

Homeopathic Pathogenetic Trials Produce Specific Symptoms Different from Placebo

Short Title: Homeopathic Pathogenetic Trial

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Abstract

Homeopathy uses information gathered from healthy volunteers taking homeopathic substances (pathogenetic trials) for clinical treatment. It is controversial whether such studies produce symptoms different from those produced by placebo.

Objective: To test whether homeopathic preparations produce different symptoms than placebo in healthy volunteers

Methods: Three armed, double-blind, placebo controlled randomised experimental pathogenetic study in 25 healthy volunteers who took either one of two homeopathic remedies, natrum muriaticum and arsenicum album in 30CH or identical placebo.

Main outcome was number of remedy specific symptoms per group.

Results: On average, 6 symptoms typical for arsenicum album were experienced by participants taking ars. alb., 5 symptoms typical for natrum muriaticum by those taking nat. mur, and 11 non-specific symptoms by those in the placebo group. Differences were significant overall ($p = 0.0002$, Kruskal Wallis) and significantly different from placebo ($p = 0.001$, Mann-Whitney).

Conclusion: Homeopathic remedies produce different symptoms than placebo.

Key words: homeopathy, placebo, double-blind, RCT, pathogenetic trial

Zusammenfassung

In der Homöopathie werden Symptome für die Therapie verwendet, die von gesunden Freiwilligen bei der Einnahme homöopathischer Substanzen beobachtet wurden. Es ist unklar, ob diese Symptome sich von Placebosymptomen unterscheiden.

Ziel: Untersuchung der Frage, ob Arzneimittelsymptome und Placebosymptome bei gesunden Freiwilligen unterscheidbar sind.

Methode: drei-armige, doppelblinde, placebokontrollierte, randomisierte, experimentelle Arzneimittelprüfung an 25 gesunden Freiwilligen, die entweder zwei homöopathische Arzneien, Arsenicum album oder Natrium muriaticum jeweils in CH30 einnahmen, oder ununterscheidbares Placebo. Zielkriterium war die Zahl der arzneimitteltypischen Symptome je Gruppe.

Ergebnisse: Personen, die ars. alb. einnahmen berichteten im Durchschnitt 6 Symptome, die für Arsen typisch sind. Personen, die nat mur einnahmen, berichteten durchschnittlich 5 Symptome, die für Natrium mur. typisch sind, und Placebo-Probanden berichteten durchschnittlich 11 Symptome die unspezifisch waren. Die Unterschiede waren signifikant zwischen den Gruppen ($p = 0.0002$, Kruskal Wallis) und die experimentellen Ergebnisse der homöopathischen Gruppen signifikant von Placebo verschieden ($p = 0.001$, separate Mann-Whitney Tests).

Schlussfolgerung. Homöopathische Arzneien erzeugen von Placebo verschiedene Symptome.

Stichwörter: Homöopathie, Placebo, doppelblind, randomisierte kontrollierte Studie, Arzneimittelprüfung

A Homeopathic Pathogenetic Trial Produced Specific Symptoms Different from Placebo

Introduction and Background

Homeopathy is considered a subtle form of placebo by most writers [1], although this claim is contested [2,3]. One of the pillars of homeopathic therapy and practice are homeopathic remedy provings or pathogenetic trials [4,5]. In such trials, healthy volunteers ingest a homeopathic substance and report the symptoms they experience. The collection of symptoms from such trials together with a host of toxicological information makes up the homeopathic materia medica, a collection of symptoms produced by substances in healthy individuals. This information is used for treating patients by matching the symptom pictures of patients to the symptoms a particular remedy has produced in volunteers over time. While some of these symptoms are commonplace, each remedy also has very particular, specific symptoms that define the particular pattern of a remedy. Homeopathy can be conceptualised as the art of pattern-recognition on the level of symptomatic changes. There are more than 1500 remedies in the homeopathic arsenal, about 150 of which are considered so called polychrests, because they can be used for different and often chronic diseases. Most of them date back to Hahnemann, the founder of homeopathy, himself and have been applied and tested again and again. However, rigorous pathogenetic trials have been mostly inconclusive so far [6-10].

We have reported previously on a new method of combining the quantitative approach of science with the qualitative approach used by homeopathy [11] of collecting many individual, idiosyncratic symptoms [12,13]. We were able to show in those pilot studies that homeopathic remedies seem to produce symptoms which are typical for the remedy and distinct from non-specific placebo symptoms, and that in tendency such typical symptoms can be seen more frequently in the group receiving homeopathic remedies. We recently replicated our findings in two separate studies that were analysed conjointly. One of the studies tested two remedies against placebo, the other study used a two armed design, testing the same remedy as in one of the arms of the three armed study against placebo. Selection of the remedies, as well as all methods, was strictly blinded. When analysing the remedy that was common to both studies against placebo, we found significantly more symptoms specific for that remedy in the remedy group than in the placebo group. This was the first time such a clear cut result was seen in a recent, rigorous study [14].

