Original Article

From pharmaceutical standardizing to clinical research: 20 years of experience with fifty-millesimal potencies

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ABSTRACT

Background: 20 years ago we began to standardize the procedures of preparation and use of fifty-millesimal dilutions (LM or Q) according to indications in the 6th edition of Hahnemann's *Organon*. Aim: to describe the main stages in standardization as well as our teaching and research experience on *Organon* 6th edition. Results: with the use of standardized LM dilutions we observed a lower incidence of homeopathic aggravation than with our earlier experience with non standardized preparations. *Organon.modus*, a clinical-pharmaceutical protocol derived from the standardization was adequate for the teaching of homeopathy at Faculty of Medicine of Jundiai (São Paulo), the first Brazilian medical school with a graduate course on homeopathy. A randomized double-blind trial comparing individualized homeopathic medicines prescribed in LM dilutions and fluoxetine showed the former not be inferior to the latter in the treatment of moderate-to-severe depression. Conclusion: protocol *Organon.modus* showed to be adequate to graduate-level teaching of homeopathy and efficient in a controlled clinical trials, favoring its use as common denominator between the art of healing and medical science.

Keywords: Homeopathy; LM (Q) dilutions; *Organon* 6th edition; clinical-pharmaceutical protocol; medical education; randomized double-blind clinical trial.

> *"... during the last four or five years, however, all these difficulties are wholly solved by my new altered but perfected method. The same carefully selected medicine may now be given daily and for months, if necessary in this way, namely, after the lower degree of potency has been used for one or two weeks in the treatment of chronic disease, advance is made in the same way to higher degrees, (beginning according to the new dynamization method, taught herewith with the use of the lowest degrees*)."
>
> Hahnemann, Organon, 6ª edição, § 246, footnote [1].

Introduction

Homeopathy was formulated by Samuel Hahnemann in 1796 grounded on the law of similarity and experimentation on healthy individuals [2]. Through experiments aiming to develop a homeopathic dosage system both effective and safe, Hahnemann discovered what he called "dynamization" or "potentiation". Although the first publication describing the preparation of a "dynamized" medicine is dated 1801 [3], he

would only introduce "dynamization" as a new physical or biophysical property of substances in 1827, initially adopting a centesimal scale – more particularly, dilution 30c – in his clinical studies [4]. During the following 15 years Hahnemann improved "dynamization" and the dosage system to finally reach what he regarded as his most perfected system to prepare and use homeopathic medicines: dilutions currently known as fifty-millesimal (LM, Q), employed in solution, in doses that can be frequently repeated provided they are further agitated through succussion. When a same medicine must be taken for a long time, dilutions must be gradually increased, starting from the lower degrees upwards (§ 246 [1]).

Hahnemann must have rated these innovations so important that he decided to write a new edition, the 6th, of his *Organon* to make them known at about 1842, when he was 87 years old. However, his passing away the following year and the hindrances put by his widow delayed publication by 80 years, during which the new method fell into oblivion [5]. So much, that e.g. in São Paulo, Brazil, even in 1989 only a few doctors regularly employed LM dilutions according to *Organon* 6th edition [6]. Among the multiplicity of schools and guidelines that constitute present-day homeopathy [7], our group chose to follow Hahnemann's indications, particularly as stated in *Organon* 6th edition. To do so, we first reviewed Hahnemann's principles and then designed a clinical-pharmaceutical protocol that guided our homeopathic practice for the last 20 years [8]. In what follows, we describe the main stages of this path.

