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# Prognostic factor research in Homoeopathy

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## ABSTRACT

Validation of homoeopathic medicines is about validating effectiveness in individual cases. Homoeopathic practitioners base their expectation that a medicine will work on the experience that specific symptoms of the patient indicate specific medicines. The prevalence of such symptoms is higher in a population responding well to a specific medicine than in the remainder of the population. This principle has a solid mathematical foundation in Bayes' theorem, identifies homoeopathic symptoms as prognostic factors, and offers an interesting perspective of individualized research. This kind of research depends on recording symptoms and results of treatment. An important challenge in this research is establishing causality between medicine and improved health. Prognostic factor research could become one of the main pillars of Homoeopathy's scientific identity.

**Keywords:** Bayes' theorem, Causality, Homoeopathy, Prognostic factor

## INTRODUCTION

Treating a patient is, in fact, forecasting his future: You predict that the therapy you prescribe will improve his health. At least, that is what the patient may reasonably expect. In our article "Homoeopathy: Discussion on Scientific Validation" elsewhere in this issue, we claimed that there is a difference between allopathic and homoeopathic prescribing in this respect. When a doctor states that an allopathic (conventional) medicine will work, he refers to a considerable amount of certainty that the medicine works better than a placebo in the average patient, not excluded from randomized controlled trials (RCTs) and provided his/her diagnosis is correct.[1] It is impossible to tell if the patient in front of him/her is that patient, but probably he/she is not. However, if a doctor with adequate training prescribes a homoeopathic medicine he/she can give an estimate of the chance the medicine will work for the patient in front of him, based on the symptoms this individual presents. This may be no more than a chance of, say, 60% with a considerable amount of uncertainty, but it is relevant for the individual patient. It is also not possible to know if this cure is due to the effect of the prescribed homoeopathic medicine or other factors such as spontaneous recovery or placebo-effect. Apparently it is difficult to combine scientific validity with clinical relevance, but clinical relevance is becoming more important. This is partly due to recent developments in genetics, pointing to the fact that a medicine should fit the patient, not only the complaint.[2] This is an interesting opportunity for



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Homoeopathy because individualized/personalized medicine is the essence of Homoeopathy. We have two centuries of experience in relating symptoms and personal characteristics to specific medicines.

Conventional medicine, on the other hand, has more knowledge about epidemiological research. There are several epidemiological techniques that can be useful for Homoeopathy, such as diagnosis and prognosis research.[3] The technique of diagnosis research is straightforward and is easily applicable on homoeopathic symptoms. Results can be translated into repertory symptom-rubrics, repairing the systematic mistakes that hamper the reliability of present repertories.

## Handling Variation

We have to reestablish practice experience as a scientific entity, but first we must realize the shortcomings of this knowledge and understand why we need statistics. In "Homoeopathy: Discussion on scientific validation", we demonstrated the influence of variation on the knowledge of individual doctors. A group of 15 experienced doctors in the Netherlands discussed their assembled 23 best chronic cases regarding the homoeopathic medicine *Sulphur*, with improvement lasting longer than 1 year.[4] All doctors agreed that there was no doubt that *Sulphur* was responsible for the cure in all cases. Only one of 23 patients (4%) had the symptom "Fear of death," but for the doctor treating this patient the symptom "Fear of death" was related to *Sulphur* because 50% of his two best *Sulphur* cases showed the symptom. The other doctors did not relate "Fear of death" to *Sulphur* because none of their *Sulphur* cases had the symptom.

This example of a consensus meeting of experienced homoeopathic doctors shows two things: (1) If a homoeopathic doctor sees a specific symptom in a cured case, he/she relates the symptom to the homoeopathic medicine that caused the cure, and he/she will think of that medicine when that specific symptom is present in a next case. (2) Collecting a large number of cases makes sense: In this example, all 15 doctors learned something about the relationship between the symptom "Fear of death" and the homoeopathic medicine *Sulphur*; 14 doctors became aware that the symptom "Fear of death" does not totally exclude *Sulphur*, and the one doctor with the patient with Fear of death realized that this symptom does not clearly include *Sulphur*.

