A Pilot Study of Prospective Data Collection by Italian Homeopathic Doctors

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Homeopathy

Abstract

Objective The main purpose of this article is to report the systematic data collection pertaining to the consultations of a group of qualified homeopathic physicians. Studies have been performed concerning: (1) the most frequently treated pathologies; (2) the symptoms reported by patients, with a particular focus on "fear" symptoms; and (3) the evaluation of the outcomes of the treatment, including likelihood ratio (LR) for fear symptoms of mostly prescribed remedies.

Design Prospective observational study.

Setting Individualized homeopathic treatment at private homeopathic surgeries in Italy.

Participants Adult patients asking for homeopathic therapy for a series of common ailments.

Outcome Measures Types of diseases and remedies used and clinical parameters (frequency of acute attacks, and their intensity and duration); the overall outcome of the cure was registered using the Outcome Related to Impact on Daily Living (ORIDL) scale.

Results Only 94 patients could be enrolled by eight homeopathic doctors in a 2-year period between 2015 and 2017. Ninety (72 females, 18 males) patients completed the observation period. The most represented pathologies belonged to the group "Anxiety and anxiety disorders" followed by gastrointestinal ailments. The most prescribed remedy was *Phosphorus* (9 cases), followed by *Natrum muriaticum* (4 cases) and *Ignatia* (4 cases). The intensity of the symptoms and the frequency of the attacks decreased during the course of the study. Most patients reported a positive outcome (ORIDL scale). In the "*Phosphorus*" group, LR values were calculated for fear symptoms: LR+ for fear of dark = 2.25 (95% confidence interval [CI] = 0.56 to 9.02), LR− for fear of crowds = 1.27 (95% CI = 1.13 to 1.42), and LR− for fear of ghosts = 1.12 (95% CI = 1.04 to 1.22).

Conclusion The recruited group was smaller than expected, but data from most participants could be collected. Positive clinical outcomes were recorded and LR of a few specific fears contributed to distinguish *Phosphorus* patients from the remaining population.

Keywords
- homeopathy
- individualized homeopathy
- observational study
- anxiety
- gastroenteritis
- phosphorus
- likelihood ratio

received
March 28, 2018
accepted after revision
June 5, 2018

DOI https://doi.org/10.1055/s-0038-1667069.
ISSN 1475-4916.

Introduction

In the homeopathic community, priority is often given to the descriptive study of individual successful cases. However, an approach of this kind does not allow quantitative conclusions to be drawn, putting the homeopathic clinical practice at risk of lacking scientific, reproducible, and shared evidence. Often, the database of homeopathic knowledge—and in particular for the symptoms used to prescribe the different remedies—was implemented based on experience from a small number of similar cases. If such evidence is not supported by a sufficient number of cases and statistical validation, it may give rise to errors or uncertainty in prescriptions. Therefore, it is necessary to obtain data on the remedies used and the results obtained from a large population, studied in a systematic manner, and using adequate protocols. The experts have already proposed some methods, based on Bayesian logic, which could be used to this end.[1–7]

Because in homeopathy people with the same diagnosis, but with differences in their individual symptoms, may require different remedies, it is necessary to ascertain what symptoms are associated with certain remedies in a statistically verifiable manner. Although various studies have been published, they have not found general application yet. Many further new initiatives and studies are needed in this field. This protocol is proposed as a prospective observational study on cases of patients who consulted a physician asking spontaneously for homeopathic treatment. It follows the guidelines of the Liga Medicorum Homoeopathica Internationalis, issued in 2013, for the "Clinical Verification of Homeopathic Symptoms" (http://www.wisshom.de/dokumente/upload/ae78e_e2dd4_2013_guidelines_clinical_verif_hom_symptoms_third_edition.pdf).

The principal aim was to verify the feasibility of a systematic collection of data pertaining to the consultations of a group of qualified homeopathic physicians working in their private surgery. Studies have been performed concerning: (1) the most frequently treated pathologies; (2) the symptoms reported by patients, with a particular focus on "fear" symptoms; and (3) the evaluation of the outcomes of the treatment. A specific object of this investigation was the determination of likelihood ratio (LR), a tool of prognostic factor investigation that, in homeopathy, can be used to relate the presence of a certain symptom with the prescription of a given remedy. This approach should support, using statistically validated evidence, the use of a homeopathic remedy for the treatment of a patient who complains of certain symptoms, providing an estimate of probability on its effectiveness.[8–10] Positive LR (LR+) expresses the ratio between the probability that an individual who was cured with a remedy had the symptom, and the probability that the remaining population who did not take the specific remedy (or was not cured by it) had the symptom. Negative LR (LR−) expresses the ratio between the probability that an individual who was cured with a remedy did NOT have the symptom, and the probability that the remaining population who did not take the specific remedy (or was not cured by it) had the symptom.

The clinical observations were made by expert homeopathic physicians who have been working for at least 5 years and graduated in homeopathic schools that follow the European Committee of Homeopathy educational program. The participant doctors were Federico Allegri (Venezia), Mattia Canetta (Roma, Modena, Novara, Milano), Marco Colla (Biella, Torino), Monica De Lucchi (Genova), Vincenzo Falabela (Reggio Calabria), Gennaro Muscari Tomaioli (Venezia), Pierluigi Tubia (San Donà di Piave, Venezia), and Bruno Zucca (Brescia). The data collection began on January 1, 2015 and ended on January 31, 2017.

