneficial effects [25]. On the basis of this strong evidence of the reality of the “Simile”, an intriguing hypothesis also emerges: unexpected paradoxical effects of drugs (frequently observed in clinics after withdrawal of a drug, also called rebound effect) could be due to “homeopathic” effects – in this case undesired – triggered by residual ultra-low doses of the same drug remaining in the blood following its clearance. If this is the case, the problem of inversion of effects could have wide implications in medicine.

An important point that should be clarified is that the homeopathic principle of Similarity is not based on the minimum dose nor on the dynamization only, but mostly on the different response of healthy versus sick organisms, according to which a substance that causes the symptoms of a disease in healthy people will cure similar symptoms in sick people. This was formulated in other words as *“when a substance is capable of inducing a series of symptoms in a healthy living system, low doses of the same substance can cure these symptoms under certain circumstances”* [26], or *“substances causing symptoms in healthy biological systems can be used to treat similar symptoms in diseased biological systems”* [27].

The Similarity principle is a "heuristic" principle, that is a way to find the right medicine, individualized for the patient seen as whole psychophysical and complex system[28, 29]. The aim is not so much to remove the symptoms as to provoke a healing response in the body itself: in Homeopathy (when it works) is not the drug that heals, is the organism itself which - thanks to "pathogenic" information received by the medicine – can find the road to recovery (change of dynamic attractor). This is the most valuable contribution to the clinic while it is not fully integrated and valued yet in modern medical thinking.

The dilution/dynamization

The dilution of natural compounds to be used in therapy was introduced after the Simile principle, in order to decrease or eliminate toxic effects of venoms or powerful herbal compounds. That a venom can be used as a drug upon suitable dilution (or vice-versa a drug can cause toxicity when used at high dosage) is a concept so well established in pharmacology (e.g. hormesis) that it appears to be undisputable. We also repeatedly showed its validity and application in our laboratory models in vitro [13, 30-35] and in vivo [36-39];

That a medicinal product may act in extremely low doses (those dilutions until the ninth Centesimal) is not surprising that no one who is minimally updated on biological and pharmacological literature. But the first to say so and prove it (albeit with rudimentary systems) were homeopaths.

Homeopathy "goads" physics and chemistry to look for the explanation in condensed matter physics and dissipative systems [1, 40-43]. The topic is so vast that is beyond the scope of this presentation. Multidisciplinary competences in water chemistry, physics of condensed matter, and systems biology are needed to appreciate theories of highly diluted homeopathic drugs. How could such small amounts of molecules act? The question of how these medicines may work concerns the identification of biological targets at various levels (cellular, molecular and systemic), the ways of

drug-receptor interactions, the complex mechanisms of signal transmission and amplification, including bioelectromagnetic interactions and chaos theory.

Even if the matter is undoubtedly complex, a few main points can be summarized as follows [2].

A) **Action at receptor level.** Action of ultra-low doses claims the existence of amplification mechanisms at some stage of the signal transmission chain, from signal-receptor interaction to the wide range of transduction pathways. Of course, the first target candidate of specific regulatory drugs are cell receptors and this is true also for homeopathic drugs, that do not “violate” any scientific knowledge but instead perform a specific action at the level of highest biological sensitivities. In a recent paper [44] we have shown how the action of extremely low doses of drugs is compatible with a modern view of receptor functions where these structures are not seen as in traditional “key-lock” models, but as dynamic and far-from equilibrium systems that can be modulated by allosteric interaction with ligands, electromagnetic waves and also water clusters.

At least three laboratory models have shown that the action of highly diluted compounds is inhibited by antagonists of receptors (Figure 4).

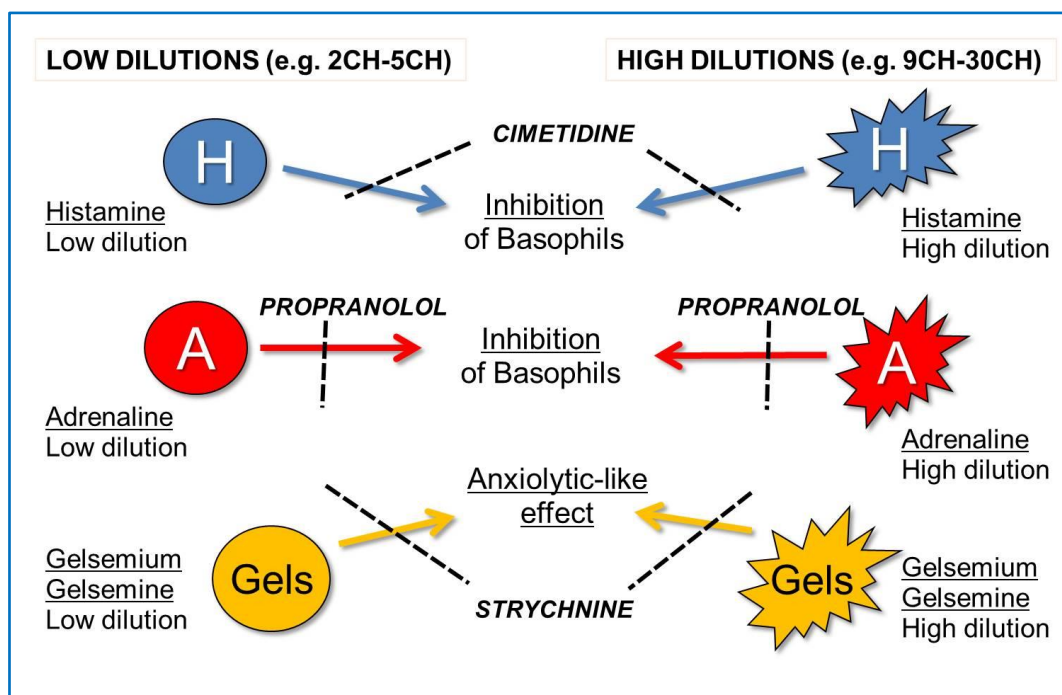


Figure 4. Receptor-mediated effects of compounds tested at low and high dilutions. Both kind of interactions are sensitive to the same receptor antagonists. Results from published studies of Ste-Laudy and Belon, [45], Mannaioni [46], Venard[47], Bellavite [48-50], groups.

Interestingly, the action of low dilutions/dynamizations seems in the same direction of action of high dilutions: in other words, the hormesis concept (inversion of the effect at different “doses”)

seems not applicable in the domain of homeopathic dilutions. Of course it is too early to draw definite conclusions on this important aspect of the homeopathic action mechanism.

