

## ORIGINAL PAPER

# New repertory, new considerations

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**The criteria for entering medicines in repertory rubrics are unclear and partly incorrect. A new repertory should be based on clear and objective criteria.**

**Retrospective and prospective assessment of medicines and symptoms by the Dutch Committee for Methods and Validation gives an indication of the validity of existing repertory entries. Reliance on the experience of one expert is the cause of part of the shortcomings of the repertory. This experience is highly influenced by chance. Another part is due to the use of absolute rather than relative occurrence of symptoms. Yet another part is caused by not comparing prevalence in the population 'cured' by a medicine with the remainder of the population. In many cases we need better definitions of symptoms.**

**A clear protocol and prospective research could overcome many shortcomings of the repertory. Statistics help to get more objective criteria, but we still need to reach consensus about how to handle probabilities of outcomes of our assessments. *Homeopathy* (2008) 97, 16–21.**

**Keywords:** likelihood ratio; Bayesian analysis; repertory; clinical symptoms; expert opinion; probability

## Introduction

A repertory of homeopathic symptoms, such as Kent's, is an impressive work, but Kent's Repertory is now a century old. There are systematic mistakes in the existing repertory, for instance using absolute occurrences instead of relative, as we have previously pointed out.<sup>1,2</sup> If we were to start a new, to make a repertory according to modern standards, would this be the same repertory? We should start with a protocol, including rules covering which entries should be made, definitions of symptoms, methods of data gathering, reference standard (gold standard), handling of bias and of statistical uncertainty.

We cannot disregard the existing repertory, or the fast growing number of variations on Kent's original repertory. We all suspect that many entries in the repertory are wrong, but it is still unclear which and why. To get rid of old, and prevent new, false entries we need clear and objective criteria.

The problem is that expert opinion is one of the most important sources of the repertory. Medicine cannot do without it, but its validity is much criticised. We can estimate the value of expert opinion from a theoretical perspective using statistics and especially Bayes' theorem. This paper presents some points arising from preliminary results of a prospective assessment of the symptom 'Sensitive to injustice'. This is one of six symptoms we investigated. Our group is also organising consensus meetings retrospectively gathering best cases of the use of a single medicine by 10–20 experienced homeopaths.<sup>3</sup> Some of the retrospective and prospective data can be compared with each other and with entries in the existing repertory. The symptom 'Sensitive to injustice' was present in some of the retrospectively analysed medicines. In this paper we compare retrospective and prospective data with each other and with the existing repertory rubric.

There are many different versions of the symptom rubric 'Sensitive to injustice'. For this purpose we used RADAR-Synthesis version 8.1.40, 'modern to 1987', which is as follows:

Calcarea carbonica (Calc), **Causticum** (Caust), Cuprum (Cupr), Drosera (Dros), *Ignatia* (Ign), Mercurius (Merc), Nux-vomica (Nux-v), Sepia (Sep), **Staphisagria** (Staph), Veratrum album (Verat).

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The entry of *Ignatia* in Italics indicates that the symptom is a stronger indication for *Ignatia* than for the medicines in plain type. Entries in bold type indicate that the presence of the symptom is a strong indication for those medicines. The authors referenced are C.M. Boger, C. Coulter, Gallavardin, S. Hahnemann, O. Hansen, R. Sankaran, T. Smith and G. Vithoulkas. *Nux vomica* is attributed to Hahnemann.

If the patient presents an interesting symptom we consult the repertory to see which medicines could be indicated. The repertory entry of a particular medicine is, among others, based on the fact that the symptom is seen in former cases cured by that medicine. This means that experience from the past tells us what to expect in the case at hand. There is a sound statistical theory to back this procedure: the law of conditional probability. Reverend Thomas Bayes (1702–1761) stated this law as Bayes' theorem.<sup>4</sup> If we translate this theorem for homeopathy, we can calculate the (posterior) odds (and chance) that a medicine will work given the presence of a certain symptom, (see Box 1).