## Learning from Experience

By collecting a larger number of cases we know that the symptom "Fear of death" occurs in one in 23 (4.3%) cases of *Sulphur*, in statistical terms: The prevalence of the symptom "Fear of death" in the "*Sulphur*-population" is about 4%. This is still uncertain, and our certainty about this prevalence would have been greater if we had four patients with Fear of death in 100 *Sulphur* cases. This is why (homoeopathic) doctors should have some knowledge about statistics.

Does the symptom "Fear of death" indicate *Sulphur*? Will the patient with the symptom "Fear of death" have a greater chance of being cured by *Sulphur* than the patient without this symptom? The prevalence of 4% is not much if the prevalence would have been 50% we would definitely be more certain. Why? Because our experience tells us that the symptom "Fear of death" appears in much less than half of all our patients. It is, however, hard to estimate the prevalence of "Fear of death" in our practice population. We actually asked our 15 participating doctors to estimate the prevalence of "Fear of death" in their practice populations; their estimations varied between 1% and 20%.

Now, we arrive at a surprising conclusion: Doctors are intuitively statisticians; they have an idea about how often symptoms occur in their practice populations.[5] Moreover, they also have an idea about the prevalence of symptoms in populations that respond well to medicines they prescribe, based on their experience. As we saw above, these estimates can be wrong because of statistical variation, but this is how Homoeopathy works: We learn from experience. The problem is accuracy, and we do not know how accurate our estimates are. For this purpose we need statistics.

When is a specific symptom an indication for a specific medicine? At first, doctors find it hard to answer this question, but if we persist the answer is like this: "If the prevalence of the symptom in the population that responds well to the specific medicine is greater than in the whole population." You may have to read this sentence several times, but this is the essence of Homoeopathy. Moreover, this is a quantitative statement, which can be confirmed or rejected by scientific research.

## Experience and Bayes' Theorem

It is an error to think that learning from experience has no relation with science. Experience in the past helps us to forecast the future; this is based on hard mathematics, expressed in a statistical formula named Bayes' theorem.[6] This theorem goes as follows:

Posterior odds = Likelihood ratio (LR) × prior odds

Odds = Chance/(1 − chance);
Chance = Odds/(1 + odds)

LR = (Prevalence in the target population)/(prevalence in the remainder of the population).

Bayes' formula means that the chance that a medicine works (posterior chance) increases if the prevalence of the symptom in the population that responded well to the medicine in the past is larger than the prevalence of the symptom in the remainder of the population, more so if this difference is larger. In this formula, "odds" is a bit awkward to handle, but the essence of the formula is the convenience of likelihood ratio (LR), because if LR >1, the odds and the chance that a medicine will work increases. This corresponds with the essence of Homoeopathy that the prevalence of the symptom in the population that responds well to the specific medicine should be greater than in the whole population. Table 1 shows how chance and odds are related to some values.

## Systematic Mistake in the Homoeopathic Repertories

Every homoeopathic practitioner has some doubts about homoeopathic repertories. We know that many larger rubrics (frequently occurring symptoms) are unreliable, especially because they contain all "polychrests" (the most prescribed medicines). As a result, computer-repertories offer the possibility to exclude polychrests from repertorization, but this solution is too rigorous: Frequently occurring symptoms can also indicate polychrests. The problem is caused by a systematic mistake in adding repertory-entries.[7]

A medicine is added to a repertory-rubric if it is seen in a proving or a cured case if it is seen repeatedly the grading of medicine will be increased to italics or bold type. The problem is that we prescribe some medicines very frequently, some less frequently, and some seldom. This does not influence the acceptance as a repertory-entry, nor the grading of the medicine. Intuitively, we can understand that this is not correct. If the symptom "Fear of death" is seen in one *Cenchris contortrix (Cench)* case and one *Sulphur* case, both medicines will be entered in plain type in this rubric following the present methodology. However, we know that *Sulphur* is much more frequently prescribed than *Cench*. In a prospective assessment of this symptom in the Netherlands, there were 88 *Sulphur* cases and four *Cench* cases and in each of both groups, there was one patient with Fear of death. Translating this into relative occurrence (= prevalence) of the symptom renders 1% "Fear of death" in the *Sulphur* population and 25% "Fear of death" in the *Cench* population. In this research project, we inquired 4094 patients about their "Fear of death," 158 patients (4%) were afraid of death [Table 2].

