

## LETTER

## Bias and adverse effects of homeopathy: is scientific criticism in homeopathy a “mission impossible”?

To the Editor::

I read with a great interest the latest debate about homeopathy in this journal. Particularly, the paper by Posadzki et al. (1), elicited an animated discussion about the plausibility and reliability of homeopathy (2–5): in summary, the paper criticised the presumptive undisputable safety of homeopathic remedies, an issue that was addressed and reviewed just few years ago (6). The big hoax that homeopathy cannot bear adverse effects is one of the central dogmas of this odd medicine: actually, any presumptive therapy approach, since it includes a pharmacological action, may give rise to possible adverse effects. Homeopaths do not feel to care about this matter, they are used to misinterpret homeopathy-related side effects as a way by which recovery is running its course; furthermore, they are persuaded that adverse effects are a hallmark of only official medicine and pharmacology. As a matter of fact, the main concern of this issue lies in the disregard from homeopaths to any polite debate. In this contribution, I will try to provide some explanation of the strange way by which homeopaths participate in whatsoever is coming up from a scientific debate, by reporting episodes and examples where they dismiss its value with “only their own” prejudices.

I recently participated in this debate because I found many bias and mis-interpretations in using homeopathy to treat a very complex pathology such as anxiety. In anxiety models, potentially genotoxic and neurotoxic alkaloids from the genus *Gelsemium* are considered good therapeutics for anxiety, especially as homeopathic remedies. Most of the components in a homeopathic plant-derived mother tincture are poisonous or toxic compounds: therefore they potentially could elicit an adverse effect, when administered into an organism. The belief that homeopathic remedies, as high diluted substances, should not trigger any side effect is clearly a naïve point of view, since homeopaths should provide the readers with the contradictory evidence that homeopathy justifies remedies as fresh water, in few words. Moreover, the odd fashion by which homeopathy manages the fundamental rules of chemical stoichiometry, is another main concern. By indicating only an “obscure” dilution factor, without reporting the starting composition of the plant extract, the physical parameters of the different compounds, their viscosity, diffusion coefficient, mixing rates and water/lipid partition param-

eters of the different hydrophilic and hydrophobic compounds, in order to achieve a better overview of the plant extract behaviour in the aqueous environment during serial dilutions (7,8), homeopaths hinder an honest scientific peer reviewing, yet trusting the simple fact that working dilutions of homeopathy do not contain any trace of harmful substance. In the case of homeopathic *Gelsemium*, this means that possible anxiolytic or even depressant/sedative effects may be because of synergistic or antagonistic actions exerted by different decreasing concentrations of an alkaloid respect to another, which is present in the starting plant extract, or even by a sedation/depressant activity of ethanol used as solvent with water, being therefore the major component in a diluted preparation. This simple consideration should suggest that bias and misinterpretation about the presumptive effect and the absence of side effects of a homeopathic remedy, depend on a proper knowledge of the chemical composition and behaviour of the latter. Therefore, the misleading approach to possible fatal accidents sprouts from the performing of a certain type of *in vitro* research and methodological setting: there are people who are not inclined to discuss fairly about their research work. And yet homeopaths are going ahead on their ideological struggle.

Few years ago, the *European Journal of Internal Medicine* offered the opportunity to Mr C. Boiron to write an article (9) in the form of a response to a previous paper by Pandolfi, which Boiron considered offensive for homeopaths. Mr Boiron’s Letter was commendable, as it showed, by talking about his father and grandfather, how homeopathy belongs with full rights to the history of medicine, interpreted as the human concern for patients, illness and the search for a successful therapy. Curiously, I had in my hand a first proof of the Letter, and even the possibility to appreciate Prof. Boiron’s efforts to make people aware of the great opportunity homeopathy holds for medicine, at least according to his respectable opinion. Obviously, someone would object that the overture of his Letter, having reported an “un-scientific” rebuttal, might be interpreted as a “throwing down the gauntlet”, but we do not mind, anyway: we all acknowledge that this would make the debate much intriguing and appealing for the reader. Nevertheless, in his Letter, Prof. Boiron stated that the Author, to whom he was posting his response, *denigrates home-*