If we disregard the awkward handling of odds, the chances that the medicine will cure increases if a corresponding symptom has been seen in the past in cured cases. According to Bayes' theorem there is one vital condition: the cured population should be compared with the remainder of the population. If the prevalence of the symptom in the cured population is not larger than in the remainder of the population the probability that the symptom will cure is not increased. As yet, there is no comparison with the remainder of the population in the present repertory.

## Methods

Since 1997 we have organised retrospective evaluation of the 'best' cases of experienced homeopathic doctors (Materia Medica Validation) to learn how medicines could be successfully chosen and how we think. During these consensus meetings results of each case are evaluated using a modified GHHOS scale.<sup>5</sup> We use the nominal group method, known in the qualitative research as a method to reach consensus.<sup>6</sup>

Participants present their best cases concerning one medicine and discuss criteria to evaluate the prescription. Before this evaluation of cases we asked participants to estimate the prevalence of some symptoms, known as 'keynotes' for the given medicines. After evaluation of cases we have a (retrospective) indication about the prevalence of the most important symptoms of each medicine.

Since June 2004, in our prospective study (LR project), 10 experienced homeopathic doctors are gathering data on all new patients older than 2 years. The study will go on until December 2007. The symptom 'Sensitive to injustice' was one of six symptoms that were checked in all patients. The participating doctors defined the symptom as 'Sensitivity to injustice done towards others, resulting in subsequent behaviour like turning off the television, writing letters, protesting, etc', but clinical judgement prevails. A paper on vagueness of symptoms was prepared for this meeting.<sup>7</sup>

Training in the use of the GHHOS was given at the consensus meetings. Consensus was also reached about required follow-up before entering results in the database. Result GHHOS 2 was entered after at least 1 month after prescription, result GHHOS 3 or 4 after at least 6 months. Participants used database programmes to enter data. The co-ordinator (AR) used an Excel spreadsheet and the statistical programme Epi-info to evaluate results. All participants met twice a year after sending their data. Participants received feedback on their output during these meetings and by e-mail newsletter.

## Results

### Retrospective data

Bayes' theorem is a learning algorithm. We learn how to diagnose appendicitis in practice, after a few cases. We learn because we see certain symptoms in our appendicitis patients that we do not see in other patients. This implicit comparison between appendicitis patients and other patients can be translated explicitly into LR and then Bayes' formula can be applied.

### Box 1 Bayes theorem

Posterior odds = LR \* prior odds

LR = Likelihood Ratio = prevalence of the symptom in the population cured by the medicine divided by the prevalence in the remainder of the population.

Odds = chance / (1 - chance), and chance = odds / (1 + odds)

Example: If 40% of the patients who respond well to *Lachesis* are loquacious and the prevalence of the same symptom in the rest-population is 8%, LR = 5.

Suppose that you estimate the chance that *Lachesis* will work for the patient before you to be 10% (odds = 0.1/0.9) and then it appears that he/she is loquacious. If we apply Bayes' formula the chance for cure by *Lachesis* will increase to 36%:

Posterior odds = 5 × (1/9) = 0.555; posterior chance = 0.555 / 1.555 = 36%.

Ten years experience of *Materia Medica* validation tells us that homeopathic doctors are able to estimate occurrences of important symptoms. We were able to compare the estimates of six symptoms with the outcome of our later prospective assessment. There is interpersonal variation but the mean of all estimates agreed with the prospective outcome within a 5-10% interval. According to those estimates interesting (keynote) symptoms have prevalence in the whole population of 15% or less. The evaluation of more than 30 medicines also showed that most 'keynote symptoms' occur in less than 50% of our best cases concerning one medicine. As an example 'fear of dark' was present in only 5 out of the 12 best *Stramonium* cases (42%).

A symptom that occurs in 45% of the patients responding well to one medicine and in 15% of the remainder of the population has a moderate LR of 3. If the symptom had occurred less, say in 5% of the remainder of the population, the LR would have been 9. This is consistent with Bayes' theorem and Hahnemann's aphorism 153 about the importance of peculiar symptoms.<sup>8</sup> Symptoms with higher prevalence in the population will have lower LR. Symptoms with much lower prevalence in the population, say less than 1%, will rarely be seen. We therefore estimate that most prescriptions are based on symptoms with prevalence between 1% and 10%. The accordance between estimates and assessed values indicate that practice experience is valuable, but it has some flaws.