B) Action at the gene expression. Recent studies conducted with modern molecular biology techniques including quantitative real-time PCR and microarrays have documented the ability of highly diluted compounds to modulate gene expression in human/animal cells and unicellular organisms (Table 1).

Test compound	Potencies	Cell type	Effect	REF.
<i>Carcinosinum</i>	MT, 30C, 200C	DLA cells	↑ specific gene expression (p53 pro-apoptotic)	(Sunila et al. 2009)
<i>Arsenicum alb.</i>	30C	Saccharomyces cerevisiae, E. coli	↑ Resistance to arsenicum toxicity ↓ ↑ expression of specific genes (apoptotic, stress response proteins)	(Das et al. 2011; De et al. 2012 of Khuda-B.group)
<i>Carcinosinum, Hydrastis, Ruta or Thuja</i>	200C	DLA cells	↑ Apoptosis , ↓ ↑ Gene expression (whole genome analysis)	(Preethi et al. 2012)
<i>Gelsemium s.</i>	2C, 3C, 5C, 9C, 30C	Human neurocytes SHSY5Y	7 genes ↑ 49 genes ↓ expression (whole genome analysis) ↓ gene expression (RT-Array, 2C)	(Marzotto et al. 2014; Olioso et al. 2014)
<i>Apis mellifica</i>	3C, 5C, 7C	Human prostate RWPE-1	↑ ↓ expression of different groups of genes (whole genome analysis)	(Bigagli et al. 2014)
<i>Rhus tox.</i>	30X	Primary cultured mouse chondrocytes	↑ specific gene expression (COX-2), ↓ specific gene expression (collagen II; de-differentiation role)	(Huh et al. 2013)
<i>Arsenicum alb.</i>	45X	Arsenic-intoxicated wheat seeds	↑ Germination ↓ Gene expression levels	(Marotti et al. 2014)
<i>Condurango</i>	30C	H460-non-small-cell lung cancer cells	↓ ↑ expression of specific genes (apoptotic), ↑ Apoptosis, oxidative stress, mitochondrial depolarization	(Sikdar et al. 2014)
<i>Arnica m.</i>	2C, 3C, 5C, 9C, 15C	THP-1	↓ expression of inflammatory genes ↑ expression chemokine genes	(Olioso et al. in preparation)

Table 1. Recent reports of the actions of homeopathic drugs on gene expression in laboratory models. References are cited in [44]

These findings support the hypothesis that homeopathic remedies could turn some important genes on or off, initiating a cascade of gene actions to correct the gene expression that has gone wrong and produced the disorder or disease. In this hypothesis the relevant target gene should be sensitive to specific and “similar” stimuli and exert a pleiotropic transcriptional regulation on a battery of genes with related functions. Our results[51, 52] prove the high sensitivity of the human neurocyte gene network to of *Gelsemium sempervirens* that modulates the expression of 56 genes involved in neuronal functions (G-protein coupled receptor signalling pathways, calcium homeostasis, inflammatory response and neuropeptide receptors).

Gene regulatory networks may be regarded as dynamically ‘critical’ systems where extreme sensitivity to initial conditions and small perturbations are known to occur. The discovery that in DNA minor grooves reside water clusters [53, 54], that appear to play a key role in stabilizing noncovalently binding of small molecules in the AT region, suggests that this site may be the target of subtle messages – direct from cell water and/or mediated by receptors and signal transduction - suitable to eventually regulate gene expression.


C) **Action on the immune system:** Evidence from laboratory, animal and clinical studies showed that the immune system, inflammation mechanisms and leukocytes are among the targets of homeopathic effects. We tested the effects of homeopathic compounds at various dilutions on free radical production by blood neutrophils and their adhesion to serum-coated plastic surfaces[55]. Free radicals were significantly inhibited by *Manganum phosphoricum* 6X and 8X and *Magnesium phosphoricum* 6X and 8X. *Phosphorus* presented statistically significant inhibitory effects, at a different extent in the course of the various experiments, even at very high dilutions (greater than 15X). In animal models *Silica* stimulates tissue healing and macrophage activation also at extremely low (homeopathic) doses. De Oliveira et al.[56] found that a complex homeopathic medication differentially expressed 147 genes in macrophages, involved in immune response, cytoprotection, enzymatic process, and receptors/ligands. High dilutions of histamine (up to 30c) are able of modulating the inflammation caused by high doses of histamine in rats[37]. Recently we have shown that *Arnica montana* modulates gene expression in human macrophages, especially those of cytokines like Interleukin-1 and CXC chemokines (Oliosio et al., manuscript in preparation)

D) **Bioelectromagnetic interactions.** There is some evidence that highly diluted solutions applied on the tongue trigger rapid electrophysiological responses in central nervous system[57]. In a further experimental trial, college students with a history of coffee-related insomnia took one bedtime dose of a homeopathic remedy (*Coffea cruda* or *Nux vomica* 30C) and those remedies significantly altered short-term nonlinear dynamic parameters of slow wave sleep[58, 59]. According to this argument, the highly diluted drug might be regarded as a complex solution endowed with structures (nanoparticles or nanobubbles or clusters) capable of communicating some pharmacological information, through a resonance process, to biological fluids and to critical cell systems such as macromolecules, alphahelices, filamentous structures, receptors, and DNA networks. This effect could be mediated by the participation of a dynamic intracellular water network which may be presumed to exist in living cells. Chaotic regimes have been found in a number of physiological systems, including heart and neural systems and this would result in enhanced susceptibility to extremely low energy inputs and to small changes of regulatory factors.

E) **The role of water in signal transmission and amplification.** Membrane proteins interact not only with signal molecules but also with water molecules and clusters, a phenomenon that leads to protein conformational change and transient proton-transfer. This leads to the hypothesis that biological effects of high dilutions can also be mediated by transmission of electromagnetic energy (and information) through water, using the ultra-fast and extremely efficient transfer of energy. The mechanism also works in so-called “water wires” that enable hopping of protons through transmembrane proteins such as bacteriorhodopsin that function as a proton pump. Such “supramolecular” organization of water in chains is similar to the proton “hopping” mechanism proposed by Grotthus, and may account for amplification of effects of drug molecules dissolved in water. An indirect confirmation that this may account for some activity of high dilutions is the increase of electrical conductivity of highly diluted/succussed solutions reported by Vittorio Elia and his group [60-62].

