Original Article

Retrospective estimation of prevalence and likelihood ratio of general symptoms of 29 less frequently prescribed homoeopathic medicines by clinical verification

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Abstract

Context: Scientific assessment of proving symptoms or already recorded symptoms in patients refers to Clinical Verification (CV). There are serious shortcomings of existing methods of CV, mostly arising from qualitative observations made on absolute occurrence of symptoms instead of relative ones. This problem can be resolved by the use of the Likelihood Ratio (LR). **Aim:** This study aims to estimate the prevalence and LRs of general symptoms of 29 less frequently prescribed homoeopathic medicines. **Methods:** The study was multicentric, open and observational. Patients were enrolled as per pre-specified eligibility criteria. Alongside, presenting complaints and general symptoms were taken into account during prescription. Medicines were prescribed in centesimal potencies. LR calculation of general symptoms was based on clinician-rated outcomes as 'improved' and 'not improved' of presenting complaints and was divided into three sections: (1) when the prevalence of a symptom was available from literature, LR was calculated by assessing the prevalence of that symptom in the responder sample, (2) in the absence of so, calculation was restricted to mean prevalence data from study sample ('confined LR') and (3) 'confined LRs' were not calculated for symptoms whose prevalence were not recorded for at least five medicines and were kept for estimation in future. **Results:** Of 166 general symptoms of 29 medicines, LRs and confined LRs >1.5 were elicited for 6 and 49 symptoms, respectively. **Conclusion:** In spite of considerable caveats, it is the first insight into prevalence and LRs of general symptoms of less frequently prescribed homoeopathic medicines. Further research is warranted.

Keywords: Clinical verification, Homoeopathy, Likelihood ratio, Prevalence, Prognostic factor research

Introduction

Clinical Verification (CV) refers to the confirmatory and systematic process of observing symptoms that are already recorded in homoeopathic literature as proving symptoms and cured cases. If these already recorded symptoms are indeed seen in cases that respond well to corresponding medicines, this confirms the relevance of the symptom in relation to the medicine. CV has been one of the most important tasks in the field of Homoeopathy. It is a process of internal validation of the basic principles of Homoeopathy, and the results can be used for improving the daily practice. During CV, every new symptom (if any) is also recorded and included in literature.

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In Homoeopathy, repertories are consulted to shortlist the medicines which are indicated for the presenting symptoms. To arrange the medicines under different rubrics and sub-rubrics, different typefaces are used according to their frequency of occurrence. These typefaces help to differentiate and signify the relative importance of the medicines for that particular rubric. Among these criteria of gradation system, CV plays a major role. For example, in Kent's repertory[1,2] there are three grades. The criteria for gradations are as follows:

1. Bold (3 marks)/1st grade: Found frequently in 'all or the majority' of provers, confirmed by reproving and verified clinically on the sick
2. Italics (2 marks)/2nd grade: Symptoms found in few provers, confirmed by reproving, but occasionally verified clinically on the sick; and
3. Plain Roman (1 mark)/3rd grade: Symptoms experienced 'now and then' in proving, not yet confirmed by reproving but verified by curing patients – so accepted as clinical symptom only.

This gradation system involves two sources of knowledge: experimental testing in proving and observational knowledge from practical experience. Hitherto, there has been no reflection about the differences between these two sources, especially the influence of mere chance. For instances: the number of provers is limited, and sensitivity varies. The number of cured patients grows much faster but is variable for different medicines. Cured patients constitute a quite different selection from the whole population than provers. This introduces some serious shortcomings of these existing repertories – qualitative observations were made on absolute occurrence of symptoms instead of relative grading; based on very few expert opinions; again those opinions were mostly on memory based, not systematically collected. Influence of chance, inadequate sample sizes and recall or expectation bias have not been addressed adequately.[3] It is quite difficult to differentiate among the indicated medicines listed under same gradations. Furthermore, commonly used medicines were verified and recorded more frequently and thus over-represented; whereas rarely used medicines were under-reported, even the most characteristic symptoms were overlooked.[4] Large rubrics had unnecessary entries and small rubrics were deprived of medicines.[5]

These types of inadequacies and misrepresentations can be addressed by reconsideration of repertorial entries by Bayes' theorem,[6,7] that is, mathematically expressed as a Likelihood Ratio (LR). Bayes' theorem, published in 1763, deals with predictions from experience in the past.[8] LR is the modern epidemiological tool for determining the characteristic and keynote symptoms of medicines.[6,9] LR comes under two variants. The first variant is:

Posterior odds = LR × prior odds

Odds = Chance/(1 − chance);

Chance = Odds/(1 + odds)

LR = (Prevalence in the target population)/(prevalence in the remainder of the population)[7,10]

And the second variant is:

$$P(M|S) = \frac{P(M) \times P(S \mid M)}{P(S)}$$

$$= \frac{P(M) \times P(S \mid M)}{P(M) \times P(S \mid M) + P(\sim M) \times P(S \mid \sim M)} \quad [7]$$

Here, M = medicine, S = symptoms. The higher score of LR will increase the posterior chance more. And with the addition of each symptom, the (posterior) chances that medicine will work will be increased by each added symptom. Chance of improvement by the medicine will increase if the prevalence of the symptoms is more in medicine responder population than in the rest of the population.[11] A large number of prospectively collected accurate data from successful prescription is needed for comparison.[6] Using LR in CV allows verification with the enhancement of the grades of medicine, eliminate bias, validate rubrics and medicines and show the importance of symptoms in relation to medicine.[3,4,12] This gives a definite indication for symptoms requirement for a case with the curative probability of medicines.[4] Positive LR is used to calculate changes in odds (or chances) if the symptom is present. Similarly, negative LR is used to calculate changes in odds (or chances) if the symptom is absent. Odds become greater when LR >1 and smaller when LR <1 (between 0 and 1); higher is better to include and lower is better to exclude. As a rule of thumb, per symptoms or rubrics, LRs <1.5 with corresponding medicines are discarded from pick listing, also because LR values between 1.0 and 1.5 hardly change posterior probability.[3,5]

A prospective verification study on *Veratrum album* rubrics from synthesis repertory showed that in some rubrics, typefaces of the medicines should be upgraded, but no new entry and elimination was found.[12] Another retrospective study was conducted to evaluate LRs of *Lycopodium clavatum* symptoms on 752 patients. Only 22/35 symptoms were confirmed as pertaining to the medicine.[13] A multicentric, prospective study on the most frequently encountered physical general symptoms illustrated that many medicines maintained their respective positions under corresponding rubrics; whereas some frequently used medicines having high gradations could not even qualify or just managed to get an entry under their respective rubrics.[3] Findings of these previous studies indicated that all the repertory rubrics could be improved by the Prognostic Factor Research (PFR).

In this multicentric study, the investigators intended to estimate the prevalence and LRs of symptoms of 29 less frequently prescribed homoeopathic medicines. As rarely used medicines remain under-evaluated due to less frequency of prescriptions, this study may help in better understanding of the symptoms of the medicines.

Methods

This study was conducted on 29 drugs with analyzable data, from 2005 to 2010 [Table 1]. Patients for the study were enrolled from the outpatient departments of 11 institutes of the Central Council for Research in Homoeopathy (CCRH). As per the inclusion criteria, the patients from all age groups and both sexes, having symptomatic similarity with the 29 study medicines, and willing to participate were included in the study. If the patients were taking any acute medicine, they were included in the study after a washout period of 1 week. Exclusion criteria were patients unwilling to participate, patients having a clinical presentation not corresponding with the study medicines, and patients on regular medication for any systemic disease. Ethical clearance for the study was taken from ethical committee of the Council. After providing patient information sheet in local vernaculars, informed written consent was obtained from the eligible participants or the guardians in case of minors before participation in the study.

The study medicines were procured from a good manufacturing practice-compliant homoeopathic pharmacy in various potencies, namely, 6C, 30C, 200C and 1M and were distributed to all the 11 institutes. After that, the symptoms were repertorised using a repertory manually prepared for CV programme of the CCRH (unpublished), and then, a specially developed Materia Medica was consulted for the final selection of the remedy. Two examples of such repertory rubrics are given below [Table 2].