Bayes' theorem and our knowledge from bringing cases from several doctors together also explains the problem with expert opinion. During *Materia Medica* validation 10-20 experienced doctors bring their best cases of one homeopathic medicine. It appears that even experienced doctors seldom have more than 3 'best' cases of one medicine. In November 2002 our consensus meeting (retrospectively) showed that 2 out of 18 *Staphisagria* patients (11%) were sensitive to injustice. The prevalence of the symptom 'sensitive to injustice' in the whole population was estimated to be 10%. Later (June 2004), prospective LR research confirmed that the prevalence of the symptom was indeed 10% in 2506 patients, and 2 of the 23 patients (8%) who responded well to *Staphisagria* during the LR research were sensitive to injustice (see later).

Many entries in the repertory are based on the opinion of one expert. Suppose that the editor of the repertory asks the opinion of an experienced homeopath with 5 good *Staphisagria* cases. Exact binomial chance calculation based on the data of our prospective research indicates that the chance that one of these 5 patients is sensitive to injustice is about 47%. So 1 out of 2 doctors with 5 cases responding to *Staphisagria* estimates that the prevalence of the symptom in the *Staphisagria* population is 1 out of 5 (20%), more than his estimate of 1 out of 10 (10%) for his whole practice. So in the experience of this doctor from his *Staphisagria* population the symptom 'sensitive to

injustice' is an indication for *Staphisagria*. There is a possibility of 11% (corresponding with 1 out of 9 doctors) that 2 out of 5 *Staphisagria* cases (40%) are sensitive to injustice, meaning that 'sensitive to injustice' is a rather strong indication for *Staphisagria*. The gathering of cases of several colleagues in our consensus meeting and LR assessment increased numbers and showed that the real prevalence of this symptom in the *Staphisagria* population is less. 'Sensitivity to injustice' might be not be an indication for *Staphisagria*. This demonstrates that many entries in the repertory could be influenced by chance. Bias, like confirmation bias, could also influence expert opinion.

### Prospective study

After 33 months (February 2007) 3367 patients entered the study and 3246 prescriptions were evaluated. The symptom 'Sensitive to injustice' was present in 330 patients (10%). Outcomes for these patients is shown in Table 1.

This table has some resemblance to the existing repertory rubric: Calc, Caust, Ign, Merc, Sep and Staph are repeatedly observed in relation to this symptom. But the medicines *Anacardium* (Anac), *Aurum* (Aur), *Belladonna* (Bell), *Carcinosinum* (Carc), *Carcinosinum con cuprum* (carc-c-c), *Cocculus* (Cocc), *Kalium bichromicum* (Kali-bi) *Natium muriaticum* (nat-m) and *Phosphoricum acidum* (ph-ac) are new. The symptom has also been seen in the *Natium muriaticum* population not much less than in the *Causticum* population.

### Discussion

The fact that a symptom is repeatedly observed in a population cured by a certain medicine was so far enough to include the medicine with emphasis in the repertory-rubric, but is not enough to apply Bayes' theorem. If the symptom is not infrequent (italics or

**Table 1** Preliminary outcome of the assessment of the symptom 'Sensitive to injustice'. Number of patients in each population with result GHOS 2-4, absolute occurrence

Medicine, patients with result GHOS 2-4	Sensitive to injustice
anac	5
aur	2
bell	4
calc	6
carc	8
carc-c-c	4
caust	15
cocc	4
ign	6
merc	7
nat-m	13
nux-v	2
ph-ac	3
sep	7
staph	2

bold) occurring and if the medicine is often used, like *Calcarea* in this case, it is possible that the symptom is not characteristic for *Calcarea* patients as a group. We must also know how many patients cured by that medicine are not sensitive to injustice. see Table 2.