Pharmacotechnics

By the end of the 1980s about 10 homeopathic pharmacies in the city of São Paulo had some medicines in LM dilutions, stocked in inert, irregular and yellowish globules. These medicines had been brought by physician George Washington Galvão Nogueira from Mexico, in dilutions 6 and 30 LM. Dilutions 7 and 31 LM could, then, began to be distributed among pharmacies at that time, that thus were able to dispense dilutions 8 and 32 LM. This practice continued for a while, until it became possible to prepare the following dilutions (9, 10, 11 and 33, 34, 35 and so on). For this reason, in the beginning doctors prescribed first 8 LM and then 32 LM, but later were able to pass from 8 to 9 and 10 LM, to continue with 32, 33, 34 LM. In order to meet that demand, some pharmacies began to permute intermediate dilutions from the available microglobules. By the same time, inert globules entered the Brazilian market from Argentina, but their shape was irregular and their weight was above the standards laid out by Hahnemann.

Pharmaceutical standardization of LM dilutions only began when our group became aware of the importance standardized globules have for the preparation of LM dilutions, as also does the control of the quality of the triturated substances. Standardization of globules demanded much toil, as we learned that slight variations in humidity, temperature, granulation of sugar, etc. can alter the size, weight and appearance of globules. We succeeded into having removed a derivate of cellulose – employed as aggregation agent by the manufacturer – so that globules came to be composed only of saccharose and starch, as prescribed by Hahnemann (§ 246 [1]). Figure 1 compares a sample of globules marketed in Brazil until the end of the 80s and a sample of our standard.

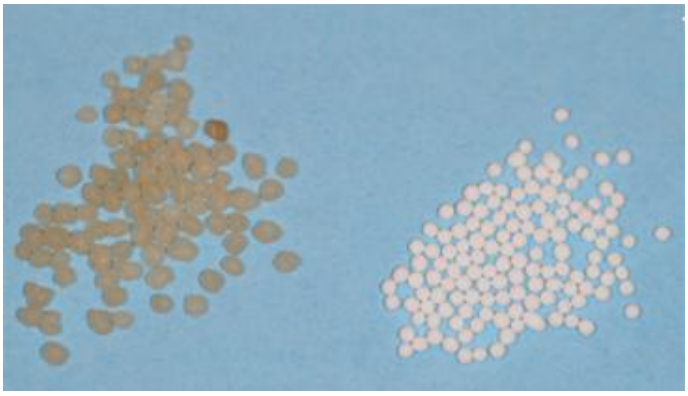

Figure 1: samples of globules used in the preparation of LM dilutions in Brazil at the end of the 80s (left) and our standardized globules (right).

Consequently, we began to replace our stock, initially with antipsoric mineral medicines, and the help of chemical engineer Antônio Sacco. However, we then realized that also other stages in the preparation of LM dilutions needed to be standardized: trituration had to be carried out powerfully, but not so strongly as to hinder the removal of lactose adhering to the mortar during the 3 – 4 minutes scraping [9]; manual succussions required strong, wide and rhythmic motions.

As there was no availability of fresh vegetal products for trituration, we bought them from English pharmacy Nelson, after a citation in Pathel [10]. In this way we received several remedies in pills of dilution 1 LM. Dissolution of these pills allowed pharmacist Ilza Márcia Anelli to prepare higher dilutions.

A few years later we met German researcher Peter Barthel, who at that time prepared triturations from fresh materials in their original habitat. Eventually, we accompanied Barthel in trips to several areas of Brazil to collect plants; this allowed us to take notice of the high quality of his preparations and to choose them for our work.

Clinical practice

Clinical use of LM dilutions is simple. A course of treatment begins by the lowest dilutions, taken by the patient once daily or in alternate days in chronic cases, or several times a day in acute conditions. Each dose is systematically preceded by succussion of the vial – for this reason, medicines are dispensed in solution. In chronic cases, a same dilution is kept as long as it elicits an improvement in the totality of symptoms of the patient provided no new significant symptom appears.

Dilutions must be periodically increased, one degree at a time, as abrupt changes favor the appearance of homeopathic aggravation (§ 276 [1]), here understood as a sign of excessive dose and that, thus, must be treated by increasing the interval between doses and/or increasing the dilution.