Clinician-rated outcomes were described as 'Cured', 'Improved', 'Not Improved', 'Worse', 'Referred', 'Withdrawal', and 'Drop out', used to measure degree of changes in presenting complaints. Any additional and clinical symptoms if present were recorded separately along with systematic recording of physical general and mental general symptoms. If the presenting symptoms of the patient corresponded with any one of the study medicine, then the medicine was prescribed in 6C potency, thrice a day till the improvement or aggravation occurred or for maximum 5–7 days allowing the medicine to act. The medicine was served by the pharmacy of corresponding institute. In follow-up visits, the changes in signs and symptoms were noted. If there was any sign of improvement, then placebo was prescribed. If there was status quo, next higher potency i.e., 30C twice a day for 3–5 days in acute cases and 5–7 days in chronic cases; 200C once a week for 2 weeks and 1M potency was given once a fortnight. These potencies were repeated twice only. If adequate responses were not elicited, the cases were restudied, and next higher potency was prescribed. If no change was observed even after the change of potencies also, then the case was closed and considered as a clinical failure, that is, cases showing "not improved", "worse", and "referred" were considered as clinical failure. If the patient presented with new symptoms of mild intensity, placebo was prescribed. The appearance of severe symptoms (new or aggravation of existing symptoms) with sufficient strength to cause considerable discomfort to the patient called for a change of medicine or therapy. Such case was considered as a deteriorated one. 'Clinical success' was defined 'a priori' as cases showing clinical improvement, objective or subjective, of the present complaint(s) as judged by the investigating physician(s) and/or as reported by the patient(s). All the data, including clinical failure, were collected and compiled in specially designed Excel Spreadsheet for analysis and estimation of LR. Although there was provision for assessing both the acute and chronic cases in the CV project, for the purpose of LR calculation of general symptoms, we segregated the chronic cases only, where general symptoms were noted down properly.

The calculation of LR was divided into three sections:

1. When the prevalence of a symptom under question was available from literature[3] (i.e., the denominator), prevalence of that symptom in the responder sample of the study was estimated; thus, enabling calculation of LR
2. If no concerned literature data were available, then, the calculation was restricted to the sample with available data only; hence called as 'confined LR' i.e., the prevalence of the symptom in responder population/prevalence of the symptom in rest of the study (not general) sample where the symptoms were recorded. The denominator was actually the mean prevalence data; mean calculated from the recorded study sample data
3. However, as a rule of thumb, 'confined LRs' were not calculated for those symptoms whose prevalence was not recorded for at least five medicines. For such symptoms, only prevalence was reported, and LRs were kept to be estimated in future.

As the denominator depended either on literature data or mean prevalence of study sample, naturally, it was changeable. Thus, denominator value was not merely an assumption, rather based on either valid reference or sound statistical grounds.

Results

Alongside targeted particular symptoms, a total of 166 general symptoms were evaluated under this CV programme during 2005–2010. A total of 4652 records were considered for analysis, of which 3705 were improved and 947 were not improved. Among these, LRs(+) were calculated for 12 symptoms using prevalence of symptoms in the whole population from a previous symptom assessment in India (West Bengal) in 2039 patients for thermal relations and 4715 patients for food desires/aversions.[3] The prevalence of symptoms being assessed was obtained by dividing the number of patients presenting with the symptoms by the total recorded data. Out of these 12, only 6 symptoms (prevalence given along with 95% confidence interval after each symptom within parenthesis) were identified as having corresponding medicines (LR given after each medicine within parenthesis) with LRs(+) more than 1.5 and worth of consideration with their corresponding prevalence in the study sample [Table 3].

Confined LRs were calculated for 57 symptoms, based on the mean prevalence of symptoms in general population.

Table 1: List of the 29 medicines evaluated under the clinical verification programme during 2005-10

Acalypha indica	*Mangifera indica*
Acid butyricum	*Mygale lasiodora*
Alfalfa	*Ocimum canum*
Aranea diadema	*Oxytropis lamberti*
Arsenicum bromatum	*Pyrus americana*
Azadirachta indica	*Rauwolfia serpentina*
Calotropis gigantea	*Ricinus communis*
Cassia fistula	*Staphylococcinum*
Chromium Kalium Sulphuricum	*Tela aranea*
Cynodon dactylon	*Terminalia arjuna*
Euphorbia lathyris	*Thea chinensis*
Glycyrrhiza glabra	*Theridion curassavicum*
Holarrhena antidysenterica	*Tribulus terrestris*
Icthyolum	*Tylophora indica*
Magnesia sulphurica	