*opathy and its practitioners, and abusively generalising from the reports of just a few patients or physicians that he has come across!* (9). Yet this style, often endowed with taunting or animated debates, is an hallmark of most discussions about homeopathy and does not contribute to a polite peer reviewing and scientific fair play. Usually, a general outcry from homeopaths and *aficionados* follows any legitimate criticism raised on the scientific tenet of homeopathy and its reliability, often constructing a retort such as angry strikers or crowds of proletarians with their pitchforks on the road. Homeopaths hasten to answer with a collection of signatures and express indignation towards those practitioners and caregivers who consider homeopaths are not worth to be welcomed to official medicine; they raise the sacred banner of more than two centuries experience, millions of satisfied patients, astonishing recoveries and so forth. Yet, very little serious scientific reappraisals of these claims occurred. Homeopathy represents a main concern in medical debates, particularly because legitimate criticisms from the scientific community are rapidly booed by this cumbersome behaviour. However, when comments have been raised within the scientific arena (10,11), replies were not long in coming (12,13), at least apparently. For example, the effect of homeopathic *Gelsemium*, provided by Boiron Laboratories, Lyon, France, which co-funded this research (14), elicited an animated discussion about the presumptive efficacy of homeopathic *Gelsemium* in reducing anxiety in mice (14). Main addressed criticisms concerned bias such as the sedation interfering effect of ethanol (10,13,15), the behavioural tests used in the experimental setting (10,15), a *post hoc* discussed statistics (10,11,13), the interpretation of results (13,15) elicited neither any serious revision, nor a point-by-point reply to the addressed issues (16). On the contrary, a Commentary with criticisms about homeopathy in anxiety, just published by this Author in *Frontiers in Neurology* (13), was initially published in the online page of the journal, but then it was unaccountably withdrawn and rejected for an “oversight” a month later the assignment of a DOI number, with the following awkward explanation: *we apologize for this error, but we feel that your paper was accepted prematurely by the associate editor and have taken corrective action.* What did occur? This sudden withdrawal, without any apparent reason, should suggest for an

**Table 1** Homeopathic and herbal remedies used in anxiety

Plant source Provider/Productor	Dilutions used Working controls	Theoretical concentration* Experiment model	Reported effects	References
Gelsemium sempervirens mother tincture and dilutions Boiron Laboratories, Lyon, France*†	4cH, 5cH, 7cH, 9cH, 30cH Diazepam–Buspirone	Gelsemine $6.5 \times 10^{-4}$ M Mouse model	POSITIVE: 5cH, 9cH and 30 cH reduced anxiety in light/dark box test. Buspirone as the best control	(14)
Strychnos ignatii mother tincture and dilutions Boiron Laboratories, Lyon, France†	4cH, 5cH, 7cH, 9cH, 30cH Diazepam	Strychnine $4.9 \times 10^{-3}$ M Mouse model	POSITIVE: 4cH ( $4.9 \times 10^{-11}$ M strychnine) reduced anxiety in OFT, 9cH ( $4.9 \times 10^{-21}$ M strychnine) reduced anxiety in LDB	(23)
Gelsemium sempervirens mother tincture and dilutions Boiron Laboratories, Lyon, France *†	4cH, 5cH, 7cH, 9cH, 30cH Diazepam–Buspirone	Gelsemine $6.5 \times 10^{-4}$ M Mouse model	POSITIVE: pooled statistics of experiments performed in (14) and (26)	(17,23,24)
Gelsemine, koumine, gelsevirine, gelsenicine from Gelsemium elegans	Gelsemine, koumine and gelsevirine 0.2–10 mg/kg Diazepam, fluoxetine, strychnine	Alkaloids range: 0.4–10 mg/kg Mouse model	POSITIVE: Reduction of anxiety in behavioural tests	(25)
Homeopathic Gelsemium. Remedies from Boiron Laboratories, Lyon, France†	5cH, 15cH Benzodiazepines	Not measured Double-blind, single-centre, randomised and placebo-controlled study	NEGATIVE: No effect in preventing anticipatory anxiety	(26)
Gelsemium sempervirens mother tincture and dilutions Boiron Laboratories, Lyon, France*†	5cH, 7cH, 30cH Diazepam	Gelsemine $6.5 \times 10^{-4}$ M Mouse model	POSITIVE: 7cH and 30 cH reduced anxiety in open field test. Diazepam did not work	(27)
Gelsemium sempervirens mother tincture and dilutions Boiron Laboratories, Lyon, France *†	5cH, 9cH, 15cH	Gelsemine ranging from $5 \times 10^{-3}$ M to $5 \times 10^{-4}$ M <i>In vitro</i> assays	POSITIVE: 5cH and gelsemine affected $3\alpha,5\alpha$ -THP neo-synthesis in H-A and SC slices. Less 9cH. No 15cH	(28)

\*Dilutions home-made from mother tincture. †European Pharmacopeia (Monograph 01/2008:0672Ph.Eu). ‡In mother tincture HPLC/mass spectrometry. OFT, open field test; LDB, light/dark box test. Dilutions: bold dilutions are considered positive in the reported literature.