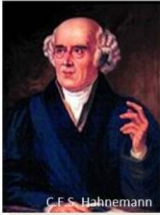
F) **Complexity science and homeopathy.** A more general model for the action of homeopathic remedies based on stimulation of the organism's biological stress response network has been proposed by Bell and coworkers.[63] This model is based on the idea that the resilience and recovery from disease is due to time-dependent sensitization of host responses with reverse pathology direction. In modern terms, the concept of “susceptibility” due to both genetic and environmental factors can be compared with the original concept of “miasm”, as an idea of chronic disorders which make humans vulnerable to diseases. Although the concept of miasm is questionable by modern pathology,[64, 65] an updated version of this view based on system biology has reformulated the multiform physiopathological changes - due to inheritable traits coupled with adaptation to environment - introducing the concept of “dynamic attractors” [28, 29, 66]. Hahnemann seemed to equate miasms to the different ways in which humans can be susceptible to various diseases; as scabies and venereal diseases were widespread in the 19th century, considering them - and their suppression with inappropriate medication of that time - as the source of vulnerabilities for other maladies is obvious.[67] Moreover, the same author pioneered the concept of disease prevention when he stated that continuous exposure to noxious environmental influences undermines health (*Organon*, par. 77) and that if a person can avoid noxious influences, he/she would lead a healthier life. Recent advances in the regulation of gene expression have confirmed that intuition showing that epigenetic changes may have transgenerational transmission.[68, 69]

As a summary, Figure 5 shows the state of the art concerning the scientific evidence in homeopathy



Science and homeopathy

The state of the art



Consolidated evidence

- The inverse effects of high vs low doses in several cellular, plant and animal models (classic hormesis, Arndt-Schulz, initial value of Wilder)
- The effects of different substances in high dilutions (beyond Avogadro) described in many different models and many different laboratories: no placebo
- Action on cell receptors and on gene expression

Major open questions

- The inter-experiment and inter-laboratory reproducibility, seasonal effects, etc.: an “intrinsic” feature of high dilutions (non-linearity, chaos theory)?
- The nature of the “physical” state of the highly diluted solutions
- The transfer of information from triturations to liquid and from liquid to granules

Figure 5. Consolidated evidence and major open question in the scientific approach to homeopathic issues.

DEFEND

Homeopathy has always provoked violent reactions and efforts to try to ban it are not new[7, 70]. Table 2 reports some old and recent representative attacks.

YEAR	PLACE	AUTHORS
1847	USA	American Medical Association
1858	UK	British Medical Association
1910	USA	Flexner Report
2005	Lancet	Shang et al.
2009	Lancet	S. Garattini
2010	UK House of Commons	Science and Technology Committee
2011	Bioethics Journal	K. Smith
2012-present	California	Class actions
2013 and 2015	Australia	NHMRC report
2015	USA	Food and Drug Administration (adverse effects ??)

Table 2. Circumstances of attacks to Homeopathy. Note that the recent FDA inquiry on the safety is not concluded and at present is open to both attacks and support of Homeopathy.

While two-centuries old debates are consigned to the history of medicine and are a proof of homeopathic resilience, recent assaults appear even more dangerous since they are prepared with seemingly scientific claims. The strategies are based on the general opinion that there is lack of scientific evidence in homeopathy, a concept that can be partially acknowledged, because the scientific publications are actually too scanty for a sector of crucial importance in medicine and in society. Figure 6 shows the number of papers cited in PubMed and dealing with homeopathic issues in the last 35 years (top). As a significant comparison, also the number of papers dealing with a single allopathic drug (aspirin) is shown.

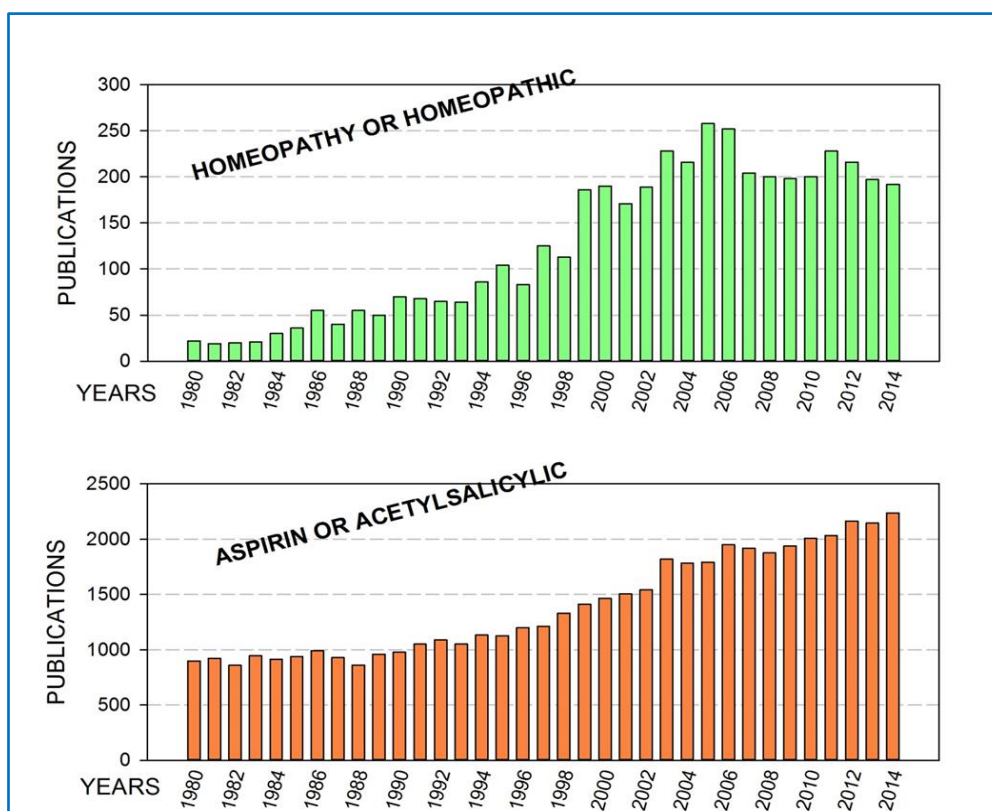


Figure 6. Number of papers retrieved from PubMed (August 10, 2015) using the keywords “Homeopathy OR Homeopathic” and “Aspirin OR Acetylsalicylic”.