In order to make transportation and use of medicines simpler, also the vial was standardized to volume 30 ml, containing 20 ml of 30% hydro-alcoholic solution of 1 globule of the prescribed LM dilution. Figure 2 illustrates the practical advantage of the standardized vial.

Figura 2**:** standardized vial for LM dilutions.

Repeated and agitated LM potencies is the main therapeutic innovation in the 6th edition of the *Organon*, however there are further clinical principles that characterize Hahnemann's homeopathy and that must be taken into account when standardizing a therapeutic method, such as: selection of the guiding symptoms of the patient (characteristic symptoms); choice of medicine grounded on the most reliable sources, namely, pure *materia medica* sources.

According to Hahnemann's guidelines, from the totality of symptoms a patient shows, the characteristic ones must be identified, i.e. alterations in the state of health, both mental and physical, which are well-defined, intense and peculiar. Mental symptoms are important, as well as local characteristic signs (§ 192 [1]), since

the 6th edition of the *Organon* supplies no rule to establish a hierarchy among characteristic symptoms [11-14].

Once the characteristic symptoms are identified, we seek for the suitable remedy directly in works of pure materia medica (§ 148 [1]) in software Ex-Libris® (now Encyclopaedia Homeopathica - Archibel, Belgium) and in our own database; we do not carry out repertory analysis, instead we analyze the exact description of symptoms as recorded by provers.

Our first clinical experiences with the repeated use of LM dilutions was disappointing, as instead of the gentle healing described by Hahnemann, we observed intense homeopathic aggravations, that compelled us to prescribe successive dilutions of remedies in the attempt to minimize them. However, parallel to the replacement of non-standardized by standardized LM dilutions, aggravations became significantly less frequent or important.

A positive outcome of those early troubled times was that we learned that dilutions of medicines can be magisterially stabilized in alcohol by pharmacies. Thus, we began to prescribe remedies in the first, second, third, etc. dilution according to the sensitiveness of each individual patient. The standardized process of dilution [15] is represented in Figure 3 and described in Appendix 1.

Figura 3: magisterial dilution of a LM potency

As a rule, we begin treatments with dilution 2 LM in order to spare the stock of 1 LM of pharmacies and avoid further trituration. The patient is prescribed 1 drop in solution according to dosage systems described in Table 1.

Table 1: approximate standardization between number of weekly doses and time until change of dilution

Dose repetition	**Time to change of dilution**
1 or more doses/day (acute cases)	10 - 14 days
1 dose in alternated days	14 days
1 dose 3 times/week	4 weeks
1 dose 2 times/week	4 - 8 weeks

The lower the number of weekly doses, the longer the patient remains with a same dilution. The need to change a dilution is clinically identifiable: patients stop responding well to a given dilution after some time of use, or exhibit homeopathic aggravation immediately after a change of dilution.

From the work done and seeking for accurate definition, we called *Organon.modus* the clinical-pharmaceutical protocol emerging from the basic principles of Hahnemann's work, emphasizing the 6th edition of the *Organon*, and that was constantly improved along the last 20 years.

Teaching

Our experience with the method described in the 6th edition of the *Organon* is the result of collective, multidisciplinary and institutionalized work; it began at the outpatient clinic of a philanthropic institution – IAKAP, Guarulhos, São Paulo – which was then presented and discussed at the outpatient clinic of the State of São Paulo Homeopathic Association (APH). This was the cornerstone for the establishment of a graduate school of homeopathy associated with a conventional faculty of medicine. Teaching assistants were trained at the outpatient facility of a health-care center (Centro de Saúde Pinheiros, São Paulo) and in 2003 our graduate school in homeopathy opened at the Faculty of Medicine of Jundiai, São Paulo (PGHFMJ), which, thus, became the first specialization course in homeopathy at a Brazilian regular school of medicine and accredited by the State of São Paulo Council of Education as well as integrated in the National Public Health System (SUS).