Since the results of our first pilot studies were inconclusive, and some colleagues pointed out that this may have been due to the fact that we had used lesser known and not well studied remedies, and since the remedies used in the second study were new ones, we decided to use major homeopathic polychrests, well known and frequently used remedies. The materia medica of these remedies is considered complete, hence not many new symptoms are to be expected in replication studies.

The study followed the design and the arguments published previously [13]. We wanted to study the hypothesis, whether, using such a methodology, homeopathic remedies administered in an ultramolecular dose, i.e. with no active molecules present, would still produce symptoms different from placebo.

Method

Healthy volunteers, medical doctors participating in a homeopathic training course offered by the German Association of Homeopathic Doctors (Zentralverein Deutscher Homöopathischer Ärzte), were invited to participate in a Homeopathic Pathogenetic Trial (HPT), as part of their training. As the participants were all medical doctors and the substance used was diluted well beyond Avogadro's number, the study was considered a safe medical self-experiment. Previous ethical advice by a specialised lawyer to the Association responsible for conducting these courses and the ethical committee of the University Hospital of Freiburg had resulted in the generic information that such pathogenetic trials, conducted on volunteer medical doctors, are deemed medical self-experiments and hence need not undergo separate ethical scrutiny each time. Conducting such HPTs for training and self-experience purposes has been part of the training to become a homeopathic doctor in Germany and many other countries at least since the training had been formalised in the decades following the Second World War. The procedure has been defined in a consensus protocol recently, which was adopted in the present study [15]. Occasionally, such as here, these experiments have been used for scientific data collection in the framework of a rigorous study. Thus, participants of the training course, all medical doctors with full medical training and with a licence to practice, were invited to participate. They were, of course, free to not participate or to refuse the usage of their data for scientific purposes. They knew that they would then receive either a homeopathic remedy unknown to them and to the proving director, or placebo. They were not told the chance to receive either one or the other.

Potential participants had to be medical doctors of the training program and had to give informed consent. They were excluded if any of the following exclusion criteria were present:

- acute illness
- chronic disease necessitating regular medication
- intake of conventional medication except contraceptives
- pregnancy or nursing
- extraordinary strain from family or job demands
- intake of any homeopathic remedies at time of trial
- intake of homeopathic remedies at C30 up to 4 weeks previously
- intake of homeopathic remedies at C200 up to 2 months previously
- intake of homeopathic remedies at C1.000 or higher up to 3 months previously.

Twenty five out of 59 course participants having given consent were randomised to receive either one of two homeopathic remedies, natrum muriaticum or arsenicum album, chosen randomly from a predetermined list of 20 remedies by an independent pharmacist despatching the substances, or an identical placebo. The list contained the names of remedies that are frequently used in homeopathic practice and whose remedy pictures are taught on the course. They are well known and widely applicable: aloe, apis, arsenicum album, aurum metallicum, aurum muriaticum, bufo, carbo vegetabilis, causticum, china, hyoscyamus, ignatia, kalium carbonicum, lycopodium, mercurius, natrum muriaticum, nux vomica, opium, platina, pulsatilla, thuja. The list of remedies was only known to the study director (HM) and the pharmacist, not to the participants, and not to the study team (HW, RS).

Thus, all participants, the study director (HM) and other personnel involved with the administration of substances were blind as to the precise name of the remedies administered and group allocation. Substances were prepared freshly by Dolisos homeopathic pharmacy, Lausanne, Switzerland, according to the European Homeopathic Pharmacopea, and sent in numbered containers to the study site. The randomisation code was created by an independent researcher (RS) from the random algorithm of RITA (Randomization in Treatment Arms) [16]. The code contained three group assignments with random numbers that were used to choose from the containers sent by the pharmacy. The code was kept safely by the study centre. The substances were prepared in CH30, a potency which had been diluted and succussed (i.e. heavily shaken) 30 times, in a separate glass vial with each dilution step, at a ratio of 1:100. They were then sprinkled over sugar globules, as is the dispensing rule. A potency of CH30 corresponds to a dilution of 10^{-60} (note that this is a dilution well beyond Avogadro's number which is 6.023×10^{23} , the number of molecules in one mol of substance; hence a dilution beyond 10^{23} is not expected, statistically, to contain any molecules). Placebo was sprinkled with the same amount and batch of alcohol, which is used as the carrier for the homeopathic production process.