Above we mentioned another project in the Netherlands retrospectively assessing 23 *Sulphur* patients, with one patient (4%) with Fear of death. In a population of 23 *Sulphur* patients, 4% had Fear of death and in a population of 88 *Sulphur* patients, 1% had Fear of death. Again, we see the advantage of larger numbers: We can better estimate the prevalence of a symptom. The prevalence of Fear of death in the *Sulphur* population is probably between 1% and 4%, and probably less than the prevalence in the whole population of 4%. We can translate that into an LR <1. Intuitively and according to Bayes' theorem, this means that the chance that *Sulphur* will work becomes less if the patients have Fear of death! *Sulphur* should therefore not be included in the repertory rubric "Fear of death." *Cench* should

**Table 1: The relationship between chance and odds for some values**

| Chance (%) | Odds |
|---|---|
| 1 | 0.01 |
| 10 | 0.11 |
| 33.3 | 0.5 |
| 50 | 1 |
| 66.6 | 2 |
| 90 | 9 |
| 99 | 99 |

**Table 2: Absolute and relative occurrence (prevalence) of the symptom "Fear of death"**

| | Whole population | Sulphur | Cench. |
|---|---|---|---|
| Fear of death | 158 | 1 | 1 |
| Total (sub) population | 4094 | 88 | 4 |
| Prevalence | 4% | 1% | 25% |

be in this rubric, maybe even in a higher grade, despite the fact that there is only one case of *Cench* with Fear of death. We should collect more *Cench* cases, but a prevalence of 25% of "Fear of death" is remarkable. By the way, *Cench* is not included in this rubric in Kent's original repertory.

Our prognostic factor research on the symptom "Fear of death" confirms that polychrests are over-represented in repertory-rubrics. This is due to mere chance: If you prescribe a medicine frequently, sooner or later every symptom will turn up in a patient responding well to this medicine, more so in common symptoms (represented by large symptom-rubrics). In our assessment in 4094 patients, we found LRs <1 for *Natrum muriaticum*, *Pulsatilla*, and *Sulphur*. These medicines should be discarded from this rubric. Discarding all polychrests, however, would be a bad idea because we found LRs >1 for *Calcarea carbonica*, *Ignatia*, *Lachesis*, *Lycopodium*, *Nux vomica*, *Phosphorus*, and *Sepia*. For these medicines, the entries are rectified, but they should be downgraded to plain type.

This example demonstrates that we can greatly improve our repertories by prognostic factor research, i.e., the assessment of homoeopathic symptoms. Especially symptoms that occur in a considerable number of patients will become more accurate indicators for homoeopathic medicines, which will lead to considerable improvement of the effectiveness of Homoeopathy.

## Counting Cases

To increase the accuracy of our repertories, we have to record and count cases. To know the prevalence of a symptom such as "Fear of death," we have to ask every patient if he/she has a Fear of death. To know how many *Sulphur* patients have Fear of death, we must record that the patient had a good result on *Sulphur*.

After this procedure we conclude two things:

- The prevalence of a recorded symptom in the whole population
- The prevalence of a recorded symptom in "medicine-populations," populations responding well to specific medicines.

Now, we can calculate LRs for specific medicines for this symptom. Prognostic factor research is, in fact, very simple. It requires some discipline and some time to record symptoms and results rigorously in all patients. Our main concern is that the symptom is really there if we record it and not if we do not record it and that the medicine populations really consist of patients where the medicine actually caused the improvement.

## Recording Symptoms

Prospective recording of symptoms for research is mostly different from normal daily practice. In prospective research, you do not wait until the patient tells you the symptom spontaneously, but you take the initiative and ask about it. Imagine that you ask every patient if he/she is sensitive to injustice. Probably many patients will confirm this, much more then when you only note the symptom when it is mentioned spontaneously. This is because sensitivity to injustice is regarded as desirable. On the other hand, are you sure that every patient who is sensitive to injustice will tell you this spontaneously? Probably not, because many patients are not aware of their own mental characteristics.