This figure shows that only about 200 homeopathic papers are published every year, as compared with 2000 on a single allopathic drug. Considering that conventional medical publications are hundreds of thousand every year, the discrepancy between the relatively large use of homeopathic drugs by populations and the paucity of recognized scientific support is surprising. Another interesting note can be drawn from this figure: the publications in homeopathic issues raised from about 20 in 1980 to over 200 in 2005, with a ten-times outstanding growth (in the same

time period Aspirin studies grew only twice). One wonder if the abrupt stop after y. 2005 could be due, at least in part, to the “Lancet campaign” that proclaimed the “death of Homeopathy” and had a high impact on medical profession, regulation authorities and academia. Difficult to interpret this evident phenomenon as a simple coincidence.

That said, the controversies surrounding Homeopathy are rarely characterized by a genuine scientific debate. The strategies used by homeopathic opponents and “skeptics” are the following:

- Homeopathic principles are implausible, absurd, etc...
- To identify Homeopathy=placebo as a shameful thing, dismissing the fact that in every medical treatment a significant role is played by self-healing capacity of the body and that homeopathic method exploits this function as its very program, probably better than allopathic approach.
- To rely only on double-blind-placebo-controlled trials closing eyes to observational and equivalence (comparative) studies.
- To pick-up so called “best quality” studies, but with unclear or subjective “qualitometric” judgements, including a tricky confusion between “quality” and “sample size”; this was one of the errors of the 2005 Lancet paper (that paradoxically showed how homeopathic trials are of the same quality, if not better, than the respective allopathic trials).
- To conclude the literature reviews with subjective judgements of what is “sufficient evidence” to recommend homeopathic drugs,
- To subtly introduce a tricky confusion between “lack of evidence of efficacy” and “evidence of lack of efficacy”; this strategy was widely used to publicize the recent Australian report.
- To disregard that most “conventional” medical interventions (including some recommended or even compulsory vaccinations) lack sure evidence of efficacy.
- Recent insinuation: Homeopathy causes adverse effects.
- To try to block funding for research, the worst scientific attitude.

These efforts to destroy the credibility and even the very existence of a traditional medical discipline can be counteracted with better-quality information to public and by crucial political actions, but the best ways to defend Homeopathy are two: good treatment for patients and good Science for all. Science – the true Science - can be strongly instrumental for the defence of Homeopathy from repeated attacks of declared or obscure enemies. Science can confute the opinions that there is no credible scientific evidence to support homeopathic principles.

After much study and research in this field (our first review on Homeopathy was published in 1990 by “Annali dell’Istituto Superiore di Sanità” [71]), our research group has given several contributions that can confute the opinions, often repeated by opponents of Homeopathy, according to which there is no credible scientific evidence to support the “principle of Similarity”. As a matter

of fact, we and others have published a number of papers in the peer-reviewed scientific literature showing that the principle of Similarity is profoundly rooted in modern scientific knowledge and there is much evidence supporting it [5, 27, 29, 72-74, 74-76]. That the treatment with low doses of pathogenic substances may cure diseases that are caused by the same substances (when given to healthy people or in different doses) is a principle that has been more and more exploited by modern pharmacology and immunotherapy: clear examples are the treatment of allergy with very low doses of allergic compounds given sublingually[20, 21], the treatment of heart failure with beta-blockers (compounds that normally decrease heart strength)[77], and the therapeutic vaccination of cancer patients with components of cancer cells [78, 79]. So, these opinions regarding the homeopathic Simile are usually based on an inadequate knowledge of related scientific literature.

Another popular idea among professional “skeptics” is that the effects of homeopathic drugs can be explained entirely in terms of the placebo response. This opinion is apparently appealing for the “common sense”, but is contrary to scientific evidence for the following reasons:

(a) Most homeopathic products on the market cannot be defined as “placebos,” because they contain substantial amount of molecules of active principles (under the Avogadro’s limit) whose action can be explained using the conceptual and experimental tools of pharmacology and phytotherapeutics, including the high sensitivity of biological systems to low-dose and ultra-low dose regulation of receptors [80], enzymes [81], and even of gene expression [56];

(b) Highly diluted/succussed solutions (beyond Avogadro’s limit) have shown detectable pharmacologic activities in cell systems [45, 50, 52, 82, 83] and in laboratory animals [84-87] in rigorous experiments using sample controls made of solvent solution only.

(c) The clinical efficacy of homeopathic medicines has been proved in dozens of placebo-controlled studies reported by meta-analyses and systematic reviews [10, 88-92]. The existence of some negative reports [93] does not dismiss the proven effectiveness of homeopathic remedies, because occurrence of negative results is common in all fields of scientific medicine. It is also important to state that the famous review by Shang, et al. [11] actually was not so negative as publicized, and was wrongly interpreted due to methodological flaws. Moreover, it is important to state that double-blind, placebo-controlled clinical trials are not the only way to evaluate a complex medical system like Homeopathy [92, 94].

The so called “water memory” notion is often repeated as an insurmountable objection to homeopathic high dilutions. However, a number of theoretical and experimental approaches, including quantum physics, conductimetric and spectroscopic measurements, thermoluminescence, and model simulations investigated the peculiar features of diluted/succussed solutions. It is likely

that the molecules of the original active substance act as nucleation centres, amplifying the formation of supramolecular structures and imparting order to the solvent. Three major models for how this happens are currently being investigated: the water clusters or clathrates, the coherent domains postulated by quantum electrodynamics, and the formation of nanoparticles from the original solute plus solvent components. The concept of aqueous nanodomains has been introduced to explain high potentization in Homeopathy. It is argued that thanks to the shearing forces exerted by dynamization, the particle aggregates, by serving as templates inducing specific adsorption layer structures, transmit their structural information to the solvent, inducing conformational changes of molecular organization. The problem of the physicochemical nature of high dilutions is still far from clarified, but current evidence strongly support the notion that the structuring of water and its solutes at the nanoscale can play a key role [1].

Concerning the safety issues, there are several publications indicating that homeopathic drugs, when correctly prepared, are well tolerated and safe[95-98], certainly much safer than common allopathic drugs sold also over-the-counter (see for example Table 3)

			OUTCOMES			
	Total cases mentions	Treated In Health Care Facility	Minor	Moderate	Major	Death
Homeopathic	10,311	697	265	47	3	1
Acetaminophen	33,065	11,631	2,472	1,522	443	49
Ibuprofen	83,608	12,701	3,559	890	69	4

Table 3. Total number of mentions of possible adverse effects possibly attributable to homeopathic drugs and to two common allopathic drugs. Data are from the 2013 Annual Report of the American Association of Poison Control Centers [99]. Note that the category “Homeopathic” is not clearly defined in this report and possibly contains some cases belonging to herbal products.