Participants were advised to take 5 globules on the first day, 2 * 5 globules on the second day, or until symptoms appeared and then stop intake. Symptoms were observed for two more days, i.e. four days following ingestion. Symptoms were noted down by participants into an unstructured diary, and verified by personal interviews with the proving director each day. After data collection, all symptoms across all subjects were collated according to the familiar head-to-foot- scheme. This is a scheme known from homeopathic repertories (i.e. books that are meant to help find the right remedy by ordering symptoms and listing all potential remedies associated with these symptoms). It starts with mental symptoms, followed by symptoms experienced in the head, in eyes, ears, mouth and so forth down the anatomical locations of the body and ends with general symptoms such as feelings of heat or cold. That way, all symptoms were decontextualised from the original volunteer experiencing it and broken down in units familiar to homeopathic practice.

Finally, a materia medica expert otherwise unconnected with the study was given the list of symptoms, ordered according to the head-to-foot scheme, and the names of the remedies tested. The expert was blind to group allocation, and he was not given the original protocols, but a collated list of symptoms which did not allow him to attribute symptoms to individuals, nor to groups. The expert used a commonly used and commercially available computer repertorisation program (Synthesis by Archibel, Namur, Belgium) to decide for each symptom, whether it is typical for one of the two remedies tested or not. Note that through this method it was impossible for the materia-medica expert to second guess which volunteer might have produced which series of symptoms. He was strictly bound to make a decision for each individual symptom, irrespective of other symptoms.

This procedure yielded our final outcome parameter: The number of symptoms typical for each remedy. This, and the number of untypical symptoms was calculated and submitted to non-parametric statistical testing, using SPSS.

Results

Altogether, 25 volunteers, 6 men and 19 women with a mean age of 42.3 years (standard deviation 6.58 years), all medical doctors, participated in the experiment. Ten were randomised to receive natrum muriaticum, eight to receive arsenicum album, and seven to placebo. They experienced altogether 165 symptoms over the course of four days. On average they reported 6 symptoms when taking arsenicum album, 5 symptoms when taking natrum muriaticum and 11 symptoms when taking placebo.

Place figure and table about here

The results are presented in the figure, and a selection of typical symptoms are presented in the table. As can be seen, symptoms typical for the respective remedy were more frequent both in the natrum muriaticum group and in the arsenicum group, while non-specific symptoms were more frequent in the placebo group. A non-parametric Kruskal Wallis analysis showed significant differences between groups ($p = 0.0002$), and a pre-planned separate Mann-Whitney tests confirmed that significantly more specific symptoms ($p < 0.001$) were observed in the respective groups compared with the placebo control group.

Discussion

To our knowledge this is the first time that in a homeopathic pathogenetic trial clear and statistically significant differences could be found in symptoms specific for a remedy between placebo and treatment group, using classical homeopathic remedies and apart from a similar result we found with new remedies [14]. Please observe that the *overall number of all symptoms* was roughly the same in the homeopathic groups and nearly twice as high in the placebo group, a difference that is obvious but not statistically significant. The statistical difference is only obvious if symptoms *specific* for the remedy in question are counted. What is interesting in this study is the fact that there were virtually no specific symptoms in the placebo group, and no cross-specificity in the two remedy groups, i.e. symptoms that are typical for the other remedy tested, as we found in our previous studies [12-14]. This may have to do with the fact that these well known remedies have been repeatedly used and tested, such that it is unlikely that new symptoms would arise. Thus the margin for insecurity on part of the materia medica expert was smaller and made it easier to judge the symptoms. Since both remedies have well defined and quite distinct remedy pictures, it was easier to not confuse them.

Other rigorous studies have not found a lot of indications that homeopathic remedies produce anything different from placebo symptoms [6,7,17-19]. However, these studies used a much cruder approach to data collection, in using predetermined categories of symptoms or global definitions as outcome parameters. In the study reported here, we did not restrict the variability of data. In fact we encouraged participants to be as precise with their experiential description as possible, collecting a host of qualitative data in the diaries. They were converted into quantitative data only at the final step, where the materia medica expert had to make a decision as to whether a particular symptom was a symptom typical for a particular remedy or not.

The latter is clearly the weak link in the methodology, as the result is only as good as the materia medica expert's skill. However, the materia medica expert used a standard computer software repertory that is used in homeopathic practice a lot and that

contains all symptoms of all remedies, a reverse version of the homeopathic materia medica. Hence, this final step is very close to standard homeopathic practice and thus ecologically valid, if not completely ideal. We feel that our method offers a benefit over methods hitherto practised. It is faithful to the wide variability and phenomenology observed in homeopathic practice, while at the same time employing the rigour of modern experimental methodology. It might be used to conduct a series of such studies, which would produce essentially similar databases, namely number of symptoms typical for a remedy tested. Such data could be accumulated across studies, independent of remedies tested, and then pooled for final analyses.