To record all, but only those, patients with sensitivity to injustice, we need confirmatory questions, such as are you in your social group of, say, 20 people (class, club, etc.) the most sensitive to injustice? or "Do you organize protest meetings, write letters to politicians, etc.?"

## Cutoff Value

Many symptoms are not easy to check in prospective research, like "Being warm" in a warm country. There are persons who are more warm than others, and we have to find a "cutoff" value, when is the patient warm enough to be relevant as a homoeopathic symptom? Questions like "are you warmer than most people you know?" can help in this respect. Symptoms with a low cutoff value, so that, say, half of all patients confirm the symptom, are worthless because such symptoms do not differentiate between medicines.

The essence of a relevant homoeopathic symptom is a clear difference between the whole population and respective medicine populations. The higher this difference, the higher the LR. This is consistent with Hahnemann's aphorism 153 about peculiar symptoms because peculiarity is correlated with low prevalence.[8] As a rule of thumb we can say that symptoms with prevalence <20% in the whole population can be meaningful as a homoeopathic symptom. Peculiarity can also be defined by cutoff value: A common symptom such as headache can

become peculiar if the severity of the headache is present in only 1% of the population.

### Causal Relationship

If factors other than the prescribed medicine cured the patient, the symptoms of that patient should not be linked to that medicine. Doctors like to think that their therapy worked; a patient wants to please the doctor who is so friendly and tries so hard to cure him/her. The actual role of a medicine in a cure is often overestimated. For reliable information about a medicine, we should use only those cases that most likely responded well to that medicine.[9]

The best way to assess a causal relationship between cure and medicine is the RCT, but this method is not suited for individual cases. There are, however, tools to investigate the causal relationship between effect and medicine in individual cases, used to assess adverse effects of medicines. Such a tool is the Naranjo algorithm.[10] An obvious reason to suspect a causal link between an adverse effect and a medicine is a time-effect relationship, including repeated effect after repeated administration of the medicine. A strong argument to doubt a causal relationship is another explanation for the effect.

Homoeopathic cures have some characteristics that are unlikely for spontaneous recovery, such as an initial aggravation of complaints and a specific course of improvement, as formulated by the US pioneer Constantin Hering (1800–1880). The combination of Naranjo's algorithm and specific elements of homoeopathic cure enables us to increase certainty that the medicine caused the improvement of the patient. For establishing a causal relationship between cure and homoeopathic medicine, we can use an algorithm that combines Naranjo's algorithm with specific homoeopathic courses of improvement. This adapted algorithm is shown in the Appendix 1 but it is still in the process of validation by Clinical Data Working Group of the Homoeopathic Pharmacopoeia of the United States and in a PhD project. At the moment, the weighting of all items of this algorithm is based on a consensus procedure. It is not yet possible to define a minimum score establish a causal relationship in an individual case.

## DISCUSSION

Homoeopathy has a unique opportunity to develop its own scientific identity in achieving evidence-based personalized medicine while RCT evidence fails to serve the needs of the individual patient. We can use accepted scientific methods derived from diagnosis research. There is growing awareness that prognosis is more relevant than diagnosis.[11] Prognosis (consistent with diagnosis) is a probability that the medicine will work, not a certainty that it works better than placebo in the average patient.

For assessing probabilities, we need other scientific tools than for hypothesis testing. We can apply Bayes' theorem for this purpose, which is rapidly recognized in all fields of science and incorporated in many computer programs, especially expert systems. There is growing awareness that Bayes' theorem is a leading principle in medical knowledge.

Applying Bayes' theorem in Homoeopathy is straightforward: We have to assess the prevalence of homoeopathic symptoms in our whole population and in populations responding well to specific homoeopathic medicines. Defining the populations that respond well to specific medicines is still a challenge. We are in the process of adapting existing tools for establishing a causal relationship between effect and homoeopathic medicine. Being aware of the problem of causality and getting used to more systematic evaluation of causality is an essential part of our scientific development.

## CONCLUSION

Homoeopathy has a two-century tradition of personalized medicine. The uprising of personalized medicine in conventional care offers a golden opportunity for Homoeopathy to establish its own scientific identity that is exemplary for all medicines. We can keep doing what we usually do, but we have to do it more consciously.