In its short existence, PGHFMJ has already resulted in 2 MA dissertations. From the perspective of collective health, outcomes point to the feasibility of homeopathic training in regular universities; clinical teaching is particularly concentrated on public health [16]. A second evaluation focusing on health education showed that alumni had acquired skills for homeopathic clinical practice with positive gains in the emotional, intellectual and behavioral areas, higher degree of professional and personal satisfaction and improvement of the doctor-patient relationship [17].

Systematic application of theoretical learning at the teaching clinics allows for a harmonious and coherent learning, with positive impact on medical education, as illustrated by a former student:

"I'm able to check all the symptoms of a patient with a single remedy, very different from conventional therapeutic. This is what I could see at the teaching clinic, it's nothing I was just told about! It's awesome! Not what I could have merely read in a book or learned from some, but what I actually saw! It was a true practical experience. I saw my patients improve…" [18]

Clinical research

In spite of enthusiastic, the opinion of our former students has almost no weight as scientific evidence, and much less so in the age of evidence-based medicine [19]. To comply with its requirements, we tested the efficiency of the method described in the 6th edition of the *Organon* through a randomized controlled double-blind trial (RCT) that showed that individualized homeopathic remedies in LM dilutions were not inferior to fluoxetine in the treatment of acute depression [20]. Indeed, as it was expected, the incidence of side-effects was higher in the group treated with the conventional antidepressant. Figures 4 and 5 illustrate the results.

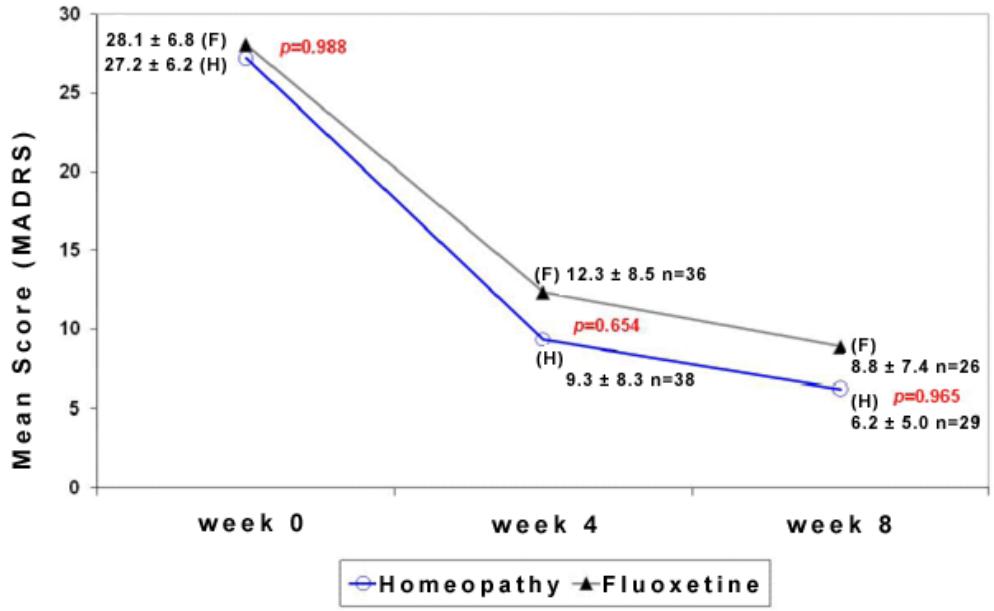

Figure 4: Average baseline MADRS (Montgomery-Åsberg Depression Rating Scale) scores at weeks 4 and 8 of randomized treatment with fluoxetine or individualized homeopathic remedies in LM dilution (ITT - intent-to-treat population).

