Homeopathy (2006) 95, 123–130

doi:10.1016/j.homp.2006.04.003, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Double-blind, placebo-controlled homeopathic pathogenetic trials: Symptom collection and analysis

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Background: **Homeopathic pathogenetic trials (provings) are fundamental to homeopathy. Since most of the data from available provings have not been statistically evaluated, it is unclear how specific reported symptoms are and how they differ from those reported by people taking placebo.**
Method: **We combine and analyse data from two different homeopathic pathogenic trials—including 10 and 11 provers, respectively, and both including 30% placebo—to test the null hypothesis that there is no significant difference between the number of symptoms in placebo and verum groups.**
Results: **The principal results were:**

- **Placebo reported less symptoms than verum groups.**
- **Symptom distribution according to predefined classes (common symptoms increased in intensity and/or duration-, cured, old, new and exceptional) was statistically different between placebo and verum group at a high level of significance ($P<0.001$). Compared to verum, placebo provers reported less new and old but more common (increased in duration or intensity) symptoms.**
- **Within repertory categories, other differences were detected.**
- **The two groups differ in terms of the duration of each symptom and kinetics of symptoms: most symptoms were more persistent in verum than in placebo groups and verum provers recorded a decreasing number of symptoms with time. Placebo provers did not show such a temporal pattern.**

Conclusions: **If confirmed by other studies these results would demonstrate the non-equivalence between homeopathic medicines in high dilution and placebo and contribute to the improvement of proving methodology and evaluation.** *Homeopathy* (2006) **95**, 123–130.

Keywords: homeopathic proving; placebo; symptoms classification; standardized methodology; pathogenetic trial

Introduction

Proving is fundamental to homeopathic medicine: symptoms experienced by healthy provers are collectively analysed to build the foundations of a new remedy. Since the time of Hahnemann, but especially

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Received 14 March 2005; revised 8 August 2005; accepted 24 April 2006

at present, the proving process has evolved and grown into a multi-facetted mode of investigation. Hahnemann was what we would call today a research scientist and the provings he conducted were of a the high standard for his time. He called for medicines to be used singly, not in mixtures, based on an empirical understanding of individual drug action, based on giving small daily doses of a drug to healthy people, who would then record the symptoms they experienced. Sadly, not all those who followed him were as scrupulous, and many poor and bizarre provings have been conducted over the years:[1-3] poorly standardized provings or single case reports, sometimes published merely in websites without peer-review, leading to very poor remedy pictures and contribute to making homeopathy unreliable.

It is difficult to distinguish the placebo effect from the specific effect of potentized substances.[4,5] Nevertheless, many controlled studies now available show that it is possible to demonstrate the validity of proving, by using a standardized methodology.[6-9] Some homeopathic societies and individual authors, have tried to introduce standardized proving methodologies[10-12] stressing the necessity of precise description of the substance used (source and preparation), clear instructions to subjects and accurate analysis of obtained symptoms.

In this study data from two proving's both including placebo, are analysed in terms of the number of symptoms reported by placebo and verum groups. Symptoms collected from these two provings, carried out on a small number of subjects using the same procedure, are considered together in order to increase the significance of results; the remedy pictures and differences between the two medicines are not discussed.

The aim was to test the null hypothesis that there is no significant differences between placebo and verum groups in terms of:

- total number of symptoms reported;
- number of symptoms by pre-defined categories.

Data were statistically evaluated and significant differences are reported. We also report the time course of symptom appearance.

The first proving was of potentized *Etna Lava*:[9] volcanoes are known as sources of useful but poorly understood remedies, eg *Hecla Lava*, the aim of the study was to enrich homeopathic knowledge on this class of remedies. The second proving was of potentized H_2O_2 (hydrogen peroxide, *Hydrogenium peroxidatum*): this molecule is a reactive oxygen species (ROS), responsible for tissue injury with consequent disease if not efficiently detoxified; ROS have been implicated in over 50 diseases and in the ageing process (see general reviews eg see reference[13,14]). The toxicological effects of H_2O_2 in humans have been thoroughly reviewed,[15] but recently this compound has been suggested as a specific diffusible signalling molecule in the central nervous system.[16] All these facts make H_2O_2 an interesting candidate for a homeopathic medicine.