Methods

Protocol

The protocol is of an observational prospective type, meaning that the data have been collected in two stages: Stage 1: enrolment and first consultation; Stage 2: follow-up consultation and outcome evaluation. The time necessary to evaluate the outcome of the therapy was decided by the doctor according to the type of illness and the normal homeopathic follow-up. Between the first and second stages, a maximum of 6 months had to pass, then the second stage report had to be referred.

The patients, on their own initiative, visited a homeopathic physician and were followed over time, without the observational study altering the progression of the treatment. The data collection took place in the offices of the physicians who took part in the protocol, without any interference with normal clinical practice. The collection tool consisted of a few forms, into which the necessary data could be entered, and which the physician could complete in less than 15 minutes at the end of the medical examination.

The data were collected anonymously using a unique code assigned to the patient by the physician on the first consultation. The candidate patient for inclusion was adequately informed about the homeopathic treatment and the study design. The patient was given an information sheet and completed the necessary documents, which had to be stored in original as documentation by homeopathic doctors. All the participating patients provided a written informed consent to data collection and to health data storage according to the rules of privacy. Just after collection in the two stages, all data were sent to the coordinator of the study and collected in a dedicated Excel database.

Inclusion criteria were: (1) age 18 to 80 years; (2) patient on a first consultation, not treated during the 2 preceding years with an individualized single-component homeopathic remedy; and (3) patient with a pathology included in a list of 18 conditions among those most frequently treated by homeopathic practitioners (see Results)

Exclusion criteria were: (1) inability to express a valid consent, (2) neoplastic pathologies, (3) therapies with antibiotics, anti-inflammatory drugs, psychoactive drugs or anti-epilepsy drugs that have begun recently (in the last 2 months). Occasional therapies and chronic therapies with such drugs, begun more than 2 months previously, and which the physician considered necessary, were not grounds for

exclusion. Use of those medications was adapted to the patient's clinical progression.

Once the prescription was received, the patient took the homeopathic medicine as instructed by the doctor and returned to the control visit within the normal time frame to evaluate the effects of the therapy. It was also possible to have a telephone consultation while taking the therapy, validating the need not to change the medicine before correctly recording the result, whatever it was (positive or negative). It was recognized that in the course of the therapy the doctor could change the dosage of the same remedy.

A specific point of the protocol consisted of the collection of data related to the presence or absence of certain fears in the patient: dark, crowd, fly, death, ghost, dogs, birds, insects, spiders, snakes. Each fear was ranked in three grades: grade 2 = much; grade 1 = little; grade 0 = none. This is a novel feature, which makes it possible to obtain a comparable set of data for all the included patients. To standardize the questions and with the aim of avoiding that the doctor might "guide" the responses, the presence or absence of fears were reported by the patient in a specific form, at the end of the visit. The presence or absence of fears was then used to calculate the LR. Since in homeopathy the strong symptoms take on particular significance, in the calculation of LR the presence of the symptom was considered valid when referred to grade 2 (much fear), while grades 0 (no fear) and 1 (little fear) were considered as absence of the symptom. Calculating the LR requires four pieces of information:

a = number of patients presenting the symptom in the medicine population;
b = number of patients presenting the symptom in the remainder population;
c = number of patients not presenting the symptom in the medicine population;
d = number of patients not presenting the symptom in the remainder population.

Medicine population: the patients with a positive reaction to the medicine under study.

Remainder population: all other patients; that is, patients receiving no or other medicines plus patients receiving the medicine under study without positive reaction to that medicine.

LR + = [a/(a + c)]/[b/(b + d)]
LR − = [c/(a + c)]/[d(d + b)]

In the two stages of the study, parameters concerning the clinical severity of the case (frequency of acute attacks, their intensity and duration) were also collected by the physician. "Frequency" was reported as the number of days in the last month that symptoms of the patient's pathology have been present. Intensity of symptoms was reported in a scale from 0 to 10 (0 = absence, 10 = maximum intensity of the symptom). The working protocol included advice to the doctors concerning the multiple factors or events that can have effects on the quality of daily life: for example, trauma, surgical operations, drastic changes to family or employment situation, moving house, and financial success/difficulty. The possible effect of such concomitant factors, including the use of other conventional or unconventional medications, was considered in evaluating the outcome. Moreover, the protocol included the information that, in prognostic factor investigation, cases with a neutral or negative outcome are of equal importance to those with a positive outcome.

At the time of the second stage, besides the clinical data concerning the severity of symptoms, the overall outcome of the cure was registered using the Outcome Related to Impact on Daily Living (ORIDL) scale, which has been already validated,[11] and uses a score range from –4 to +4. The ORIDL score allows one to obtain from the patient a neutral evaluation regarding the effectiveness of the homoeopathic therapy.[12,13] The result can be either positive (improvement), negative (worsening), or neutral (no change). For the purposes of this study, the English version was translated in the appropriate manner to obtain a validation of the instrument in Italian ("translation/back translation"). The correct compilation methodology required the doctor to explain this specific question to the patient in a neutral way without influencing the answer: "*Compared to how you were before the initial appointment, what has been the overall effect of your treatment on (a) your main complaint (the one that you came to get treated) and on (b) your general well-being?*", assigning a numerical value for each of (a) and (b). The possible answers and relative results are: +4 Cured/back to normal; +3 Major improvement; +2 Moderate improvement, affecting daily living; +1 Slight improvement, no effect on daily living; 0 No change/unsure; −1 Slight deterioration, no effect on daily living; −2 Moderate deterioration, affecting daily living; −3 Major deterioration; −4 Disastrous deterioration. To help the patient understand the question, which is central for the evaluation of the outcome, the physician gave the patient a printed copy of the question along with the scores for the possible responses, in the Italian language.