We calculated LR knowing that the prevalence of the symptom was 10% in the whole population. Then we see that the prevalence of this symptom is less among *Nux vomica* and *Staphisagria* patients than in the remainder of the population, and therefore  $LR < 1$ . Sensitivity to injustice is therefore not an indication for *Nux vomica* and *Staphisagria* although we have several patients with this symptom. For *Calcarea* and *Sepia* LR is just below 1, in other words it is a contra-indication!

### Translating LR into type

To make a comparison with the existing entries of Kent's repertory we have to translate type (expressing importance of the symptom related to that medicine) into numbers. Such a translation is rather arbitrary; a possible translation from type into LR is shown in Table 3.

The choice of  $LR > 6$  for bold type could be justified as follows: There is consensus that three good symptoms pointing to the same medicine indicate a reliable prescription. Three symptoms with  $LR = 6$  give a combined LR of  $6 \times 6 \times 6 = 216$  (LRs are multiplied). Suppose that the prior chance that any medicine works is 1%, then the posterior chance after three symptoms with  $LR = 6$  becomes 69%. We don't know prior chances that a randomly selected homeopathic medicine would work, but these values of prior chance and LR reasonably fit the results of our assessment so far. If we have five symptoms with  $LR = 3$ , the resulting combined  $LR = 3 \times 3 \times 3 \times 3 \times 3 = 243$ . With this combined LR the chances go from 1% to 71%. So five symptoms with  $LR = 3$  do not greatly increase the chances compared to three symptoms with  $LR = 6$ . Our choice of  $LR = 1.5$  for a plain type entry is arbitrary.

### Developing a new repertory

As far as we know ours is the first prospective assessment of the prognostic properties of homeopathic symptoms, and assessment of the prevalence of symptoms in the whole population. Our retrospective validation of medicines just indicated the prevalence of the most important symptoms in the population 'cured' by that medicine. If we want to enter our results into the repertories we should make a new start guaranteeing reliability and reproducibility of new entries, and maybe we should discard old entries that these results make questionable. But we must not lose or disregard useful information, and existing entries should be handled carefully.

What would a scientifically sound repertory rubric look like? According to our preliminary results for the rubric 'sensitivity to injustice' it would be:

Anac, Aur, Bell, Carc, *Carc-c-c?*, *Caust*, *Cocc*, Ign, Merc?, Ph-ac?

Numbers are still small, particularly for *Carcinosinum con cuprum* and *Phosphoricum acidum* so these results should be handled cautiously. Still, this rubric is based on a better defined and more reliable process than most existing repertory entries. There are a few problems. The fact that there are no *Cuprum* and *Drosera* cases could be explained by the fact that those medicines are not commonly used. It could be that our group had no 'specialists' in prescribing those medicines.

Prospective research slightly alters the assessment of symptoms. If you ask every patient if he is sensitive to injustice many patients will answer affirmatively. We defined this symptom more precisely, but the process is still rather subjective. In this population the prevalence of the symptom was 10%. But if a patient has a very

**Table 3** Repertory entries translated into LR values

Type	LR
Plain	1.5-3.0
<i>Italics</i>	3.0-6.0
<b>Bold</b>	> 6.0

**Table 2** Preliminary outcome of the assessment of the symptom 'Sensitive to injustice', prevalence of the symptom in each 'medicine-population' and LR. Prevalence in the whole population is 10%. 95% CI ... 95% Confidence Interval

Medicine	Sensitive to injustice	Not sensitive to injustice	Prevalence (%)	LR	95% CI
anac	5	6	45	4.69	2.44-9.04
aur	2	7	22	2.28	0.67-7.76
bell	4	13	24	2.42	1.02-5.73
calc	6	58	10	0.96	0.44-2.06
carc	8	27	23	2.37	1.28-4.39
carc-c-c	4	4	50	5.15	2.56-10.38
caust	15	23	39	4.17	2.78-6.27
cocc	4	6	40	4.12	1.92-8.86
ign	6	17	26	2.69	1.34-5.40
merc	7	38	16	1.60	0.80-3.19
nat-m	13	116	10	1.03	0.61-1.74
nux-v	2	28	7	0.68	0.18-2.60
ph-ac	3	16	16	1.62	0.57-4.59
sep	7	69	9	0.94	0.46-1.92
staph	2	23	8	0.82	0.21-3.09

strong sensitivity to injustice, such as occurs in, say, only 1% of all people the LR would be larger than those we measured. This is intuitively understandable: a stronger symptom is a stronger indication.