Methods

Recruitment, provers, supervisors and coordinator

Both pathogenetic trials included volunteer provers, supervisors, and a coordinator. Supervisors were recruited among homeopathic doctors from schools of homeopathy connected with FIAMO the Federation of Italian Association of Homeopathic Medical Doctors. Each participating association nominated a coordinator and recruited volunteer provers among students of their schools or people interested in homeopathic medicine. All volunteers signed a consent form. As Italian National Bioethical Committees do not consider homeopathic pathogenetic trials, an approval from a bioethical committee was not sought.

Inclusion criteria

- Knowledge of homeopathic proving (most had participated to other trials).
- In a general state of good health according to the proving coordinator, proving supervisor and the subject (no drugs, oral contraception pills, etc, no mental pathology, no chronic physical pathology, etc).
- Agreement to comply with instructions for keeping a proving diary.
- No elective medical treatment (such as surgery or dental procedures) for the duration of the homeopathic drug proving.
- At least 6 months clear of any previous homeopathic remedy.
- No major life changes and continuation of usual habits and patterns of daily life.
- Over the age of 18.

Volunteers were also blind concerning the nature of the remedy and the group composition and were instructed to have no contact with other provers or supervisors.

Supervisors were homeopathic practitioners with at least 10 years experience, medical doctors, teachers in Italian homeopathic schools, experts in provings studying and supervising. He/she was blind concerning the remedy and placebo distribution. The supervisor's role was to assist the prover in relating and recording symptoms effectively, and to monitor any strong reaction or adverse event, etc. Frequent meetings (once a week) between supervisor and each prover were scheduled and phone contact was permitted when necessary. A total of six supervisors participated in the trials, each supervising a maximum of five provers.

Supervisors had contact only with the coordinator, and could not communicate with each other.

The coordinator was responsible for the entire process of proving. He monitored the quality of work of the supervisors: received prover's symptomatology weekly from the supervisors, conducted the extraction, collection and editing of the symptoms. Symptoms from the daily diary where analysed according to Sections of Kent's Repertory[17] classified by chapter. No contact was allowed between provers and the coordinator for the duration of the study.

Test substances

The remedies were *Etna Lava* for proving 1 (verum-1) and *Hydrogenium peroxidatum* for proving 2 (verum-2). They were produced by Cemon-Unda, Italy. Lava samples were collected on Etna during the August 2000 eruption. Trituration and subsequent dilution in 50% ethanol were performed according to the manufacturer's procedures. Chemical composition of lava had been previously reported.[9] 30% H_2O_2 (hydrogen peroxide) was of the best chemical grade (Sigma-Aldrich St Louis, USA). It was directly diluted in 50% ethanol for the centesimal potency preparations. Placebo was the same diluent solutions (50% ethanol).

The remedy was taken in the 30CH potency, 10 drops sublingually, three times per day (08.00, 14.00 and 20.00) for no more than 2 days. Provers were instructed to stop taking it if a new symptom appeared.

Study design

For both trials the design was double blind, randomized, multicentric, placebo controlled experimental study. The trials lasted 2 months each. The two provings HPTs included a total of 11 and 10 provers, respectively. In each trial approximately 30% of subjects took placebo: for *Etna Lava* proving, 8 provers took verum and 3 placebo; for *Hydrogenium peroxidatum* 7 and 3, respectively. The composition of the two groups is reported in Table 1.

There was a run-in phase of prover training of at least 2 weeks: it consisted of prover self-observation without medication and instructions from the supervisor as to how to complete the diary and describe symptoms. Provers were instructed to carefully record all symptoms, modalities, time of occurrence and concomitants in the diary. During this phase, the supervisor recorded the prover's medical case including past physical and mental symptoms and states.

Table 1 Group demographics for both provings

	Verum-1 Etna Lava	*Verum-2 Hydrogenium peroxidatum*	*Placebo*
Provers	8	7	6
Sex			
Females	5	4	4
Males	3	3	2
Age (mean and range)	41 (30–54)	37 (26–48)	38 (30–45)

Randomization and blinding

Supervisors and provers were blinded to the nature of the homeopathic medicines used and to the proportion of placebo. Randomization, with the aim to minimize the differences among groups by equally distributing people among all the trial arms, was performed as follows: verum and placebo preparations were provided in 10 ml bottles, they were indistinguishable by colour, taste and smell. They were numerically coded by the coordinator and delivered to each supervisor who blindly and randomly distributed them to provers (each prover chose a bottle from a box). Coding and assignment were known only to the coordinator.