intervention on somebody's behalf, maybe the Author to which criticisms were previously raised. This is a very unusual way to meet a discussion, there is no denying it. Much of the research performed in anxiety models with homeopathic remedies have taken into account preparations from Boiron and most of the results were attributed to a positive interpretation (Table 1). Readers can realise that a major weakness reported in the table is the high level of positive results using remedies from the same funding sponsor, especially if compared with a low reproducibility of results and controls (Diazepam) in different experiments (11). Honestly, we do not know if a "new fascinating discovery" is just round the corner, at least according to some authors but, anyway, this must be widely discussed within the scientific community. Despite from this respectable point of view, a cumbersome behaviour performed by tripping someone in order to hush him, seems to characterise many interventions of homeopaths within the scientific community. For example, Luigi Cervo and Valter Torri from the Mario Negri Institute, Milan, attempted to reply to an article concerning homeopathy in anxiety models (14). Initially, the Journal declined

their submission; then, an Author from the discussed paper (14) ridiculed their legitimate attempt to give a response, by showing their rejected letter in a slide during an International Congress in Brazil, suggesting therefore an example of Mario Negri Institute failure in debating about the issue. The Editor-in-Chief of the Journal *Psychopharmacology*, Prof. Robbins, was informed by L. Cervo about this "trip", so a response was successively accepted and published (11).

Homeopathy fell into a mummery.

Sincerely, I am shocked about the creative fashion by which some colleagues tried to hush any licit right in raising comments and questions. When Cervo and Torri forwarded the valuable opinion that *In conclusion, when an experiment has low biological plausibility – as in the case of highly diluted products – it is important to be extremely critical in conducting and interpreting the results* (11) a cumbersome objection to Cervo occurred as: *We believe that critical thinking is always essential: not only when plausibility is low, but also when it is high as it may seem in some fields of conventional pharmacology. Otherwise, paradigms prevailing in medical thinking and even wrong theories endowed with apparently high plausi-*

*bility are likely to continue dominating without critical control* (17). Therefore, conventional pharmacology and medical thinking are endowed with wrong theories to be subjected to critical debating, according to the Author of Ref. (17). Certainly, I have to feel in full agreement with this Author about the usefulness of critical thinking, when I am thinking to the "scientific" tenet of high dilutions, as I strongly believe that particularly homeopathy, which asks for a plentiful recognised role within official medicine and pharmacology, must be subjected to critical thinking, as it has prevailing paradigms and odd theories. The Author of Ref. (18), while discussing the evidence reported on his paper in *Psychopharmacology* in 2010, stated: *we believe that it merits attention because it may represent a milestone in the two-centuries lasting—and often conflictual—relation between homeopathy and official pharmacology. Milestone? When did critical thinking end? I wondered. Actually, when most homeopaths are invited to any civil and polite match, prejudices appear to overwhelm any good debate. This fact does not allow the review of any reported evidence and rejection or confirmation of what it is forwarding to the readers as a true scientific*

novelty. If comments arise within the official (or dogmatic?) scientific literature homeopaths cry scandal, as official medicine has a prejudice against homeopathy (according to most of them) – when comments come from researchers with an expertise in the field (19), they interpreted criticisms as “personal attacks” and injury (20): *Considering the language and the concepts presented, it is difficult to escape the impression that this dissertation was a direct attack on our group and our research project and more over... are manifestly unfounded and/or represent offensive aggressions that do not reserve reply* (20). Offense, aggressions, defamation: the final cut of this raving strategy is represented by summons and venue (21), even against this writing Author.

Is there any truth? According to some author, homeopathy is not supported by clinical evidence and is not physically plausible (22): this consideration should oblige homeopaths to discussion, since they show to have “feet of clay” within the scientific community. I wrote several critical papers about this strange way of studying homeopathy and addressed many comments about the absence of point-by-point replies to important and fundamental issues in behavioural pharmacology when homeopathic remedies are investigated, but unfortunately I experienced a wild-goose chase. Although I spent some time of my scientific experience studying homeopathy, I must contract out from the regrettable intent of homeopaths to exacerbate, decline or turning private matters to any serious discussion raised by colleagues worldwide, probably because homeopaths have the purpose to hamper any good revision. Moreover, the absolute certainty without addressing any raised comment cannot be welcomed in science; even more so when criticisms compel a journal's Editor to make a note as follows: *Controversy is a manifestation of life, that is of the person... At the meantime, the Journal regrets publishing any expression that may be constructed as a personal attack and wishes to apologize to the individuals that might have taken offense from its printing. The journal welcomes controversy and disagreement, but does not condone any form of verbal assault and does not wish to become a venue for personal confrontation* (19,20). Will we perform next forthcoming investigations in court? I wonder.

Homeopaths still remember the cumbersome figure of Jacques Benveniste, who became, probably against his will, a symbol of a self-pitying attitude, the “whipping boy” of inexhaustible assaults against free-thinkers: actually, with the exception of very few col-

leagues, the awkward heredity he left is a community of people who use to show themselves as victims and are not inclined to a fair scientific debate including peer reviewing, criticisms and reappraisal. This would not surprise us if people may suffer from homeopathy or yet may die because of the assumption of diluted water instead of well recognised drugs.

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## Disclosure

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