Statistics

To evaluate the changes of the pathologies during the course of the study, the paired *t*-test was applied when the distribution was normal, as assessed by the Shapiro–Wilk test. The difference before/after of the frequency of symptoms was evaluated using the Wilcoxon signed-rank test, since the values were not normally distributed. Statistical calculations were done using Stata software. LR+ and LR– and confidence intervals (CI) were calculated using MedCalc easy-to-use statistical software (https://www.medcalc.org/calc/diagnostic_test.php).

The percentages of the single fears of *Phosphorous* patients were compared with those of the remaining population by chi-squared or Fisher's exact test, as appropriate.

To identify the number of the underlying components of the initial questionnaire, the Pearson's correlation matrix was explored by means of principal component analysis.[14] The number of components was determined on the basis of eigenvalues of the correlation matrix greater than 1, and by looking for sharp breaks in the size of the eigenvalues using a scree plot. Varimax rotation and item-component correlations —that is, "component loading", greater than 0.42, in absolute value—were chosen to identify a simple component structure.

Results

A total of 97 clinical cases were collected. Three were not included because they did not conform to the protocol setting of the present study (retrospective cases). There were four drop-outs: one control visit missed because the patient had moved to another country; two failures to send the control visit data by the participating doctor by January 31, 2017 (data collection closing date); one failure to collect all the data required in the follow-up visit because of inadequate patient compliance. Excluding the above, data from 90 patients were confirmed and entered in the final database and used for statistical processing (►**Table 1**).

The patients who completed the follow-up included 72 females and 18 males. The age of patients was < 30 years in 9 (10%) cases, 30 to 50 years in 36 (40%) cases, and > 50 years in 45 (50%) cases. The most represented pathologies were those belonging to the group "Anxiety and anxiety disorders". This group included the following list of pathologies: panic attacks, agoraphobia, specific phobias, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder. The pathologies and the relative subgroups have been defined following the classification of "ICD-10 (International Classification of Diseases)".

Table 1 Number of cases included and completed in the various groups of pathologies

Group no.	Pathology	Included cases	Completed
	All	**94**	**90**
1	Anxiety and anxiety disorders	43	41
2	Asthma (allergic and non-allergic)	2	2
3	Chronic bronchitis (excluding asthma)	0	0
4	Primary cephalalgia (tension-type and migraine)	6	6
5	Recurring or chronic cystitis	2	2
6	Climacteric and menopause disorders	3	3
7	Allergic, atopic, or contact dermatitis	3	2
8	Sleep disorders not due to physiological causes or substances	4	3
9	Pain and other complaints associated with the menstrual cycle	3	3
10	Fibromyalgia	4	4
11	Chronic gastritis and gastroduodenitis	9	9
12	Gastroenteritis and/or non-infectious colitis	8	8
13	Essential hypertension	0	0
14	Hypothyroidism	2	2
15	Tonsillitis	0	0
16	Allergic oculorhinitis	3	3
17	Gastroesophageal reflux/reflux esophagitis	1	1
18	Chronic or recurring vaginitis	1	1

The average days of therapy were 134 ± 67 (standard deviation, SD; min 28, max 288), including all 90 cases. The most prescribed remedy was *Phosphorus*, for a total of nine patients (10% of the total). Remedies prescribed four times were *Natrum muriaticum* and *Ignatia*. Remedies prescribed three times were *Lycopodium*, *Belladonna*, *Lachesis*, *Nux vomica*, *Pulsatilla*, *Sepia,* and *Silicea*. Remedies prescribed twice were *Folliculinum*, *Graphites*, *Staphysagria,* and *Stramonium*.

The results were statistically processed only for the complete group (90 cases), then separately for the pathologies represented by a number ≥ 4 patients who completed the study, and precisely: "Anxiety and anxiety disorders" (39 patients), "Chronic gastritis and gastroduodenitis" (8 patients), "Gastroenteritis and/or non-infectious colitis" (8 patients), "Primary cephalalgia (muscular tension and migraine)" (6 patients), and "Fibromyalgia" (4 patients).

Intensity and Frequency

The intensity of the pathologies reported and the changes during the course of the study are shown in ►**Table 2**. A significant decrease was noted in all groups except fibromyalgia. Even in smaller groups (3 patients), a decrease in the intensity of the disease was observed, but probably due to the small sample size it was not statistically significant (not shown).

The frequency of the disease attacks before therapy was on average equal to 14.9 ± 11.5 (SD) days per month in the 90 overall patients and was quite different in the different clinical groups. In the patients of the "Pathology group 1" (Anxiety and anxiety disorders), the frequency of pathology per month was on average equal to 9.2 days; in patients of the "Pathology group 4" (Primary cephalalgia) it was 16.6 days; in patients of "Pathology group 10" (Fibromyalgia), 15.5 days; in patients of the "Pathology group 11" (Chronic gastritis and gastroduodenitis), 21.9 days; and in patients of the "Pathology group 12" (Gastroenteritis and/or non-infectious colitis), 12.6 days.