For these symptoms, 'LR' is only valid as a comparison between medicines samples with available data, hence the term 'confined'. For example, 'Desire for milk' was recorded only for six medicines – *Aranea diadema*, *Glycyrrhiza glabra*, *Acid butyricum*, *Magnesia sulphurica*, *Acalypha indica* and *Azadirachta indica*. However, whether this very symptom was present in the other 23 drugs has not been addressed as there was no detailing of every desire. Therefore, the general sample for this 'Desire for milk' symptom comprised of 1563 only instead of 2922, which was the prescribed population as a surplus to the absence of prevalence data in general population. Even then, we cannot be sure that the symptom was checked in every patient in the population with available data. Forty-nine symptoms with corresponding medicines with LRs(+) >1.5 are listed below [Table 4]. There is considerable systematic error in this data, probably more significant than statistical error. Hence, statistical confidence intervals are not given to avoid the suggestion that the point estimate is really within the statistical confidence interval.

Discussion

Overall, of the total 166 general symptoms evaluated of 29 medicines under this CV programme of CCRH during 2005–2010, medicines having LRs and confined LRs >1.5 were elicited for 6 and 49 symptoms, respectively; much were under-reported and kept for calculation in future. Thus this compilation allows further insights on general symptomatology of some of the less frequently prescribed homoeopathic medicines subject to further systematic and rigorous explorations and use in clinical practice. CV concept was present from the very beginning of homoeopathic era, and the programme was launched by the Council almost 4 decades back, much before the concept of LR and assessment of the prevalence of symptoms came into use for validation of symptoms. In our study, we intended to validate these verified symptoms statistically using LR, regarding the prevalence of symptoms instead of absolute occurrence.

Table 2: Example of rubrics taken from the unpublished repertory of clinical verification programme of CCRH

Anger: *Arsenicum bromatum, Cynodon dactylon, Magnesia sulphurica, Phyllanthus*, *Tarentula cubensis*, *Theridion curassavicum*, *Tribulus terrestris*
Causeless: *Cynodon dactylon*
Contradiction from: *Tribulus terrestris*
Easily: *Magnesia sulphurica*, *Phyllanthus*
Hurt, desire to, with: *Holarrhena antidysenterica*
Pains from: *Tarentula cubensis*
Anguish: *Tela aranea*, *Thea chinensis*
Examination, during: *Tela aranea*
Neurosis with: *Rauwolfia serpentina*
Anxiety: *Aranea diadema*, *Azadirachta indica*, *Butyricum acidum*, *Curcuma longa*, *Thea chinensis Magnesia sulphurica*, *Mygale lasiodora*, *Ocimum canum*
Phyllanthus, *Pyrus americana*, *Rauwolfia serpentina*, *Tarentula cubensis*, *Terminalia arjuna, Thea chinensis*
Morning, on walking: *Magnesia sulphurica*
Evil, apprehension: *Azadirachta indica, Magnesia sulphurica*
Fear, with: *Rauwolfia serpentina*
Foreboding: *Magnesia sulphurica, Thea chinensis*
Future, about: *Curcuma longa*
Afternoon: *Curcuma longa*
Health, about: *Pyrus americana*
Trifles, about: *Butyricum acidum*
Headache, during: *Butyricum acidum*
Heat
Flushes of: *Rauwolfia serpentina*
Sensation of: *Curcuma longa*, *Glycyrrhiza glabra*, *Tarentula cubensis*, *Thea chinensis*
Amel: *Bellis perennis*, *Cynodon dactylon*
Morning: *Curcuma longa*
Air, open, amel: *Tribulus terrestris*
Fever, during: *Curcuma longa*
Siesta, after: *Curcuma longa*
Vital, lack of: *Aranea diadema, Pyrus americana, Thea chinensis*
Heated
Becoming: *Rauwolfia serpentina*

The protocol was designed for CV prospectively and collected data already published in book form. Retrospective assessment of LR was planned afterwards.

Another major caveat in retrospective assessment of symptoms in PFR is substantive confirmation bias increasing LRs. We are actually unaware whether the symptom has the same definition among patients and observers; thus, it is uncertain how the symptom was recorded, and we cannot be sure that the symptom is checked in all patients. Cut-off values can vary greatly and are sensitive to confirmation bias.

Some observers are more pertinent in their questions and leave few rooms for the 'don't know,' or 'not applicable' answer. Symptoms are more likely to be checked if they belong to the preferred medicine pictures.