That homeopathic drugs may have some rare adverse effects is not surprising because they are active drugs, not placebos. However, homeopathic adverse effects are of different nature from those

of conventional drugs, because low or ultra-low doses of natural substances have no toxic effects on biological systems. Homeopathic drugs may have some adverse effects when wrongly given to some hypersensitive patients. Moreover, in some (rare) cases the homeopathic drugs can induce some disturbing symptoms as the consequence of the stimulation of healing process (“homeopathic aggravation”), a phenomenon that is well known and can be recognized and controlled.

The possible occurrence of some slight disturbing reactions is not a sufficient reason to make limitations to those highly safe products. A website collecting a series of FDA-reports on adverse effects of all medicaments (<http://factmed.com>) show that adverse effects by homeopathic drugs are extremely rare as compared to conventional drugs. For example, in this list the reports of any possibly side effect of paracetamol are 15,006; FDA reports of any possibly side effect of homeopathic drugs are a few dozen (accessed the 11 June 2015). So, the study of possible applications of homeopathy (not only in human medicine but also in veterinary and agriculture) is ethically worthwhile and there are no safety reasons to restrict the freedom of cure with homeopathic products, provided that they are well manufactured and proper information is given to public. In any case it is essential to set up an efficient system of surveillance for potential adverse effects and to include this issue in prospective research, to better document this important problem.

IMPROVE

Homeopathic science has not the only role of allowing theoretical advancements, but also of a great contribution to the possible improvement of medical practice, of medical assistance to sick people in this era. This is because conventional medicine has not resolved all the problems generated by modern diseases, instead, modern medicine has a great responsibility in the iatrogenic burden of modern pathology.

Together with the unprecedented increase in scientific and technical knowledge of recent decades, there has been an increase in the prevalence of complex conditions, characterized by plurimorbidity, and associated with the aging of the population. This calls for an individualized treatment approach, something that modern medicine may be ill equipped and ill prepared to do.

Randomized clinical trials of medical treatment are essential to provide evidence of the efficacy or lack thereof of a specific treatment in a given population of subjects united by a common diagnosis. But the results of these trials may not pertain to the complex clinical situation of the individual patient. Currently, the majority of diseases are multifactorial processes that may not be manageable with a single intervention but require a multifaceted approach. Complex diseases, such as diabetes, schizophrenia, cancer, atherosclerosis, may involve hundreds of genomic variants that interact with one another and with environmental factors. This very complexity shows the

inadequacy of a reductionist approach, aiming at discovering and correcting one or few molecular defects using targeted drugs.

Chronic and degenerative diseases are both an effect and a cause of increased health care cost, which by itself may limit access to care especially in poorest countries. In addition to a more cost-effective utilization of current medical resources, the solutions may include a novel anthropological attitude of medicine, where treatment is individualized and each patient is allowed to choose the form of treatment that appears more valuable in the particular situation. Alternative and complementary medicine may be part of the solution [100] when critically examined and adopted in accordance with the criteria of informed freedom of therapy and evidence-based medicine.

The crisis of Western medicine, inadequate to the challenges of chronic diseases, and the failure of the technological myth are taking us to a new era, the current one, which is characterized by an epistemology characterized by the discovery of the complexity. This change, which may coincide with the change of the century and the end of the project "genome", opens the way to greater understanding of the approach based on the Simile and low doses. From this point of view, Homeopathy is part of that great tradition emerging biomedical Science that is called "systems biology".

There is no space in this context to analyse all the possible ways of collaboration between scientists and homeopaths, we deal only with the role of statistics and systematic collection of homeopathic cases. Statistical science can give an outstanding contribution to improve homeopathic therapy in various ways. As universally recognized, there is need of more research done with rigorous methods, that respect the peculiar features of homeopathic care. Randomized trials with high internal validity are only one of the possible approaches. Here we give mention particularly of the clinical verification of homeopathic symptoms – also called prognostic factor research - in the perspective offered by Bayesian approaches.

In this field, the need of a larger scientific research is recognized, since most of the knowledge accumulated in two centuries can and should be updated using the most modern methodologies. Often, the homeopathic database - in particular, the one collecting the symptoms used for the prescription of the different remedies - has been implemented by the experience in a few similar cases. However, this could generate mistakes and uncertainty in prescription, if not sustained and confirmed by an adequate number of cases and by statistical analysis. In Homeopathy, people with the same diagnosis, if reporting different homeopathic symptoms, can require different remedies. For this reason, it is necessary to verify the association between symptoms and remedies with statistical and reproducible analysis.

Consequently, it is necessary to collect data about the administered remedies and their effectiveness in an extended population, analysed systematically and with adequate protocols. Experts have already proposed methods based on bayesian logic, useful for this aim: with likelihood ratio (LR) method, the repertory will gradually change as more symptoms are assessed.[101, 102]. The essence of Bayes theorem is that experience tells us that a specific symptom has a higher prevalence in the population with a specific diagnosis or a curative effect from a specific medicine than in the remainder of the population. The higher this difference the greater the increase of the probability of the diagnosis or the curative effect. The magnitude of this difference is expressed in the homeopathic repertories with typeface, like *Italic* or **bold**. There is one problem, though: typeface in the repertory refers to absolute occurrence of a symptom (often reported by approximate estimates) - not to relative occurrence or prevalence as Bayes theorem requires[103].

Like a diagnosis, the probability that a homeopathic medicine will work (prognosis) increases if the patient has a specific symptom with high LR, i.e. indicating this medicine. Adding other symptoms indicating the same medicine stepwise increases the chance that the medicine will work. Figure 7 shows a scheme of how the LR is calculated for two different symptoms in two different remedies, provided that the frequencies of occurrence of those symptoms are known in the observed population.

Several experiences have been already published on this subject [104-107], but they have not found a general application, so there is need of new initiatives to build wide databases. In collaboration with Verona Homeopathic Medicine School and in agreement with FIAMO we are going to start a new protocol set as an observational pilot study, conducted on patients which ask for an homeopathic treatment. It follows LMHI (Liga Medicorum Homoeopathica Internationalis) guidelines for “Clinical Verification of Homeopathic Symptoms” published in 2013. The main purpose of the study is to collect systematically and prospectively the clinical data, obtained from the practice of a wide group of qualified homeopathic practitioners. It will be possible to conduct analysis about: (a) the most treated conditions, (b) the symptoms lamented by patients, (c) the most prescribed remedies, (d) the judgement about the effects of the treatment, (e) the LR of most frequent symptoms of most frequent remedies (this latter outcome largely depends on the number of cases that will be included in the study). Details of the protocol will be soon made available on “Il medico Omeopata” Journal, first to Italian homeopaths for a pilot study[108].