The difference before/after in the whole group of patients, whose data of the two phases were available (►**Fig. 1**) was highly significant according to Wilcoxon signed-rank test ($z = 6.477$, $p < 0.001$, $N = 81$). Significant differences before/after therapy were observed also in the groups "Anxiety and related disorders" ($z = 4.923$, $p < 0.001$, $N = 38$); "Chronic gastritis and gastroduodenitis" ($z = 2.521$, $p = 0.0117$, $N = 8$); "Gastroenteritis and/or colitis" ($z = 2.342$, $p = 0.0192$, $N = 8$); "Primary cephalalgia" ($z = 2.108$, $p = 0.0350$, $N = 6$); while in "Fibromyalgia" the difference was not significant ($z = 0$, $p = 1.0$, $N = 4$).

Impact on Daily Living

The study evaluated patient-reported outcome from homeopathic therapy by means of the ORIDL scale, referring to the

Table 2 Symptoms intensity before and after homeopathic therapy in the whole sample and in the major groups of patients

Group	*N*[a]	Phase	Mean	SD	*t*[b]	*p*-Value
Total population	84	Before	7.3	7.0		
		After	3.7	2.4	12.86	<0.0001
Anxiety and related disorders	39	Before	7.4	1.4		
		After	3.8	2.5	9.60	<0.0001
Chronic gastritis and gastroduodenitis	8	Before	8.0	1.8		
		After	3.3	1.9	4.26	0.004
Gastroenteritis and/or colitis	8	Before	6.6	1.6		
		After	3.7	2.6	2.52	0.039
Primary headache	6	Before	7.8	1.2		
		After	3.3	2.7	3.43	0.018
Fibromyalgia	4	Before	7.0	0		
		After	6.5	1.2	0.77	0.495

Abbreviation: SD, standard deviation.
[a]The indicated numbers of patients are those for which sufficient data for paired comparisons (phase1/phase 2) were available.
[b]Paired *t*-test.

main symptom (reason for the visit) and to overall well-being. The scale goes from –4 to +4 and the evaluation has to be expressed by the patient without any conditioning. The overall results are shown in ►**Fig. 2**.

The data collected indicated that in most patients the result of the therapy was perceived as positive; in particular, the most represented value was +3, indicating a "major improvement", both as regards the main symptom and general well-being. All nine patients who received *Phosphorus* as treatment showed improvement according to ORIDL (one patient scored +2, other patients scored > +2).

LR for Selected Fears

Given the limited number of patients enrolled in the study, it was not possible to perform LR analysis regarding repertorized symptoms, because they were too dispersed. We conducted LR analysis regarding the 10 selected fears and for which a specific questionnaire was administered to patients.

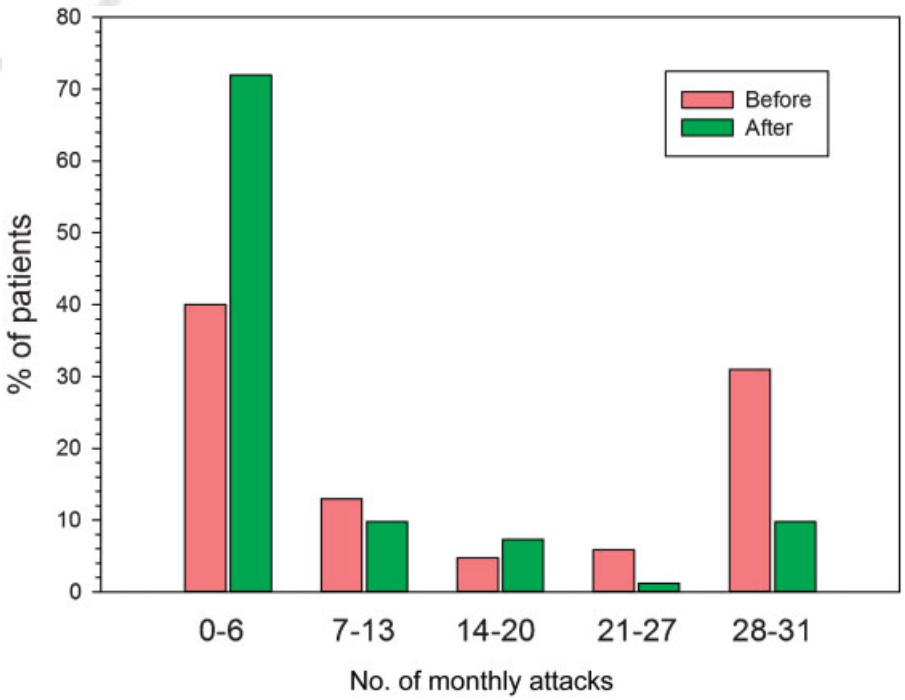

Fig. 1 Frequency of the disease attacks before and after homeopathic therapy.