When a symptom is not recorded in a particular case, this could mean two things:

1. The patient did not have the symptom
2. The symptom was not checked.

Table 3: Six rubrics along with list of medicines having likelihood ratio of more than 1.5

1. Sensitive to both heat and cold (4.4%; 95% CI 3.6%-5.4%): *Icthyolum* (2.4)*
2. Desire for sweet (16.9%; 95% CI 15.7%-18.4%): *Acalypha indica* (2.0),[14] *Mygale lasiodora* (2.0)*, *Terminalia arjuna* (1.9)*, *Ocimum canum* (1.8)*, *Cassia fistula* (1.8)*, *Alfalfa* (1.7),[15,16] *Icthyolum* (1.7)*, *Mangifera indica* (1.7)*, *Acid butyricum* (1.6)*, *Aranea diadema* (1.6)[14]
3. Desire for salt (11.5%; 95% CI 10.4%-12.7%): *Tribulus terrestris* (4.7)*, *Pyrus americana* (3.7)*, *Mangifera indica* (2.7)*, *Calotropis gigantea* (2.7)*, *Alfalfa* (2.3)*, *Tela aranea* (2.2)*, *Theridion curassavicum* (2.0)*, *Icthyolum* (1.9)*, *Ricinus communis* (1.9)*, *Rauwolfia serpentina* (1.9)*, *Mygale lasiodora* (1.9)*, *Cynodon dactylon* (1.9),[17] *Ocimum canum* (1.8)*, *Holarrhena antidysenterica* (1.7)*, *Tylophora indica* (1.7)*
4. Desire for spicy food (6.4%; 95% CI 6.6%-8.6%): *Thea chinensis* (2.4)*, *Glycyrrhiza glabra* (1.9),[17] *Euphorbia lathyris* (1.9)*, *Cynodon dactylon* (1.8)[17]
5. Desire for sour (3.6%; 95% CI 3.0%-4.4%): *Thea chinensis* (1.9)[15,16,18-20]
6. Desire for cold food (1.5%; 95% CI 1.2%-2.1%): *Ocimum canum* (1.9)[16]

*New symptoms; prevalence in the whole study sample along with 95% CI are given after each symptom within parenthesis; LR is given after each medicine within parenthesis. LR: Likelihood ratio, CI: Confidence interval

As the case recording pro forma provided open-ended questions, so there was definitely a chance of missing a point. Estimating the homoeopathic value of a symptom in individual patients requires considerable skills. In prospective research, we monitor the data from the start, and we can detect if a patient answers positive to many questions, or if some observers have lower cut-off values than others. This is not possible in retrospective research.

In this perspective, polar symptoms deserve a special mention. Polar symptoms are those with opposite values, such as aversion/desire for food, or aggravation/amelioration. If we look retrospectively at patient records, we can detect patients with an 'aggravation from cold' and with 'amelioration from cold,' but 'no influence from cold' is seldom noted. It is therefore difficult to distinguish pseudo-bipolarity from real bipolarity. False bipolarity can be detected by looking at the database; if a considerable number of records have both opposite values, then the bipolarity is real; otherwise, the records of one pole compensate for part of the other pole.[26] Ideally, polar symptoms (e.g., thirst and appetite) should be checked by offering the choice 'decreased, normal, or increased.' Checking symptoms with this kind of Likert scales renders a frequency distribution with a peak at 'normal.' The essence of polarity analysis is subtraction of the opposite values for each symptom, thus estimating the average of both poles.[27] Likewise, we must be extra careful when interpreting all polar symptoms for all medicines, because results are very sensitive for the way the symptoms were elicited, more than in non-polar symptoms.

Strength of this CV project includes multicentric gathering of 4652 records (3705 improved and 947 not-improved) from 11 institutes of the Council from 2005 to 2010. This naturally increased the external validity and generalisability of the study findings. The study design was aimed at minimal interference of routine Homoeopathy practice, thus corroborating with the guidelines of PFR and allowing calculation of LR. However, the project had some in-built limitations. In this CV programme, it was not possible to have estimations of all the symptoms under question in the 'rest of the population;' hence, for calculation of LRs, we frequently referred to the prevalence as reported in the literature. It is, however, impossible to know if cut-off values for symptom-intensity were the same in literature as in this project. Moreover, food desires vary greatly because they are influenced by many variables such as climate, culture, and age etc.[28] This could be a problem. Specific symptoms were not checked in all populations. The 'total' population for a specific symptom should be the population where the symptom was checked. So, the 'total' population is different for every symptom. For example, the prevalence of 'dullness/laziness' was found to be very low, only 0.97%. It was quite possible that the symptom was not checked in many populations. Few symptoms were related closely, for example, 'Irritable' and 'Angry', but were recorded separately by the investigators. In Kent's repertory also, these two have been mentioned as rubrics with similar meanings. These necessitate the requirement of a refined and standardised checklist of the symptoms to be studied.