It goes without saying, though, that such a method is only applicable, where a remedy picture of a substance has already been worked out through traditional HPT methodology and won't be useful for detecting new remedy pictures or in remedies with limited information. However, where such remedy pictures are known, it is a powerful method for re-proving and for using the generic set-up of a HPT for further experimentation.

Our results are unlikely to be due to bias or fraud: Volunteers and investigators did not know which remedies were tested. Hence it was not possible to produce the "correct" symptoms by suggestion or fake. Everyone involved in the trial itself was blind as to group allocation. Hence even if the tested remedies had been known, it would not have been possible to cheat, as no one knew which person was receiving which substance. Treatment and control substances were absolutely identical in appearance and taste, the only difference being the potentisation process originating from two separate substances. The products were freshly produced by a well known homeopathic pharmacy, according to legal standards applicable in Europe. They were dispatched in coded containers such that no inference could be made from them. The randomisation code was concealed such that nobody involved in the trial had anything to do with the creation of this code or the creation of the experimental groups, or had access to the code. The materia medica expert who determined whether a certain symptom was typical for one of the two remedies or not, was blind as to group allocation, and otherwise not involved with the organisation or conduct of the study. The only way this person could have cheated would have been by having access to the code and coding symptoms accordingly. This was impossible, as the code existed only in its full version - i.e. allocation of code numbering to remedies - at the research centre and was only fully revealed once the database of symptoms was classified by the materia medica expert and the statistical analysis had been done blindly. Thus, to the best of our knowledge these data are valid, if surprising.

One might argue that a lot of HPTs are being conducted in the context of such trainings, and hence just by chance one might pick the right symptoms in the right group. This is true. But one would have to consider the counterargument that, if fully blinded, the chances to experience just those symptoms that count as symptoms typical for one remedy, are very small, considering the host of symptoms one might experience. The gist of specific homeopathic symptoms is that they are quite unusual and distinct (see table). For instance, a typical symptom of *natrum muriaticum* might be bleeding cracks in the lips, or the unwillingness to talk to someone about one's problems and find consolation, or feeling better when fasting the whole day. While these symptoms are not infrequent, they would have to be rather new and unusual in a trial participant who is otherwise healthy in order to count as remedy symptoms. Each remedy has such typical symptoms associated with it. To experience just these symptoms by chance in

the right group, while otherwise healthy, is a very unlikely occurrence. It is difficult to quantify this as no one knows the baseline probability for such occurrences. Just how unlikely our result is by chance is quantified by the omnibus statistical test we used, namely 2 in 10.000. If one wants to use the more conservative testing of single groups against placebo and correct for multiple testing it would still be a small chance of 2 in 1.000. While chance can never be completely ruled out by research, we feel that we have produced valid data that show that homeopathic remedies administered to healthy volunteers can, at least sometimes, produce symptoms qualitatively different from symptoms produced by placebo in the same study and typical for the remedy tested.

We conclude, then, the jury is still open, whether homeopathy is only placebo or more. Our data suggest it is not placebo. They encourage an in-depth scrutiny.

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Competing Interest:

None

Author Contributions:

HW developed the design of this study, oversaw the study process and wrote the final manuscript.

RS did the statistical analysis, wrote parts of the manuscript, participated in discussion of the data and editing of the final manuscript.

HM organised the study and the data collection process, as well as the qualitative analysis of the study.

Figure – Mean number of symptoms (95% confidence intervals) specific for arsenic or natrium, respectively, and non-specific symptoms in the three experimental groups