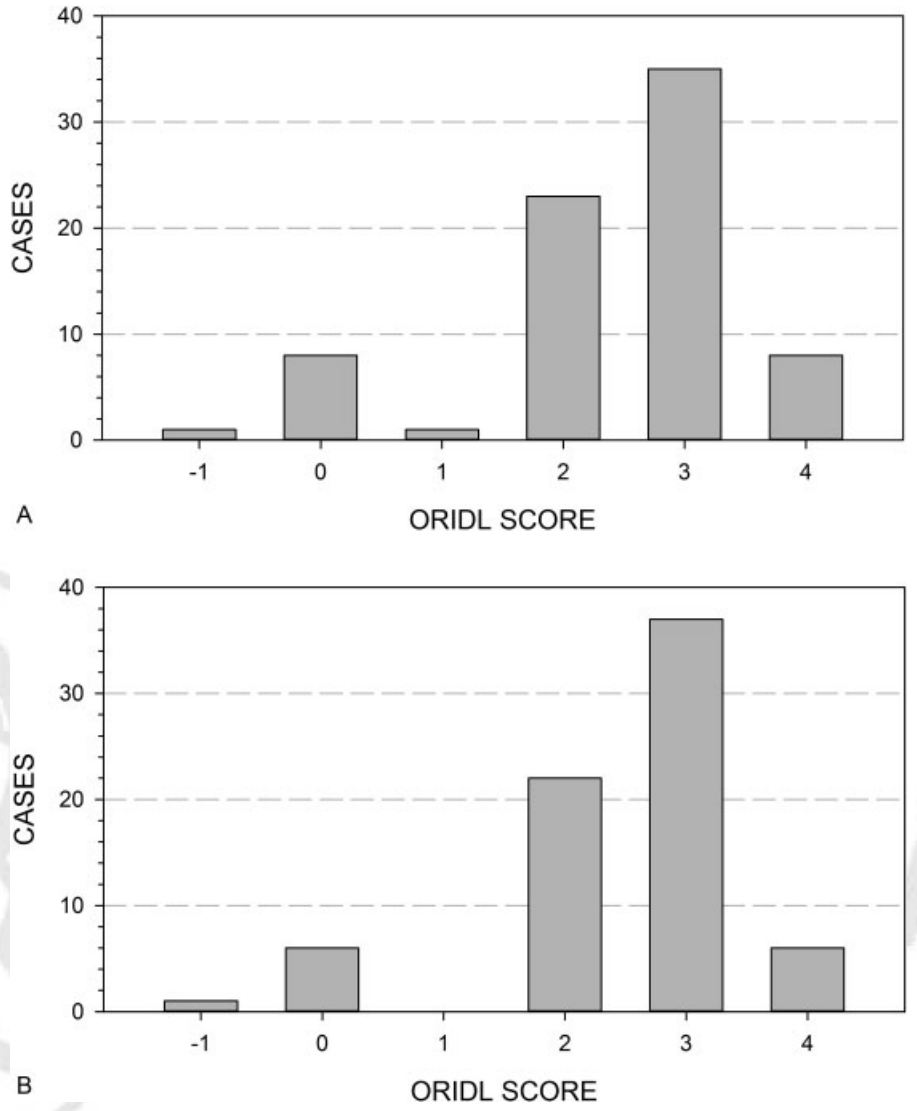

Fig. 2 Outcome in relation to impact on daily living scores of the homeopathic therapy. (**A**) Main complaint, (**B**) general well-being.

In particular, this analysis was conducted on patients who have been prescribed *Phosphorus*, which represented the largest group ($N = 9$). They are shown in ►**Table 3**.

It can be noted that in the *Phosphorus* group there are significant LR values referring to the *absence* of certain fears: crowds (LR– = 1.27), ghosts (LR– =1.12), dogs (LR– =1.08), and birds (LR–= 1.04). The LR of fear of light is positive (+2.25), but the 95% CI is not significant since the same fear is present also in 9.9% of patients of the remaining population.

The difference in the level of fear between *Phosphorus* patients and the remaining population was analyzed also by the Fisher's exact test, and the only significant difference between the two groups was detected in fear of crowds (►**Table 4**).

Correlation of Symptoms

The data concerning the 10 different fears of the whole population were analyzed to verify if there was some correlation between different symptoms. ►**Table 5** shows that several symptoms are correlated, while others are more "unusual" and separate. For example, fear of dark is correlated with all other symptoms, indicating that it is a quite unspecific marker of fear, while fear of crowds is unrelated to fear of animals. Fear of death—that is the most common fear according to ►**Table 3**—is clearly separated from fear of dogs and birds. Interestingly, fear of insects is not correlated with fear of dogs but is strongly correlated with spiders and snakes (animals perceived as poisonous).

A principal component analysis (►**Table 6**) demonstrated that the different fears in the study population are grouped by three significant components. Fifty-seven percent of variability is explained by the model. The first component includes crowds, flying, death, and birds; the second includes dark, ghosts, and dogs; and the third includes insects, spiders, and snakes. This analysis could not be done on sub-groups of patients treated with different remedies due to small sample size.