The major drawback of this study was that symptoms which were not found in the available (unpublished) repertory and Materia Medica developed by the Council for CV project were not recorded systematically and those cases were treated in general outpatients without further record keeping. It is unlikely that these symptoms were not there in the population where other medicines were prescribed. Confidence intervals of confined LRs have not been mentioned here, because the uncertainty of the numbers is caused by recall bias than by statistical uncertainty. A confidence interval only accounts for statistical uncertainty. This means that we could not calculate the prevalence of the symptom in the whole population. For such symptoms, we have to restrict the denominator of LR to prevalence of the symptom in rest of the study (not general) sample, thus generating 'confined' LRs for those symptoms. Even, 'confined LRs' could not be calculated for those symptoms whose prevalence was not recorded for a sufficient number of medicines (Five was chosen as a cut-off value, as a rule of thumb). Thus the CV project suffered from under-reporting to some extent. Besides, instead of the use of validated outcomes (e.g., Glasgow Homoeopathic Hospital Outcome Scale; GHHOS), relying on clinician-rated outcomes such as 'Cured,' 'Improved,' 'Not Improved,' and 'Worse' definitely drew some sort of assessment biases and further dichotomising the outcomes into 'improved' and 'not improved' resulted in considerable loss of information.

In sharp contrast to the recently published papers on CV,[29-34] we shifted our focus from drug-oriented approaches to symptom-centric and calculated LRs and 'confined' LRs

Table 4: Forty nine rubrics along with list of medicines having confined likelihood ratio of more than 1.5

1. Desire for milk (0.6%): *Aranea diadema* (2.3)[16]
2. Aversion to sweet (4.2%): *Tribulus terrestris* (3.2)*, *Tela aranea* (1.7)*
3. Aversion to sour (3.7%): *Cassia fistula* (1.7)*
4. Aversion to bitter (1.4%): *Euphorbia lathyris* (2.4)*, *Oxytropis lamberti* (2.2)*
5. Aversion to fried food (2.2%): *Thea chinensis* (2.6),[17] *Magnesia sulphurica* (2.0)*
6. Aversion to meat (1.3%): *Magnesia sulphurica* (3.5)[16]
7. Aversion to milk (0.9%): *Oxytropis lamberti* (2.5)*
8. Aversion to fish (0.5%): *Cynodon dactylon* (2.0)*
9. Aversion to vegetable (0.8%): *Holarrhena antidysenterica* (2.4)*, *Mygale lasiodora* (1.8)*
10. Aversion to egg (0.8%): *Pyrus americana* (5.9)[14]
11. Appetite decreased (34.6%): *Mangifera indica* (1.6)[14]
12. Appetite increased (5.1%): *Acid butyricum* (2.9)[15,16,21]
13. Thirst decreased (12.9%): *Ricinus communis* (2.6),[14] *Rauwolfia-s* (1.6)[14]
14. Thirst increased (15.8%): *Oxytropis lamberti* (2.3),[14] *Glycyrrhiza glabra* (2.2),[17] *Icthyolum* (1.7)[15,16,22]
15. Tongue white coated (19.4%): *Icthyolum* (2.8),[21] *Azadirachta indica* (1.7)*
16. Tongue clean and dry (5.8%): *Thea chinensis* (2.5),[16,18-20] *Ricinus communis* (1.6)[16,18,20]
17. Tongue yellow coated (2.2%): *Ocimum canum* (4.1),[16] *Theridion curassavicum* (1.7)*
18. Tongue imprint of teeth (0.5%): *Acid butyricum* (1.9)*
19. Taste bitter (9.4%): *Pyrus americana* (2.9),[14] *Terminalia arjuna* (2.3),[15] *Thea chinensis* (1.6)[16,18-20]
20. Taste loss of (3.8%): *Oxytropis lamberti* (3.4),[14] *Ricinus communis* (1.7)*
21. Taste bad (1.3%): *Icthyolum* (3.6)[21]
22. Stool loose, watery, mucoid, frequent, undigested (6.0%): *Mangifera indica* (2.7)*
23. Urine frequent, scanty (2.9%): *Tela aranea* (1.7)[17]
24. Urination, burning during (1.6%): *Cynodon dactylon* (3.3)*
25. Sweat in axilla (7.1%): *Pyrus americana* (3.2)*, *Tribulus terrestris* (3.2)*, *Rauwolfia serpentina* (2.3),[16] *Ricinus communis* (1.8)*, *Alfalfa* (1.7)*
26. Sweat in face (5.7%): *Tribulus terrestris* (3.3)*, *Pyrus americana* (2.7)*, *Ricinus communis* (2.1)*, *Oxytropis lamberti* (1.7)*
27. Sweat scanty (5.7%): *Azadirachta indica* (1.6)*
28. Sweat in forehead (1.8%): *Alfalfa* (2.4)*, *Pyrus americana* (2.0)*
29. Sweat in head (2.1%): *Oxytropis lamberti* (2.8)*
30. Sweat in chest (2.0%): *Staphylococcinum* (2.1)*, *Cassia fistula* (1.6)*
31. Sweat offensive (1.6%): *Rauwolfia serpentina* (3.9)[14]
32. Sweat in back (1.6%): *Oxytropis lamberti* (2.8)*, *Ricinus communis* (2.0)*, *Staphylococcinum* (1.8)*
33. Sweat in palm and sole (0.6%): *Tribulus terrestris* (3.6)*
34. Sweat in groin (0.5%): *Theridion curassavicum* (3.3)*
35. Sleep disturbed (12.3%): *Rauwolfia serpentina* (3.4),[14] *Alfalfa* (3.1),[14] *Tela aranea* (1.8)*
36. Irritable, peevish (10.7%): *Staphylococcinum* (2.1),[17] *Ricinus communis* (2.0),[14] *Alfalfa* (1.8)[15,16,21]
37. Forgetful (11.0%): *Icthyolum* (1.7),[15,16,21] *Oxytropis lamberti* (1.6)[16,19-21]
38. Angry (6.1%): *Tribulus terrestris* (5.8),[14] *Theridion curassavicum* (2.0)[14]
39. Mild (6.4%): *Terminalia arjuna* (1.9)*