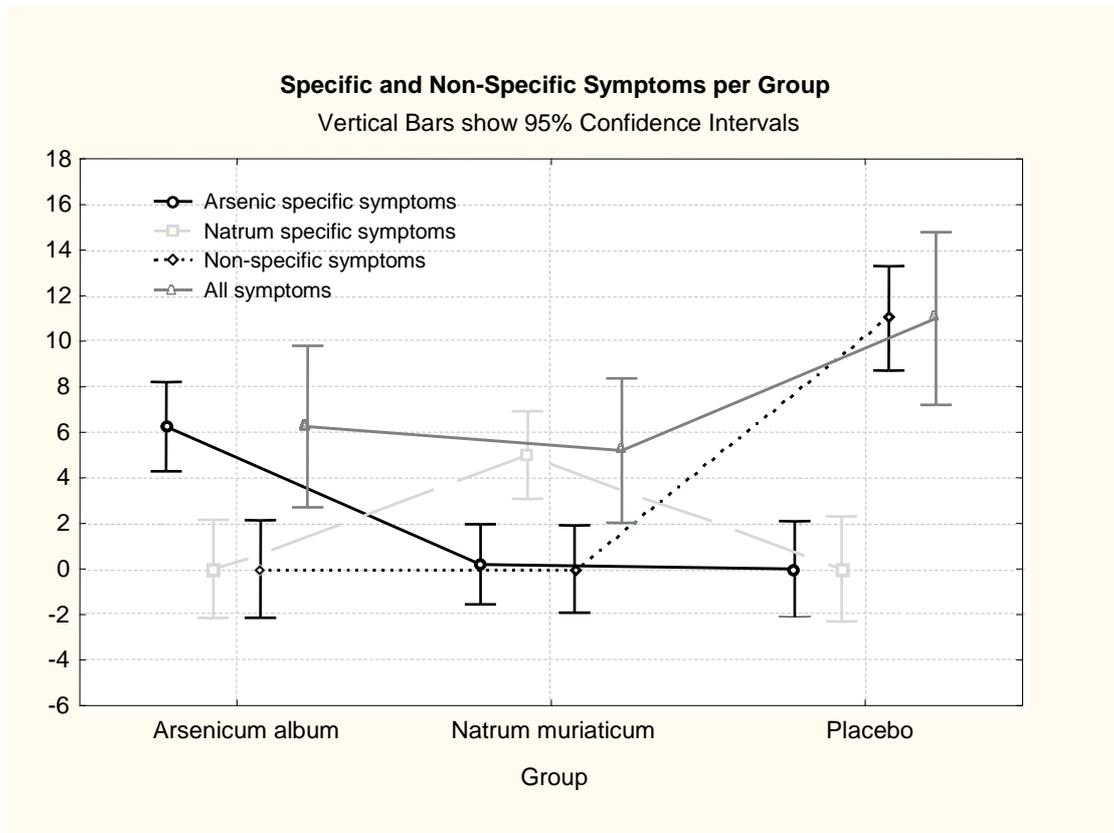


Table – Samples of symptoms as described by volunteers in different groups – representative examples ordered according to the traditional head-to-foot scheme

Symptoms Typical for Arsenicum Album	
Mind	Strange restlessness; nearly incapable to correctly guess time or duration. I come an hour earlier for teaching, rush through with my material and then have lots of time left (very unusual and disturbing for me)
Mind	I have misplaced or forgotten things continuously, glasses, books, etc.
Mind	Did not know, when writing, how words are spelled – extremely many spelling mistakes
Mind	After the end of the course unable to remember for a short while where I had parked my car – slight mental disturbance
Throat	Increased desire to swallow, feeling of dryness in throat, thirst
Stomach	Canine hunger
Bladder	Again I notice a lack of desire to urinate; even the cup of coffee I had at 3:30 pm that normally brings me to the toilet within a short period of time had no effect whatsoever
Stool	Gushing stool, diarrhea like, stinking, no pain

Symptoms Typical for Natrium muriaticum	
Mind	Very clear, no wavering of attention
Mind	Difficulties concentrating with letters, and difficulties with the alphabet
Mind	Very loquacious all day
Vertigo	Slight vertigo when seated, gone after 3 pm
Head	Tearing pain in scalp, right side, parietal, upper frontal part, worse pressure on skin, but no „headache“, better next day
Eye	Twitching right eye, for 2 minutes
Nose	Sneezing, three times (described by multiple participants)
Mouth	Bad odour, like from garlic
Stomach	Surprising lack of appetite, feeling of fullness
Female Genitals	Cramping, strong pain in lower abdomen, like labour, getting stronger; hot bottle and later movement improve pain; then, when sitting during the course, increasing pain; ibuprofen 400 helps; minor bleeding

Symptoms with Placebo

Mind	Difficulty concentrating
Mind	Slight problems with language, stuttering
Mind	My inner hectic feeling has gone completely
Mind	I make mistakes, loose my stuff, afterwards feeling to be flying; I am thinking: will the others notice? Deaf; I loose oversight; clumsy when eating
Head	Very strong headache, frontal, extending into eyes with nausea
Head	Headache, right, frontal, dull, pressing, extending to upper mandibules
Eyes	Both eyes red, right worse than left
Vision	Worse when reading or writing
Vision	Improved again
Ears	Left ear suddenly free; I had not realised that it was blocked
Ear	Pressure in right each
Nose	Tickling, coryza, right worse than left