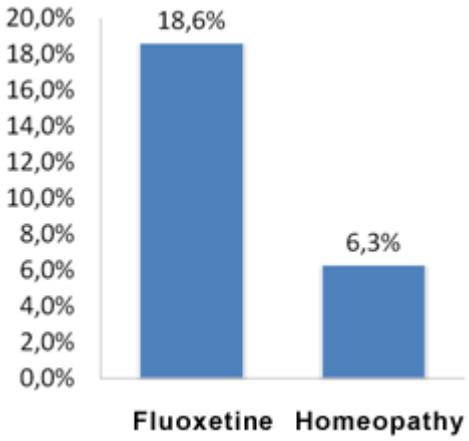

Figure 5: relative number of patients in whom treatment was interrupted due to side-effects in both study groups (p=0,071).

Discussion and conclusions

In this paper we presented our experience with the method described in the 6th edition of the *Organon*, from pharmaceutical standardization to clinical research.

The limiting factor was the lack of availability of standardized homeopathic remedies in LM dilutions; after such medicines became available, the clinical-pharmaceutical standardization of this method proved easy to apply into practice, which is an advantage for both treatment of patients and teaching of homeopathy.

A point to emphasize in the evaluation of our graduate program is that alumni do not trade conventional medicine for homeopathy, but add homeopathy as a further therapeutic resource, not as a mere technique of

prescription by similarity, but as a more humane approach to medicine, due to the requirement of individualization [18].

Our first RCT showed that the clinical protocol described in Organon 6th edition can be adapted to the methodology of clinical studies. Patients comply easily with the dosage system: 1 drop of the individualized remedy, 3 times/week (standardized to Mondays, Wednesdays and Fridays); dilutions were changed every 4 weeks beginning from 2 LM.

To choose remedies directly from works on pure materia medica – and in this regard, we prioritize antipsoric remedies, first those corresponding to Hahnemann's provings – is not common practice among homeopaths, more used to make repertory analyses and employ sources on clinical materia medica. Nevertheless, it is something feasible even in much demanded for public health-care facilities; moreover, the results of the RCT suggest that homeopathic remedies prescribed were as effective as a second-generation conventional antidepressant as measured by a specific score for depression. In fact, the evaluation of patients was not restricted to the manifestations of depression; these were only highlighted in the context of that research project.

Other strategies for selecting homeopathic remedies, when sufficiently standardized, can also be useful in RCTs. Frei et al., e.g., used repertory and polarity [21] analysis and showed the superiority of individualized homeopathic remedies in LM dilutions by comparison to placebo in children with attention-deficit hyperactivity disorder [22]. In their study, randomization was carried out after the selection of the homeopathic remedy, which would not be feasible in the case of acute depression. A placebo substitution design (with an open-label phase preceding the randomization) would be recommendable, but in depression studies such a design is used for continuation or maintenance trials and not to assess the treatment of the acute episode [23].

It has been said that homeopathy is an "eminence-"rather than evidence-based medicine [24] as practitioners are more influenced by eminent professors than by the evidence supplied by RCTs. In this regard, if protocol *Organon.modus* can help carrying out clinical trials confirming the specific efficacy and effectiveness of homeopathic treatments in different clinical conditions it will serve to build up a common denominator between the art of healing and medical science as well as among the different schools of homeopathic thinking, inasmuch as all in one way or another arise from Hahnemann's work.

"The true art of healing is by nature
pure experimental science".

Hahnemann, *Organon*,
Preface to the 2nd edition

Appendix 1. Standardized preparation of an LM dilution for stabilization in alcohol

Preparation of the 1st dilution

1. Place 120 ml of water in a 250 ml beaker.
2. Dissolve 1 microglobule of the prescribed remedy in the prescribed LM dilution.
3. Make fast circular motions with a glass rod, spoon or pipette, up to 20 rounds.
4. Take 2.5 ml of the solution with a spoon or pipette and transfer to a 30 ml amber-glass vial containing 17.5 of 30% ethanol.

5. Name the vial with the name of the remedy, scale and potency, followed by the number of the dilution (in this case, 1st dilution). Example: *Sulphur* 8 LM, 1st dilution.
6. Used beakers and pipettes must then be inactivated through exposure to heat 150ºC for 1 hour.
7. Instead of beakers and pipettes, it can be used disposable plastic cups and spoons.