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### Conflicts of Interest

There are no conflicts of interest.

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## Appendix 1: Reduced modified Naranjo criteria (see text)

| | Yes | No | Not sure or N/A |
|---|---|---|---|
| 1. Was there an improvement in the main symptom or condition for which the homoeopathic medicine was prescribed? | +2 | −1 | 0 |
| 2. Did the clinical improvement occur within a plausible timeframe relative to the drug intake? | +1 | −2 | 0 |
| 3. Was there an initial aggravation of symptoms? | +1 | 0 | 0 |
| 4. Did the effect encompass more than the main symptom or condition, (i.e. were other symptoms ultimately improved or changed)? | +1 | 0 | 0 |
| 5. Did overall wellbeing improve? | +1 | 0 | 0 |
| 6 (A). Direction of cure: did some symptoms improve in the opposite order of the development of symptoms of the disease? | +1 | 0 | 0 |
| 6 (B). Direction of cure: did at least two of the following aspects apply to the order of improvement of symptoms:<br>From organs of more importance to those of less importance<br>From deeper to more superficial aspects of the individual<br>From the top downwards | +1 | 0 | 0 |
| 7. Did "old symptoms" (defined as non-seasonal and non-cyclical symptoms that were previously thought to have resolved) reappear temporarily during the course of improvement? | +1 | 0 | 0 |
| 8. Are there alternate causes (other than the medicine) that –with a high probability- could have caused the improvement? (Consider known course of disease, other forms of treatment, and other clinically relevant interventions) | -3 | +1 | 0 |
| 9. Was the health improvement confirmed by any objective evidence? (e.g. lab test, clinical observation, etc.) | +2 | 0 | 0 |
| 10. Did repeat dosing, if conducted, create similar clinical improvement? | +1 | 0 | 0 |

**सारांश**

होम्योपैथिक औषधियों की मान्यता का आधार उनकी व्यक्तिगत प्रकरणों में प्रभावशीलता है। होम्योपैथिक चिकित्सक अपने अनुभव कि 'रोगी के विशिष्ट लक्षण विशिष्ट दवा की ओर सकेंत करते है' के आधार पर उम्मीद करते है कि यह दवा असर करेगी। इस तरह के विशिष्ट लक्षणों की उपस्थिति उन जन समूहों में अन्य बची हुई जनसंख्या से अधिक होती है जिन्हें उपयुक्त औषधि से लाभ मिला हो।

इस सिद्धांत का ठोस गणितीय आधार 'बायस प्रमेय' में है, जो कि होम्योपैथिक लक्षणों की पहचान एक भविष्य निर्धारक नैदानिक कारक के रूप में करता है और यह व्यक्ति आधारित अनुसन्धान के परिपेक्ष्य में एक रुचिकर प्रलोभन है।

इस तरह के शोध लक्षणों और उपचार के परिणामों के अभिलेखन पर निर्भर करते हैं व इनमें एक महत्वपूर्ण चुनौती चिकित्सा और स्वास्थ्य में सुधार के बीच करणीयता की स्थापना है। होम्योपैथी की वैज्ञानिक पहचान के लिए भविष्य निर्धारक नैदानिक कारक अनुसन्धान मुख्य स्तंभों में से एक बन सकता है।

## Investigación de factores pronósticos en homeopatía

**RESUMEN**

La validación de los medicamentos homeopáticos reside en demostrar su eficacia en casos individuales. Para los médicos homeópatas, la expectativa de que un medicamento funciona, se basa en la experiencia de que los síntomas específicos del paciente indican un medicamento específico. La prevalencia de estos síntomas es mayor en una población de responder bien a un medicamento específico que en el resto de la población. Este principio posee un fundamento matemático sólido en el teorema de Bayes donde identifica los síntomas homeopáticos como factores pronósticos y ofrece una interesante perspectiva de investigación individualizada. Este tipo de investigación depende del registro de los síntomas y los resultados del tratamiento. Un reto importante en esta investigación es establecer la causalidad entre el medicamento y la salud mejorada. La investigación de factores pronósticos puede convertirse en uno de los principales pilares de la identidad científica de la homeopatía.