Discussion

The protocol of this observational study was drafted with the purpose of picking up systematically the data of the visits to a

Table 3 Number of patients reporting specific fears in patients treated with *Phosphorus* or in the remaining population, and calculation of LR+ and LR− for *Phosphorus* of each symptom

	Phosphorus ($N = 9$)		Remaining population ($N = 81$)		Positive LR		Negative LR	
Fear	**Fear**	**%**	**Fear**	**%**	**LR+**	**95% CI**	**LR−**	**95% CI**
Dark	2	22.2	8	9.9	2.25	0.56–9.02	0.86	0.60–1.23
Crowds	0	0.0	17	21.0	0		**1.27**	1.13–1.42
Flying	2	22.2	15	18.5	1.2	0.33–4.42	0.95	0.66–1.37
Death	6	66.7	42	51.9	1.29	0.77–2.14	0.69	0.27–1.79
Ghosts	0	0.0	9	11.1	0		**1.12**	1.04–1.22
Dogs	0	0.0	6	7.4	0		**1.08**	1.02–1.15
Birds	0	0.0	3	3.7	0		**1.04**	1.00–1.08
Insects	2	22.2	10	12.3	1.8	0.47–6.96	0.89	0.62–1.27
Spiders	3	33.3	14	17.3	1.93	0.68–5.45	0.81	0.50–1.29
Snakes	2	22.2	28	34.6	0.64	0.18–2.26	1.19	0.81–1.74
Mean	1.7	18.9	15.2	18.8	1.01	0.64–1.58	1	0.90–1.11

Abbreviations: CI, confidence interval; LR, likelihood ratio.
Note: The statistically significant LRs are indicated in bold.

Table 4 Number and percentage of patients reporting different grades of fear of crowds

		Grade of fear			Total
		0 (None)	**1 (Little)**	**2 (Much)**	
Phosphorus	*N*	9	0	0	9
	%	100	0	0	100
Remaining population	*N*	45	19	17	81
	%	55.6	23.6	20.9	100
Total	*N*	54	19	17	90
	%	60	21.1	18.9	100

Fisher's exact test, $p = 0.047$.

Table 6 Components loadings of the various fears

Variable	Component 1	Component 2	Component 3	Uniqueness
Dark	**0.426**	0.282	**0.538**	0.449
Crowds	**0.732**	0.006	0.114	0.452
Flying	**0.697**	0.250	−0.001	0.451
Death	**0.551**	0.392	−0.123	0.528
Ghosts	**0.533**	0.119	**0.554**	0.394
Dogs	−0.052	0.065	**0.781**	0.384
Birds	**0.517**	−0.207	0.333	0.579
Insects	0.152	**0.803**	−0.019	0.332
Spiders	0.032	**0.833**	0.162	0.279
Snakes	0.081	**0.579**	**0.491**	0.417

Note: Numbers in bold indicate items with loadings > 0.42.
Loadings are correlations between items and principal components after Varimax rotation.

Table 5 Correlation between 10 symptoms of the whole observed population

	Dark	Crowds	Flying	Death	Ghosts	Dogs	Birds	Insects	Spiders
Dark	1								
Crowds	**0.320**	1							
Flying	**0.284**	**0.362**	1						
Death	**0.293**	**0.230**	**0.384**	1					
Ghosts	**0.498**	**0.322**	**0.375**	**0.220**	1				
Dogs	**0.243**	0.108	0.116	0.071	**0.240**	1			
Birds	**0.232**	**0.299**	0.164	0.055	**0.341**	0.132	1		
Insects	**0.222**	0.183	0.185	**0.221**	0.168	0.044	0.098	1	
Spiders	**0.271**	0.039	**0.228**	**0.212**	0.208	0.179	0.068	**0.628**	1
Snakes	**0.399**	0.139	0.201	**0.254**	**0.362**	**0.275**	0.006	**0.342**	**0.394**

Note: Statistically significant correlations are reported in bold ($p < 0.05$).

group of qualified homeopathic doctors. It was conceived thanks to a collaboration between the University of Verona and the Homeopathic Medical School of Verona.

The study highlighted some limits of protocol, of feasibility and of participation. The involvement of the national homeopathic community was unsatisfactory: the Italian homeopaths were informed and asked to participate in the annual homeopathic conference and through the mailing list of the Italian Federation of Homeopathic Schools, but in about 2 years it has been possible to accumulate only 90 completed cases, much fewer than foreseen in the protocol setting (we expected more than 500 cases in 2 years). The limits linked to the processing of the data obtained refer in particular to the excessively long time-frame, due above all to the lack of professional programs dedicated to data collection and complete statistical processing. A noteworthy restraint of the present protocol is represented by the "manual" data collection, which requires time and precision and multiple control steps, while an automated collection through the creation of dedicated software could allow for shorter times and greater practicality. It has been demonstrated before that the use of paper forms is problematic in this respect.[15] Possibly this complicated the protocol, but we had tested the procedure and found that it only requires 15 minutes more work to be dedicated to data collection. Therefore, it remains to be seen whether this extra work could be a reason that explains the scarce recruitment of patients and scarce participation of doctors.

The prospective protocol setting, with the sending of the data foreseen at two separate times, was also not adequately understood by all the participant doctors, and in most cases it was necessary to send frequent reminders on the need to send data of phase 2 no later than 6 months after the inclusion of the case. In 21 of the total 90 cases, the time elapsed between the first visit and subsequent check (with relative data submissions) was greater than 180 days. A single physician did not understand the structure of the protocol and its intention as a prospective data collection and sent only retrospective cases that took place several years ago, which were excluded.