Preparation of higher dilutions

1. Place 120 ml of water in a 250 ml beaker.
2. Dissolve 1 microglobule of the prescribed remedy in the prescribed LM dilution.
3. Make fast circular motions with a glass rod, spoon or pipette, up to 20 rounds.
4. Take 2.5 ml of the solution with a spoon or pipette and transfer to another 250 ml beaker containing 120 ml of purified water and repeat 20 circular motions.
5. Repeat steps 1 to 4 as many times as dilutions wanted and transfer to a 30 ml amber-glass vial containing 17.5 of 30% ethanol.
6. Name the vial with the name of the remedy, scale and potency, followed by the number of the dilution. Example: *Sulphur* 8 LM, 3rd dilution.
7. Used beakers and pipettes must then be inactivated through exposure to heat 150ºC for 1 hour.
8. Instead of beakers and pipettes, it can be used disposable plastic cups and spoons.

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Da padronização farmacêutica à pesquisa clínica: 20 anos de experiência com potências cinquenta-milesimais

RESUMO

Introdução: Iniciamos há 20 anos, uma padronização dos procedimentos para o preparo e uso das potências cinquenta-milesimais (LM ou Q) de acordo com a 6ª edição do Organon. **Objetivo**: Relatar as principais etapas dessa padronização e nossa experiência com o ensino e a pesquisa usando os princípios essenciais da a 6ª edição do Organon. **Resultados**: Observamos uma menor incidência de agravações homeopáticas com o uso de medicamentos padronizados, em relação à nossa experiência anterior com potências LM não padronizadas. O protocolo clínico-farmacêutico, que aqui denominamos Organon.modus, mostrou-se adequado ao ensino da Homeopatia na Faculdade de Medicina de Jundiaí, primeira escola de Medicina no Brasil a oferecer uma especialização em Homeopatia para médicos. Potências LM individualizadas não foram inferiores ao antidepressivo fluoxetina no tratamento de pacientes com depressão moderada a grave em um estudo randomizado e duplo-cego. **Conclusão:** O protocolo Organon.modus mostrou-se adequado ao ensino acadêmico da Homeopatia e eficaz em um estudo clínico controlado, resultados que favorecem seu uso como denominador comum entre a arte de curar e a ciência médica.

Palavras-chave: Homeopatia, escala LM (Q), Organon, protocolo clínico-farmacêutico, educação médica, ensaio randomizado.

Normalización farmacéutica e investigación clínica: 20 años de experiencia con potencias cincuenta-milesimales

RESUMEN

Introducción: ehace 20 años iniciamos una normalización de los procedimientos para la preparación y uso de potencias cincuenta milesimales (LM o Q) siguiendo la 6 ª edición del Organon. **Objetivo**: describir las principales etapas de esta normalización y nuestra experiencia en enseñanza e investigación segúnlos principios enunciados en la 6 ª edición del Organon. **Resultados**: Se observó una menor incidencia de agravaciones homeopáticas con el uso de medicamentos estándar en relación a nuestra experiencia previa con las potencias LM no estándar. El protocolo clínico-farmacéutico, que aquí llamamos Organon.modus, fue adecuado para la enseñanza en la Facultad de Homeopatía de la Escuela de Medicina de Jundiaí, la primera institución de enseñanza superior en Brasil que ofrece especialización en homeopatía para médicos. Potencias LM individualizadas se mostraron no inferiores al antidepresivo fluoxetina en el tratamiento de pacientes con depresión moderada a severa en un estdio doble ciego randomizado. **Conclusión**: El protocolo Organon.modus se mostró adecuado para la enseñanza académica de la homeopatía y efectivo en estudios clínicos controlados, sugiriendo su uso como común denominador entre el arte de curar y la ciencia médica.

Palabras clave: Homeopatia, escala LM (Q), Organon, protocolo clínico-farmacéutico, educación médica, estudio clínico randomizado.

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