Collecting, elaborating data and outcome measure

Each prover recorded in the diary, indicating time, day and duration, the following:

- Existing symptoms showing increase in intensity and/or duration (common symptoms).
- Previous symptoms that had not occurred for at least 1 year (old symptoms).
- Current symptoms that disappeared during the proving (cured).
- New symptoms, unfamiliar to the prover.
- Exceptional symptom: a new or unusual symptom concerning intensity and/or duration.

The analyst evaluated data in order to measure possible differences concerning the number of symptoms (total or divided by category) between placebo and verum groups. The analyst received data from the coordinator in tables reporting only the number of symptoms in each category or class or group, excluding dreams. To increase the statistical power each verum was compared to the pooled placebo group combining groups from the two trials. Each placebo group contained three people, verum 8 or 7. Combining placebo, the size of groups was comparable and, therefore, the statistical power higher. Such pooling is permissible when the analyst does not look for the quality of the symptoms, or how much placebo symptoms resemble the verum ones.

Standard statistical methods were used:

- Student *t*-test was used to compare data means (number of symptoms/prover) between two groups.
- When data (symptoms) were distributed into categories (classes) a bivariate tabular analysis was performed and the χ^2 test applied.
- Confidence interval were analysed when permitted by the amount of data.
- Cramer's V coefficient was calculated, when permitted, for the distribution with largest χ^2.

The 'null' hypothesis assumed homeopathic potencies to be identical to placebo. If this was correct:

- the two groups (verum and placebo) should provide a similar number of symptoms/prover;
- the two variables (symptoms/classes) and groups (placebo or verum) should be independent, and symptoms distributed into the considered categories in numbers similar to the expected values;
- Cramer's V, (a measure of the degree of association between the variables in the bivariate table) should be zero;
- the categories of symptoms (physical, mental etc) and the time course of their appearance in the two groups should be similar.

When a statistically significant difference between data was observed by χ^2 analysis, further statistical control of homogeneity was performed. The test for homogeneity answers the proposition that several individuals into a population are homogeneous with respect to some characteristic.

Results

Demographics

Subjects in the three groups (verum-1, verum-2, pooled placebo) were similar (Table 1).

Total symptoms

Table 2 shows the total symptoms and symptoms/prover for both provings. Verum-2 (*Hydrogenium peroxidatum*) and, to higher extent, verum-1 (*Etna lava*) provers produced more symptoms than placebo provers.

These differences were significant for placebo *vs* verum-1 at $P<0.05$, for placebo *vs* verum-2 at 0.05 at $P<0.1$. According to the 'null' hypothesis, verum and placebo should provide a similar number of symptoms/prover, but placebo produced fewer symptoms when compared to verum groups and the difference was statistically significant at least for one of the comparisons (Table 2).

Total symptom distribution

Table 3 shows symptoms by type and characteristic. Data was normally distributed. Verum symptom distribution was similar for both provings; a preponderance of the category 'new symptoms' (46% and 44%) with a noticeable number of 'exceptional symptoms' (13% and 15.5%, respectively): verum provers experienced about 59% of symptoms as unfamiliar (new or exceptional), whereas in placebo groups those categories represented 35% of the total notes (only 1% in the category 'exceptional' symptoms). 'Common symptoms ameliorated' represented 51% of the total in placebo groups but 17.5% in the verum groups; among the other categories were recorded 7% of cured symptoms for placebo, 3% and 4.5% in verum. 'Old symptoms' (previous symptoms that have not occurred for at least one year): were lower in the placebo group.

Verum-1 and placebo confidence intervals were between 0 and 1 and did not overlap for any class. For verum-2 and placebo common and new symptoms confidence intervals did not overlap, but cured and old symptom class overlapped at the 99% level. Corresponding 95% confidence level did not overlap in class (data not shown) (Table 3).

Chi square analysis of data, performed by a bivariate table of number of symptoms in each category, showed verum-1 (*Etna Lava*) or verum-2 (*Hydrogenium peroxidatum*) and placebo group, to be different at very high level of confidence ($P<0.001$, $\chi^2_1 = 61.37$, $\chi^2_2 = 48.52$). The overall differences in symptom distribution were statistically very significant thus the null hypothesis rejected. χ^2 analyses gave a rough estimation of the weight of single symptom categories in the results. Larger χ^2 values were found for common ($\chi^2_1 = 35.80$; $\chi^2_2 = 27.11$) and exceptional symptoms ($\chi^2_1 = 9.90$; $\chi^2_2 = 11.97$): placebo experienced more common symptoms but very few exceptional ones compared to verum; 'old symptoms' ($\chi^2_1 = 7.64$; $\chi^2_2 = 6.28$) were also distributed differently between placebo and verum.