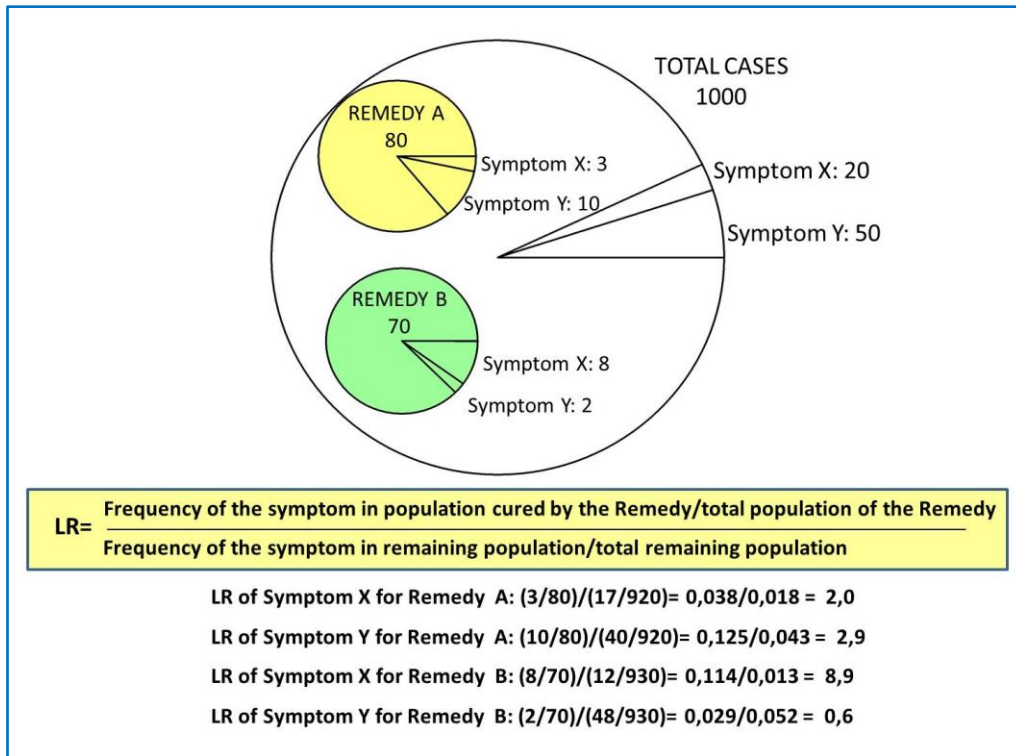


Figure 7. Example of the calculation of Likelihood Ratio for two symptoms in a population of cases treated with homeopathy. “Remedy A” and “Remedy B” indicate the subpopulations of people successfully cured by A and B respectively.

Acknowledgements

The laboratory studies by our group are supported by Italian Research Ministry and by grants of Boiron Laboratoires (Lyon) to the Verona University Department. The Authors have no conflicts of interest.

References

- [1] P.Bellavite, M.Marzotto, D.Oliosio, E.Moratti, A.Conforti, *Homeopathy* **2014**, *103*, 4.
- [2] P.Bellavite, M.Marzotto, D.Oliosio, E.Moratti, A.Conforti, *Homeopathy* **2014**, *103*, 22.
- [3] D.Levy, B.Gadd, I.Kerridge, P.A.Komesaroff, *J. Bioeth. Inq.* **2015**, *12*, 203.
- [4] K.R.Popper, *The Logic of Scientific Discovery*, Taylor and Francis e-Library, **2005**.
- [5] P.Bellavite, R.Ortolani, F.Pontarollo, G.Pitari, A.Conforti, *Evid. Based. Complement Alternat. Med* **2007**, *4*, 149.
- [6] W.B.Fye, *J. Hist Med. Allied Sci.* **1990**, *45*, 317.
- [7] L.J.Boyd, *A Study of the Simile in Medicine (edizione italiana a cura di P. Bellavite: Il Simile in Medicina. Medicina Ippocratica, omeopatia e scienza, Ed. Cortina, Verona, 2001)*, Boericke and Tafel, Philadelphia, **1936**.
- [8] C.F.S.Hahnemann, *Hufeland's Journal* **1796**, *2*, 391.
- [9] L.Betti, G.Trebbi, D.Oliosio, M.Marzotto, P.Bellavite, *Homeopathy.* **2013**, *102*, 151.
- [10] J.Kleijnen, P.Knipschild, G.ter Riet, *BMJ* **1991**, *302*, 316.
- [11] A.Shang, K.Huwiler-Müntener, L.Nartey, P.Jüni, S.Dörig, J.A.C.Sterne, D.Pewsner, M.Egger, *Lancet* **2005**, *366*, 726.