The medicines *Phosphoricum acidum* and *Mercurius* have LRs > 1.5, but this could still depend on chance. For *Nux vomica* the LR 1.5 falls within the 95% Confidence Interval.

If we are to constitute a repertory based on scientific assessment we should regard the influence of chance. How reliable are our numbers—or, if we would measure a certain value for LR repeatedly, would it always be the same? Statistics show that possible values from repeated measurements are distributed around the sample value. Figure 1 shows simplified distributions for possible values of the LR of the symptom 'Sensitive to injustice' for *Aurum* (LR = 2.28) and for *Nux vomica* (LR = 0.68). The chance that the LR for *Aurum* is larger than 1.5 is indicated by the area under the left curve (right from the vertical line) corresponding with LR = 1.5, being 85.9%, calculated as exact binomial chance. The chance that the LR for *Nux vomica* > 1.5 is 15.1% as shown in the right curve.

#### Adding or discarding entries

When should a new entry be added, when should an old entry be removed? We could discuss this question in this example regarding the entries in Table 4.

The *p*-values in Table 4 indicate chances that LRs of these medicines are > 1.5. For *Calcarea carbonica* chances are about 14% (*p* = 0.136). If we have many cases, for instance 76 for *Sepia*, we are confident (*p* = 0.100) that the LR-value will not be larger than 1.5. With a smaller number of cases, like 25 for *Staphisagria* with the same LR value, we are less confident (*p* = 0.254).

We emphasise that our aim is not to prove or falsify a hypothesis. According to the scientific method we should form a hypothesis and try to falsify it. Such a hypothesis could be that 'Sensitivity to injustice' is not an indication for *Aurum*. This hypothesis for *Aurum* is not falsified by our data, chances are 0.141 (1–0.859), so larger than *p* = 0.05, the generally accepted value for significant results. If we maintained such criteria the repertory would be very thin and most existing

entries discarded. The knowledge that 'sensitivity to injustice' has 64% chance of indicating *Mercurius* (LR > 1.5) might still be relevant for daily practice. But what should be the cut-off value for the *p*-value for adding an entry to the repertory if LR is to be larger than 1.5? And should we take LR > 1.5 as lower limit? If we take all values for LR > 1.0, the chance that the LR for *Mercurius* > 1.0 is 92%.

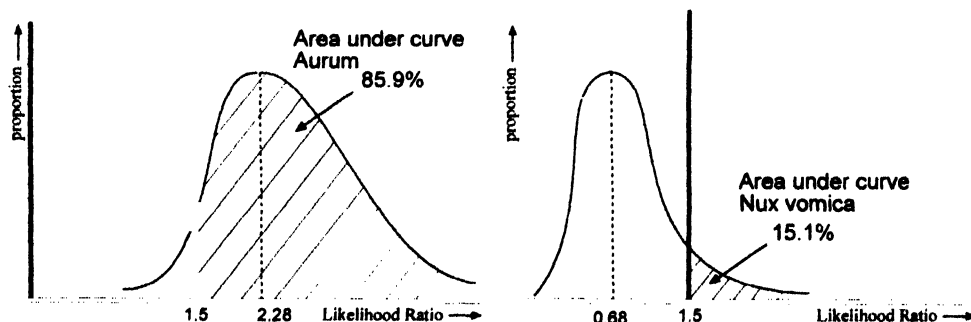
The next question is when do we discard an existing entry? According to our assessment *Nux vomica* should be deleted from the rubric 'sensitive to injustice'. The chance that the LR is more than 1.5 is 15%, the chance that the LR is larger than 1 is 41% (exact binomial chance). Should it make a difference that this entry comes from Hahnemann? He could also be a victim of chance. It is also possible that Hahnemann used a different definition for 'sensitive to injustice'.