The correlation indexes, Cramer's V, were 0.393 and 0.404 for verum-1 and verum-2 versus placebo, respectively. This index, when >0 (up to 1) indicates the tendency of the two variables (groups and symptom distribution) to be dependent. Our data showed a good level of correlation. Homogeneity test on single categories, performed by analysing data randomly selected from each group, allows us to conclude that in all the considered categories except exceptional and cured symptoms, data were homogeneous concerning distribution among group

Table 2 Total recorded symptoms, symptoms/prover into the three different groups and statistical significance (student *t*-test)

	Placebo	*Verum-1 Etna Lava*	*Verum-2 Hydrogenium peroxidatum*
Total symptoms	108	377	189
Mean (symptoms/prover) ± SE	18.00 ± 3.76	47.12 ± 5.85	27.00 ± 1.05
Significance level for the mean differences	$P<0.05$ (placebo *vs Etna lava*) $0.05<P<0.1$ (placebo *vs Hydrogenium peroxidatum*)		

individuals (data not shown). Results from homogeneity tests increased the power of statistical analysis on those categories showing the largest χ^2 values ('common >' and old symptoms).

Symptom distribution into repertory categories

When symptoms were analysed respect to the distribution by repertory categories,[17,18] some categories were found to be richer than others with respect to the number of symptoms (Table 4). The 'mental' category, for example, showed differences between groups: placebo volunteers registered more than 30% of symptoms as mental, compared to verum groups (24% and 18%, respectively). When "mental" symptoms were analysed for their distribution by predefined classes, statistically significant differences were observed between placebo and verum groups: Fig. 1 shows mental symptoms by classes. For placebo the recorded mental symptoms were in the category "common symptoms improved" in more than 50% of cases; with only 26% of new symptoms and no exceptional ones, whereas verum provers recorded 50% of symptoms as new. The overall symptom distribution was significant when analysed by the χ^2 test. The classes that mostly contributed to the large χ^2 values in both calculations were those in "common >", old and exceptional symptom categories. The repertory category "general" showed more symptoms in verum compared to the placebo group (4.63% placebo; 9.81% and 9.15% verum groups). Placebo provers recorded 100% of notes as "common symptoms improved". Verum provers only 21%. In many other repertory chapters the differences between the groups were as great: for example in the "extremities", which represented 6–10% of the total symptoms in every group, placebo showed 37.5% of common symptoms and no exceptional ones, compared to 15% and 19%, respectively, for the two verum groups.

Time course of symptoms

Fig. 2a shows the time course of symptoms after taking remedy: symptoms are reported by appearance and duration; a symptom appearing during a day and persisting for four days, is reported on all the days when it was experienced. Symptoms/prover/day were plotted against time. The figure shows the majority of symptoms appear and persist in the first few days of the proving in both verum groups (~50% during the first 10 days), they decreased over the following periods (~30%, days 11–20; ~12%, days 21–30; 5%, days 31–40). More than 50% of new symptomatology persisted for at least 6 days. Multiplying each symptom by its duration, the number of total symptoms tripled for verum-1 and increased 2.5 fold for verum-2. The time course was quite different for placebo provers (Fig. 2b): symptoms were registered constantly during the proving: they experienced 26% of symptoms during the first 10 days, 18% on days 11–20, 21%

Table 3 Symptoms distributions by classes, correspondent proportions (symptoms/total) and 99% confidence intervals for proportions

	Symptoms Etna Lava	*Proportions Etna Lava*	*Proportion confidence intervals 99% Etna Lava*	*Symptoms Hydrogenium peroxidatum*	*Proportions Hydrogenium peroxidatum*	*Proportion confidence intervals 99% Hydrogenium peroxidatum*	*Symptoms Placebo*	*Proportions Placebo*	*Proportion confidence intervals 99% Placebo*
Common >	68	0.18	0.013–0.230	32	0.17	0.142–0.197	55	0.51	0.386–0.634
Cured	11	0.03	0.0008–0.051	9	0.047	0.009–0.081	8	0.07	0.007–0.133
Old	75	0.20	0.147–0.253	36	0.19	0.116–0.263	8	0.07	0.007–0.133
New	174	0.46	0.394–0.526	83	0.44	0.347–0.533	35	0.34	0.226–0.340
Exceptional	49	0.13	0.085–0.174	29	0.153	0.083–0.226	2	0.01	n.d.*

*Not determined (too few symptoms).