- [12] S.Bernardini, A.Dei, *Toxicol. Appl. Pharmacol.* **2006**, 211, 84.
- [13] P.Bellavite, S.Chirumbolo, M.Marzotto, *Hum. Exp. Toxicol. (BELLE Newsl.)* **2010**, 16, 11.
- [14] E.J.Calabrese, W.B.Jonas, *Hum. Exp Toxicol.* **2010**, 29, 531.
- [15] E.J.Calabrese, *Homeopathy* **2015**, 104, 90.
- [16] R.A.Bond, *Trends Pharmacol. Sci.* **2001**, 22, 273.
- [17] M.Z.Teixeira, *Homeopathy* **2005**, 94, 265.
- [18] A.J.Yun, *Med Hypotheses* **2005**, 65, 815.
- [19] H.J.Malling, *Clin. Exp. Allergy* **1996**, 26, 1228.
- [20] M.G.Severino, G.Cortellini, P.Bonadonna, E.Francescato, I.Panzini, et al., *J Allergy Clin. Immunol.* **2008**, 122, 44.
- [21] G.W.Canonica, E.Compalati, F.Fumagalli, G.Passalacqua, *Immunol. Allergy Clin. North Am.* **2004**, 24, 685, vii.
- [22] C.Doutremepuich, O.De Seze, D.Le Roy, M.C.Lalanne, M.C.Anne, *Haemostasis* **1990**, 20, 99.
- [23] C.Doutremepuich, O.Aguejouf, D.Pintigny, M.N.Sertillanges, O.De Seze, *Thromb. Res.* **1994**, 76, 225.
- [24] O.Aguejouf, F.Eizayaga, V.Desplat, P.Belon, C.Doutremepuich, *Clin. Appl. Thromb. Hemost.* **2009**, 15, 523.
- [25] F.X.Eizayaga, O.Aguejouf, V.Desplat, C.Doutremepuich, *Thrombosis.* **2012**, 2012, 430460.
- [26] P.Bellavite, A.Conforti, V.Piasere, R.Ortolani, *eCAM* **2005**, 2, 441.
- [27] R.Van Wijk, F.A.Wiegant, *Front Biosci. (Elite. Ed)* **2011**, 3, 1128.
- [28] P.Bellavite, *Homeopathy* **2003**, 92, 203.
- [29] P.Bellavite, D.Olioso, M.Marzotto, E.Moratti, A.Conforti, *Complement Ther. Med* **2013**, 21, 750.
- [30] P.Bellavite, S.Chirumbolo, C.Santonastaso, D.Biasi, S.Lussignoli, G.Andrioli, in *Signals and Images* (Ed: M.Bastide), Kluwer Acad. Publ., Dordrecht, **1997**.
- [31] P.Bellavite, G.Andrioli, S.Lussignoli, A.Signorini, R.Ortolani, A.Conforti, *Med. Hypoth.* **1997**, 49, 203.
- [32] P.Bellavite, G.Lippi, A.Signorini, G.Andrioli, L.Bonazzi, I.Ferro, (Ed: C.Bornoroni), Editrice Compositori, Bologna, **1993**.
- [33] G.Andrioli, S.Lussignoli, S.Gaino, G.Benoni, P.Bellavite, *Inflammation* **1997**, 21, 519.
- [34] S.Chirumbolo, A.Conforti, R.Ortolani, A.Vella, M.Marzotto, P.Bellavite, *Int. Immunopharmacol.* **2010**, 10, 183.
- [35] S.Chirumbolo, M.Marzotto, A.Conforti, A.Vella, R.Ortolani, P.Bellavite, *Clin. Mol. Allergy* **2010**, 8, 13.
- [36] A.Conforti, S.Lussignoli, S.Bertani, R.Ortolani, G.Verlato, P.Bellavite, *Int. J. Immunopathol. Pharmacol.* **1995**, 8, 113.
- [37] A.Conforti, A.Signorini, P.Bellavite, in *Omeomed92* (Ed: C.Bornoroni), Editrice Compositori, Bologna, **1993**.
- [38] S.Bertani, S.Lussignoli, G.Andrioli, P.Bellavite, A.Conforti, *Br. Homeopath. J.* **1999**, 88, 101.
- [39] A.Conforti, S.Lussignoli, S.Bertani, G.Verlato, R.Ortolani, P.Bellavite, G.Andrighetto, *Eur. J. Pharmacol.* **1997**, 324, 241.
- [40] E.Del Giudice, G.Preparata, in *Fundamental Research in Ultrahigh Dilution and Homeopathy* (Eds: J.Schulte, C.Endler), Kluwer, Dordrecht, **1998**.
- [41] N.Marchettini, G.E.Del, V.Voeikov, E.Tiezzi, *J Theor. Biol.* **2010**, 265, 511.
- [42] L.Montagnier, J.Aissa, E.Del Giudice, C.Lavallee, A.Tedeschi, *Journal of Physics: Conference Series* **2011**, 306, doi:10.1088/1742-6596/306/1/012007.
- [43] V.Elia, E.Napoli, R.Germano, *Homeopathy.* **2007**, 96, 163.

- [44] P.Bellavite, A.Signorini, M.Marzotto, E.Moratti, C.Bonafini, D.Oliosio, *Homeopathy* **2015**, *104*, 139.
- [45] J.Sainte-Laudy, P.Belon, *Homeopathy* **2009**, *98*, 186.
- [46] P.F.Mannaioni, R.Mastroianni, D.Mastrangelo, *Med. Sci. Monit.* **2010**, *16*, BR227-BR232.
- [47] C.Venard, N.Boujedaini, A.G.Mensah-Nyagan, C.Patte-Mensah, *Evid. Based. Complement Alternat. Med* **2011**, doi: 10.1093/ecam/nep083, 407617.
- [48] P.Magnani, A.Conforti, E.Zanolin, M.Marzotto, P.Bellavite, *Psychopharmacology (Berl)* **2010**, *210*, 533.
- [49] D.Oliosio, M.Marzotto, E.Moratti, M.Brizzi, P.Bellavite, *J. Ethnopharmacol.* **2014**, *153*, 535.
- [50] M.Marzotto, D.Oliosio, M.Brizzi, P.Tononi, M.Cristofolletti, P.Bellavite, *BMC. Complement Altern. Med* **2014**, *14*, 104.
- [51] M.Marzotto, D.Oliosio, M.Brizzi, P.Tononi, M.Cristofolletti, P.Bellavite, *BMC. Complement Altern. Med* **2014**, *14*, 104.
- [52] D.Oliosio, M.Marzotto, E.Moratti, M.Brizzi, P.Bellavite, *J. Ethnopharmacol.* **2014**, *153*, 535.
- [53] C.A.Yinnon, T.A.Yinnon, *Mod. Phys. Lett. B* **2009**, *23*, 1959.
- [54] D.Wei, W.D.Wilson, S.Neidle, *J. Am. Chem. Soc.* **2013**, *135*, 1369.
- [55] S.Chirumbolo, A.Signorini, I.Bianchi, G.Lippi, P.Bellavite, *Br. Homeopath. J.* **1993**, *82*, 227.
- [56] C.C.de Oliveira, S.M.de Oliveira, V.M.Goes, C.M.Probst, M.A.Krieger, D.F.Buchi, *J Cell Biochem.* **2008**, *104*, 1364.
- [57] N.C.Sukul, A.Sukul, *High Dilution Effects: Physical and Biochemical Basis*, Kluwer, Dordrecht, **2003**.
- [58] I.R.Bell, A.Howerter, N.Jackson, M.Aickin, R.R.Bootzin, A.J.Brooks, *Homeopathy* **2012**, *101*, 182.
- [59] I.R.Bell, A.Howerter, N.Jackson, M.Aickin, C.M.Baldwin, R.R.Bootzin, *Sleep Med* **2011**, *12*, 505.
- [60] V.Elia, *Int J High Dilution Res* **2012**, *11*, 110.
- [61] V.Elia, L.A.Marrari, E.Napoli, *J. Thermal Anal. Calorim.* **2012**, *107*, 843.
- [62] V.Elia, G.Ausanio, F.Gentile, R.Germano, E.Napoli, M.Niccoli, *Homeopathy* **2014**, *103*, 44.
- [63] I.R.Bell, M.Koithan, *BMC. Complement Altern. Med.* **2012**, *12*, 191.
- [64] P.Bellavite, A.Pettigrew, *Homeopathy.* **2004**, *93*, 65.
- [65] M.Mathur, *Homeopathy* **2009**, *98*, 177.
- [66] P.Bellavite, A.Signorini, *The emerging science of homeopathy: complexity, biodynamics, and nanopharmacology*, North Atlantic, Berkeley (CA), **2002**.
- [67] R.Gulati, *Homeopathy* **2010**, *99*, 150.
- [68] L.Daxinger, E.Whitelaw, *Genome Res* **2010**, *20*, 1623.
- [69] D.Crews, R.Gillette, S.V.Scarpino, M.Manikkam, M.I.Savenkova, M.K.Skinner, *Proc. Natl. Acad. Sci. U. S. A* **2012**, *109*, 9143.
- [70] H.Coulter, *Divided Legacy, vol. III. The conflict between homoeopathy and the American Medical Association*, North Atlantic Books, Berkeley (CA), **1982**.
- [71] P.Bellavite, *Ann. Ist. Super. Sanita* **1990**, *26*, 179.
- [72] R.Van Wijk, F.A.C.Wiegant, *Br. Homeopath. J.* **1995**, *84*, 131.
- [73] F.A.C.Wiegant, R.Van Wijk, *Complem. Ther. Med.* **1996**, *4*, 90.
- [74] P.Bellavite, A.Signorini, in *Proceedings of the 51st L.M.H.I. International Congress Capri 2-6 october 1996*, **1996**.
- [75] P.Bellavite, S.Lussignoli, M.Semizzi, R.Ortolani, A.Signorini, *Brit. Hom. J.* **1997**, *86*, 73.
- [76] M.Z.Teixeira, *Br. Homeopath. J.* **1999**, *88*, 112.
- [77] S.W.Smith, M.Hauben, J.K.Aronson, *Drug Saf* **2012**, *35*, 173.