A limitation of assessment by one group is that there may be colleagues who have much experience with medicines that are not known to the doctors who participated in this assessment. This kind of assessment is also not suited for rarely prescribed medicines; existing entries should not be removed from the repertory when LR research does not indicate them. We should strive for consensus about infrequently used medicines that come up in LR research, like *Carcinosinum con cuprum*. The data for *Carcinosinum con cuprum* from this assessment come from two observers; for this medicine we could not claim that results are derived from a multi-centre assessment.

Another reason to be careful with discarding medicines from the repertory is possible interaction between symptoms. In the repertory, as in our

**Table 4** Some medicines correlated to the symptom 'Sensitive to injustice', LR and probability that LR > 1.5

Medicine	LR	<i>p</i> -Value
Aurum	2.28	0.859
Calcarea carbonica	0.96	0.136
Carcinosinum	2.37	0.931
Carcinosinum con cuprum	5.15	0.997
Cocculus	4.12	0.990
Ignatia	2.69	0.954
Mercurius	1.68	0.639
Nux vomica	0.68	0.151
Sepia	0.94	0.100
Staphisagria	0.82	0.254



**Figure 1.** Distributions of chances that *Aurum* and *Nux vomica* have LR > 1.5.

assessment, symptoms are considered as independent entities. But it is possible that the combination of two symptoms with low LR is a much stronger indication for a medicine than expected from the LRs separately. Repertorisation could be compared with a weather-forecast. You get variables like temperature, wind and rain as independent values, but your decision about what to do tomorrow depends on a complex weighting of these variables.

It does not seem wise to just discard entries with a certainty of less than, say, 80%, but we should put a certain limit. Above this limit we could indicate statistical certainties. How do we indicate certainty in a feasible way? We could use  $p =$  values as in Table 4, or confidence intervals. We could also give the measured values, as in Table 2. In any case, we have to get accustomed to replacing some of our intuition about expert-experience by statistical considerations about scientific assessment. But it will be a slow shift and the need for intuition will remain for a long time.

### Bias

The method we present here is an improvement compared to the unsatisfactory process that led to the development of existing repertories. We increased numbers to diminish the influence of chance in our retrospective assessment and we made a comparison with the remainder of the population in our prospective assessment. We got a clearer insight into the influence of chance, but bias is still possible. Maybe we used a different definition than former contributors for this symptom. We do not know if our results are valid all over the world. The symptom 'Sensitive to injustice', like many other homeopathic symptoms, is very subjective and therefore liable to confirmation bias;<sup>5</sup> it will be detected sooner if we think of *Causticum* on other grounds. Prospective investigation slightly alters our consultation; will our results differ from retrospective data and why? Our retrospective analysis of 10 best *Causticum* cases (November 1998) showed 4 patients (40%) who were sensitive to injustice, not different from our prospective research. We have seen several similarities in our retrospective and prospective data, but only for symptoms that are the most prominent for a particular medicine. Our reference is 'cure' measured according to the GHHOS scale, but is this scale valid?"

### Conclusion

The homeopathic method is, unconsciously, based on the sound scientific theory of conditional probability, but our repertories are not. Expert opinion is valuable, but liable to bias and the influence of chance. The influence of chance could be diminished by gathering more cases from different doctors. If we want to use our experience in a state-of-the-art way we must know the prevalence of homeopathic symptoms

in the populations cured by the medicines, but also in the remainder of the populations. The relation between these two values is expressed as Likelihood Ratio (LR). The best way to assess this is prospective research.

We should develop new criteria for entering or discarding entries in the repertory. We probably need a different way of handling statistical uncertainty than in hypothesis testing. Symptoms should be more clearly defined. The validity of our scales measuring cure should be validated. Most of the questions we presented here have been issues as long as repertories have existed, but were avoided. To do it right we should handle these questions properly. Our considerations are about clinical data, but many may apply to homeopathic pathogenetic trials (provings).

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