Table 4 symptoms by repertory categories: numbers and percentages in each group: placebo, *Etna Lava*, *Hydrogenium peroxidatum* (*Hyd. Perox.*)

Category	*Symptoms Placebo*	*% Placebo*	*Symptoms verum -1 Etna Lava*	*% verum-1 Etna Lava*	*Symptoms verum -2 Hyd. perox.*	*% verum-2 Hyd. perox.*
Mind	34	31.48	94	24.93	35	18.5
Generals	5	4.63	37	9.81	18	9.5
Head	5	4.63	20	5.3	17	8.99
Eye	2	1.85	20	5.3	8	4.23
Ear	3	2.78	1	0.26	1	0.53
Nose	6	5.55	14	3.71	5	2.64
Face	4	3.71	16	4.24	8	4.23
Mouth	6	5.55	5	1.32	4	2.12
Theeth	0	0.00	2	0.53	1	0.53
Throat	5	4.63	2	0.53	9	4.76
Ext. T.	0	0.00	2	0.53	2	1.06
Stomach	6	5.55	26	6.89	16	8.46
Abdomen	0	0.00	13	3.45	9	4.76
Rectum	3	2.78	12	3.18	4	2.12
Stool	0	0.00	6	1.59	0	0.00
Bladder	1	0.92	10	2.65	1	0.53
Genitalia	5	4.63	15	3.98	3	1.58
Larynx	0	0.00	1	0.26	2	1.06
Cough	2	1.85	9	2.38	3	1.58
Chest	2	1.85	1	0.26	5	2.64
Extremities	10	9.26	22	5.83	19	10.05
Sleep	2	1.85	19	5.04	12	6.35
Chill	4	3.71	4	1.06	3	1.58
Fever	0	0.00	4	1.06	0	0.00
Skin	0	0.00	14	3.71	0	0.00
Back	3	2.78	8	2.12	4	2.12

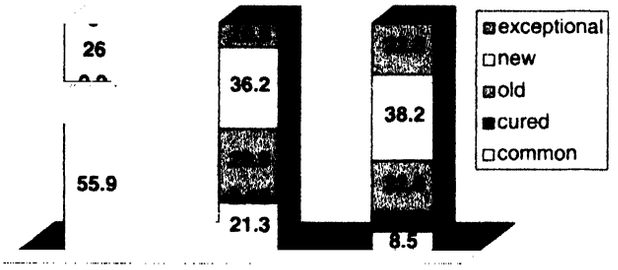

Figure 1 Percentages of mental symptoms as classified by classes (see materials and methods): placebo, verum-1 *(Etna Lava)* verum-2 *(Hydrogenium peroxidatum)*. From the bottom: common symptoms of unusual intensity and/or duration, old symptoms, cured symptoms, new symptoms, exceptional symptoms.

days 21–30 and 22% on days 31–40. Placebo provers continued to record symptoms of short duration (max 2 days) for the duration of the trials. Multiplying each placebo symptom by its duration increases total of symptoms by 1.3 fold.

Discussion

Many provings carried out during in recent years were unsuccessful in demonstrating a real effect of the homeopathic dilutions compared placebo or in confirming previous reported remedy pictures.[4,5,19 21] Different methodologies have been used: many different potencies, various periods of observation, different use of placebo symptoms and so on. Homeopathic research is at an early stage with most studies using small samples and many different measurement techniques, not permitting a systematic data evaluation. Similar limitations are seen with homeopathic clinical trials.[23 25]

We report a possible data collection and examination method. The study has to be considered as preliminary, because of the limited number of subjects, but it could be an important example of proving methodology and evaluation. Symptom evaluation showed that placebo produced fewer symptoms than verum: the difference was statistically significant and our data are in agreement with those reported by other groups.[22,6] Verum-2 group (*Hydrogenium peroxidatum*) did not show a highly significant difference in total number of notes when compared to placebo ($0.05 < P < 0.1$), but the symptom distribution showed that new symptomatology was present. The occurrence of a new pattern of symptoms is the foundation for building the remedy picture: the result indicates homeopathic remedies to be effective in perturbing the homeostasis of healthy subjects and their action to differ from placebo.