The economic limits have been important, as this was a non-sponsored pilot project in which each doctor and study team member took part in the data collection activity in a free and voluntary way. The major difficulty reported by the doctors was the time needed to recruit a patient and to collect and send data. Although the module dedicated to the compilation of each clinical case (both for the "first visit" or "inclusion" and for the "control visit") was created to allow clarity and simplicity and to be completed within a time estimated to be about fifteen minutes, often the time consumption proved to be longer. A huge difficulty experienced by the authors of the protocol was that of recruiting new homeopathic doctors, despite the constant invitations and attempts to disseminate.

A spontaneous observation emerged from more than one participating doctor is that, excluding the pediatric population and the patients with oncological diseases, a large number of the visits (or, for some, the majority of them) could not be included in the study. Finally, according to some homeopaths, the indicative time-frame of 6 months for the evaluation of the result was not sufficient: often the work to be done within the treatment was "deep" (and therefore needed more observation), and sometimes the first remedy was not the "simillimum". Sometimes it may happen that a patient benefits from a first prescription (and therefore, in the case of the protocol, the ORIDL score would be positive), but that at the time of the next control there emerges different or more typical symptoms of the person, leading to a second most "similar" prescription.

Another limitation of the study was the exclusion of children, denoting that the results are valid only for adults, while there are no repertory-rubrics "Fear of … in adults". To avoid mixing data related to children and adults, it was decided to limit the pilot protocol to the adult population; moreover, this was decided also for the possibility of having a valid consent from the adult patient to participate in the project. The homeopathic community discusses the application of repertory symptoms to the pediatric population: this is a point that could be deepened in future studies. Despite the fact there is no "adults, in" rubric in many repertoires, in the case of symptoms typically present in the child, there is the "children, in" section.

The results suggest that there has been a definite selection of patients with anxiety and fears. However, doctors were instructed to collect consecutive cases, not based on the type of illness but on inclusion and exclusion criteria and on the illnesses reported in ►**Table 1**. The fact that almost half of the patients ended up in the "Anxiety and anxiety disorders" category is probably due to an auto-selection of the patients, since the conditions listed in ►**Table 1** are those most frequently managed by homeopathic doctors in their private surgeries. The "Anxiety and anxiety disorders" category is quite wide-ranging, including several syndromes such as panic attacks, agoraphobia, specific phobias, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder. Therefore, it is conceivable—though obviously not certain since randomness could not be guarded—that patients with anxious symptoms were a fairly large sample of the population who went for visits in the given period.

Some doctors have stated that the inclusion/exclusion criteria (in particular, the pediatric age and the presence of oncological pathologies, or a recent pharmacological therapy) have significantly limited the inclusion of patients in the project, many of their homeopathic patients being in the excluded categories. This problem should be taken into consideration for future studies: if it is not possible to include every consecutive new patient, patients should be included following a scheme that does not influence the prevalence of the assessed symptoms. It remains to be understood also if the clinical population affected by anxious diseases might report some repertory symptoms in a predominant way compared with the remaining population: this is an interesting hypothesis, which had not been contemplated during the drafting of the protocol.

Despite those limitations, which should be accounted for in future replications, several interesting results emerged from the data collection. Comparing the quantitative values of intensity and frequency of symptoms of the two phases, an improvement during homeopathic cure was observed in all the groups except fibromyalgia. The positive outcome was also documented by ORIDL score in most patients (►**Fig. 2**). Of

course, this evidence is not proof of efficacy of the treatment, since the study is of an observational nature and this kind of data collection is not valid for causal assessment.

To collect valid data for the LR, it is necessary to limit the study to those symptoms for which information on the "presence" and of the "absence" is available. For this reason, we decided to explore some specific symptoms of "fears" that are present in Materia Medica. In our findings, the only significant LR values could be obtained by analyzing the fear symptoms of the "*Phosphorus*" patients, because the other groups were too small to be evaluated. We know that there are more fears present in *Phosphorus*'s Materia Medica and the subject is described as fearful, hypersensitive, restless, or indifferent. It is interesting to note that also in the patients enrolled and treated with *Phosphorus,* many fears of the selected 10 seem to emerge, which in fact are part of the Materia Medica of the remedy.

The LR+ = 2.25 for dark seems to confirm that *Phosphorus* patients have greater fear of dark than the remaining population of patients, but the very large 95% CI (0.56–9.02) makes the result not statistically significant. An LR+ of 2.25 resulted from the fact that 2/9 *Phosphorus* patients (22%) had this symptom, while 8/81 (9.9%) of the remaining population had the same symptom. Fear of dark is more frequent in the *Phosphorus* group but is not a rare and peculiar symptom in the remaining population. Within the classic homeopathic texts, especially within Materia Medica, the fear of dark is a typical note for the *Phosphorus* remedy and it is considered in a way a symptom that cannot be absent in a patient to whom the remedy can be prescribed. Regarding the repertories, in the Repertory of Schroyens (Synthesis Treasure Edition 2009) the fear of dark in *Phosphorus* is present at the second degree; in the Repertory of Boericke (Repertory English), it is present at the second degree (MIND—Fears dread—Dark, ghosts); in the Repertory of Kent (English Kent), it is present at the second degree. In the study conducted, this value of LR+ is not significant, mainly due to the insufficiently large number of subjects treated. Using the same algorithm, it is possible to calculate that with this difference between *Phosphorus* and the remaining population, to reduce the 95% CI and render the difference statistically significant (e.g., 1.45–3.48), a sample size of at least 10 times larger would be needed. Conversely, with the same sample size, to obtain a significant difference, at least 4/9 *Phosphorus* patients should have the symptom (in this case LR+ = 4.5, 95% CI = 1.7–12.0), or only 3/78 patients in the remaining population should have the same symptom (in this case LR+ = 6.0, 95% CI = 1.2–31.2).