- [78] X.Chen, C.H.Chang, D.M.Goldenberg, *Expert. Rev. Vaccines*. **2009**, 8, 567.
- [79] A.Bertoletti, A.Gehring, *Expert. Rev. Gastroenterol. Hepatol*. **2009**, 3, 561.
- [80] J.Matsumoto, *Med. Hypotheses* **1995**, 45, 292.
- [81] J.Dittmann, G.Harisch, *J. Altern. Complement Med*. **1996**, 2, 279.
- [82] C.M.Witt, M.Bluth, H.Albrecht, T.E.Weisshuhn, S.Baumgartner, S.N.Willich, *Complement Ther. Med*. **2007**, 15, 128.
- [83] P.Endler, K.Thieves, C.Reich, P.Matthiessen, L.Bonamin, C.Scherr, S.Baumgartner, *Homeopathy*. **2010**, 99, 25.
- [84] P.Bellavite, P.Magnani, M.Marzotto, A.Conforti, *Homeopathy* **2009**, 98, 208.
- [85] P.Bellavite, A.Conforti, R.Ortolani, *Evid. Based. Complement Alternat. Med* **2006**, 3, 171.
- [86] L.V.Bonamin, P.C.Endler, *Homeopathy*. **2010**, 99, 37.
- [87] J.Clausen, W.R.Van, H.Albrecht, *Homeopathy* **2011**, 100, 288.
- [88] K.Linde, N.Clausius, G.Ramirez, D.Melchart, F.Eitel, L.V.Hedges, W.B.Jonas, *Lancet* **1997**, 350, 834.
- [89] M.Cucherat, M.C.Haugh, M.Gooch, J.P.Boissel, *Eur. J Clin. Pharmacol*. **2000**, 56, 27.
- [90] W.B.Jonas, T.J.Kaptchuk, K.Linde, "A critical overview of homeopathy", **2003**, Ch. 138.
- [91] R.T.Mathie, P.Fisher, *Br. J. Clin. Pharmacol*. **2007**, 64, 396.
- [92] P.Bellavite, M.Marzotto, S.Chirumbolo, A.Conforti, *Front Biosci. (Schol. Ed)* **2011**, 3, 1363.
- [93] E.Ernst, M.H.Pittler, *Arch. Surg*. **1998**, 133, 1187.
- [94] H.Walach, T.Falkenberg, V.Fonnebo, G.Lewith, W.B.Jonas, *BMC. Med Res. Methodol*. **2006**, 6, 29.
- [95] F.Dantas, H.Rampes, *Br. Homeopath. J* **2000**, 89 Suppl 1, S35-S38.
- [96] G.Bornhoft, U.Wolf, K.Ammon, M.Righetti, S.Maxion-Bergemann et al., *Forsch. Komplementarmed*. **2006**, 13 Suppl 2, 19.
- [97] P.Marchisio, S.Bianchini, C.Galeone, E.Baggi, E.Rossi et al., *Int. J. Immunopathol. Pharmacol*. **2011**, 24, 441.
- [98] A.Michalsen, B.Uehleke, R.Stange, *Regul. Toxicol. Pharmacol*. **2015**, 72, 179.
- [99] J.B.Mowry, D.A.Spyker, L.R.Cantilena, Jr., N.McMillan, M.Ford, *Clin. Toxicol. (Phila)* **2014**, 52, 1032.
- [100] M.Verhoef, M.Koithan, I.R.Bell, J.Ives, W.Jonas, *Forsch. Komplementmed*. **2012**, 19 Suppl 1, 3.
- [101] A.L.Rutten, C.F.Stolper, R.F.Lugten, R.W.Barthels, *Homeopathy* **2004**, 93, 120.
- [102] A.L.Rutten, C.F.Stolper, R.F.Lugten, R.W.Barthels, *Homeopathy*. **2006**, 95, 88.
- [103] C.F.Stolper, A.L.Rutten, R.F.Lugten, R.J.Barthels, *Homeopathy*. **2002**, 91, 230.
- [104] A.L.Rutten, C.F.Stolper, R.F.Lugten, R.W.Barthels, *Homeopathy*. **2008**, 97, 16.
- [105] A.L.Rutten, C.F.Stolper, R.F.Lugten, R.W.Barthels, *Homeopathy* **2009**, 98, 26.
- [106] M.Van Wassenhoven, *Homeopathy*. **2004**, 93, 71.
- [107] W.M.Van, *Homeopathy* **2013**, 102, 54.
- [108] P.Bellavite, B.Andreoli, C.M.Rezzani, F.Allegri, M.E.Zanolin, *Il Medico Omeopata*, October **2015**.