Distribution of symptoms by predefined classes (common, cured, old, new and exceptional symptoms) showed that placebo and verum provers represent two different groups: the differences cannot be explained by chance alone. Confidence intervals demonstrate significant differences of registered symptoms per class: the intervals did not overlap when the placebo and verum groups were compared. Evaluation of total and specific symptoms (mental, generals etc) showed placebo provers registered fewer new, but more common symptoms improved compared to verum:

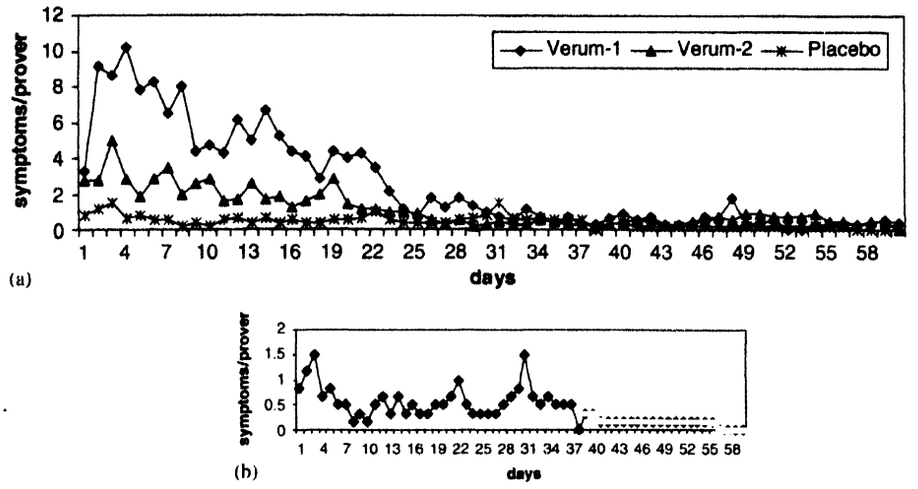

Figure 2 (a) Proving time courses. Incident and prevalent symptoms are included (verum-1 = *Etna Lava*; verum-2 = *Hydrogenium peroxidatum*) groups. Means symptoms per day per prover. (b) Placebo symptoms time course.

significant differences were observed in categories with larger number of symptoms. Placebo volunteers reported intensification in common symptomatology, but they didn't notice many strong or new symptoms.

The group taking verum experienced more "old symptoms" (which had not occurred for at least 1 year) than the placebo groups (particularly for mental symptoms). A possible interpretation of this finding may be that each person, even apparently healthy at the moment of the experiment, has his/her own complex pathobiographic history and the remedy, when effective, has the power to trigger an homeodynamic change in the direction of previous equilibria characterized by old symptoms, which have subsequently disappeared. Such an interpretation is consistent with a complexity theory interpretation of how the body functions and how the homeopathic medicines may work.[26,27] The return of old symptoms is familiar to homeopathic practitioners and is considered a positive sign during treatment: our data suggest that this type of symptom may discriminate between placebo and verum.

The placebo group experienced short-lived symptoms throughout the trials, whereas verum experienced persistent symptoms for the first 30 days. The results showed verum to trigger a quick effect, lasting 2–3 weeks. If confirmed by other studies, this observation would represent an important methodological suggestion, avoiding unnecessarily long observations. The fact that, all provers returned to baseline within 32 days is important for ethical reasons. The constancy in number and duration of symptoms in the placebo group confirms the non-specificity of the experience in the latter group.

In conclusion, we have shown a particular difference between placebo and verum in pathogenic homeopathic trials. More extensive studies are needed to confirm the specificity and validity of the procedure. More data from more provers could statistically validate some of the differences. Further analysis will be necessary to define the remedy pictures and homeopathic usage of the substances. If other similar studies are conducted and data collected following standardized and controlled methodologies will be useful to the whole homeopathic community: different comparative studies will be possible and their statistical significance evaluable.

Acknowledgements

Authors thank UNDA-Cemon- Grumo Nevano Italy for remedy preparations. Special thanks to supervisors, doctors: Massimo Beghella, Paola Belli, Armida Rebuffi, Andreina Fossati, Giusi Manuele.

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