Among the patients treated with *Phosphorus*, none reported to have fear of crowds, while the same symptom was present in 21% of the remaining population. As a consequence, the LR– for "absence of fear of crowds" turned out to be small but statistically significant (1.27, 95% CI = 1.13–1.42). The difference between *Phosphorus* patients and the remaining population was confirmed also with the Fisher's exact test, suggesting that this psychological and behavioral attitude is worthy of consideration. Moreover, an interesting point emerges from the data of correlations and principal components analysis: in the general population, the fear of crowds is correlated with other fears such as flying, death, and birds. However, *Phosphorus* patients have LR+ for fear of flying and death, but LR– for fear of crowds, evidence that diverges from other associations. This evidence reinforces the hypothesis that this emotional scheme is quite typical of *Phosphorus* patients. If confirmed with studies conducted on larger samples, the absence of fear of crowds could be used as one of the characteristic features for prescription of this medicine, together with other signs and symptoms. In fact, taken alone, an LR– of 1.27 is a minor value, which would increase a prior chance that *Phosphorus* works if the symptom is absent from, say, 20 to 24%, or from 50 to 55.9%, which is clinically hardly relevant. All this highlights once again the complexity of the homeopathic methodology and the difficulty of a reductive approach in interpreting it, linked, for example, to the presence or absence of a single symptom. On this topic, it can also be recalled that the repertory indicates a list of symptoms, but their modalities are typical of every remedy. The homeopathic repertory effectively summarizes the symptoms present in the Materia Medica, but the broader sections (for example, fears) group the same symptom even if expressed by the patient in different ways (e.g. with agitation, with anger, with apathy, with the externalization of sensation, or with total closure in on oneself). Even the same fears, for example, could be present in different remedies but express themselves (sensations, behaviors and symbolic meaning) in very different ways.

It would be interesting to conduct an international multicenter study to understand if the characteristic symptoms of the remedy, emphasized by classical Materia Medica, are confirmed in the contemporary population. Furthermore, a significant positive value of LR is easier to interpret in relation to homeopathic clinical practice, which typically interrogates the patient about the presence of characteristic symptoms in his/her history and not about their absence. Working in this way on a sufficient number of remedies, it would be possible to reconfirm, or not, over time the veracity of the symptoms present today in the different repertories, on which sometimes arbitrary additions are written.

On the basis of the experience of this pilot study, some recommendations for future prognostic factor investigation may be advanced, such as: (1) organize consensus meetings of participating observers before and during the study; (2) avoid using paper forms and use database software to minimize the time needed to record presence of symptoms and result of treatment; (3) include every consecutive new patient, if no exclusion criteria are present (if that is not possible, secure randomness so that selection of a patient is not based on the assessed symptoms); (4) try to match the assessed symptoms to existing repertory rubrics, and try to distinguish the symptoms according to different age groups; (5) carefully consider follow-up frequency and timing.

In future, large and multi-center studies of different symptoms would provide important support for the scientific value of homeopathy. In addition, a similar and well-organized data collection could potentially continue in the long term without stopping, creating a constantly expanding database that is able to bring over time more and more extensive and significant results that every homeopath in the world could and should

know. It would therefore be a progressive effort capable of improving homeopathy and possibly provide it with "evidence based" support, indispensable today.

Conclusions

The described protocol was the first practical experience in Italy for the application of the LR and its use to improve the effectiveness of the homeopathic prescription, as well as to confirm the validity of symptoms contained in classical homeopathy texts in their clinical application to the contemporary population. Despite the early expression of interest of Italian doctors, the collected cases have proved to be fewer than expected, so that it was possible to obtain a precise measure of the LR only for the symptoms of "fears" in a small group of *Phosphorus* patients. All patients who improved after the remedy *Phosphorus* reported the absence of fear of crowds, a feature that separated this group from the remaining population in a small but statistically significant way. If confirmed on a large scale, also the fear of dark appears as a useful symptom for prescription of this remedy, as well indicated in Materia Medica. In addition to data processing, the importance of this project lies in having set up a methodology for the drafting of a protocol and teaching doctors about how to use it, a task that took several months of work. It is equally interesting to have brought out the potential and limitations of this kind of study, especially the methods of data collection and validation.

Highlights

- A group of eight qualified homeopathic physicians prospectively reported clinical data of the most frequently treated pathologies observed in their private surgeries.
- During 2 years, only 90 patients completed the study, suggesting that more simple and practical protocols must be set up for large-scale data collection.
- The outcomes subjectively reported (intensity and frequency of symptoms) were positive and statistically significant as compared with the baseline.
- The determination of LR for some "fear" symptoms detected small differences between patients treated with *Phosphorus* and remaining population.
- The *absence* of "fear of crowds" was more common in patients treated with *Phosphorus* than in the remaining population.

Conflict of Interest
The authors have no conflict of interest and all doctors and study team members participated in the project for free. Technical costs were supported by funds from the Ministry of University and Scientific Research.

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