Contd...

Table 4: Contd...

40. Desire to be alone (3.7%): *Oxytropis lamberti* (2.3)[15,16,19-22]
41. Desire company (5.1%): *Terminalia arjuna* (2.3),[14] *Ricinus communis* (2.0)*
42. Anxious (2.9%): *Magnesia sulphurica* (1.7),[16,18,20,23] *Holarrhena antidysenterica* (1.6)*
43. Intelligent (3.3%): *Ocimum canum* (2.5)*, *Pyrus americana* (1.9),[16,20,21] *Ricinus communis* (1.9)*
44. Melancholic, sad, gloomy (2.0%): *Mygale lasiodora* (2.2)[15,16,18,20,22]
45. Depressed (1.9%): *Icthyolum* (2.3),[15,16,22] *Calotropis* gigantea (1.8),[20,24] *Oxytropis lamberti* (1.7)[15,16,20-22,25]
46. Fearful (2.4%): *Acid butyricum* (1.8),[21] *Glycyrrhiza glabra* (1.6)[17]
47. Lack of concentration (1.0%): *Icthyolum* (4.0),[15,16,21] *Holarrhena antidysenterica* (1.6)[14]
48. Dullness and laziness (1.1%): *Cynodon dactylon* (1.8)[17]
49. Aversion to work (0.9%): *Cassia fistula* (1.9)[17]

*New symptoms; prevalence is given after each symptom within parenthesis; LR is given after each medicine within parenthesis. LR: Likelihood ratio

with references from available literature and prevalence of the symptom in rest of the study (not general) sample respectively. This provides further insights into prioritisation and discrimination among the medicines as per prevalence and LRs, as appropriate.

In the homoeopathic repertories, we see a classification of symptoms in sections such as; mind section, parts of the body and general symptoms. Throughout these sections, we find a large number of disease diagnosis, complaints and conditions. Recently, a new dimension has been added in PFR in terms of condition confined assessment (CCA) of LRs, for example, assessment of LRs from a cough population from the IIPCOS2 study[7] and assessment of LRs of contact dermatitis symptoms of *Vinca minor*.[35] CCA can be done wherein all patients suffering from the same disease/condition are analysed. Therefore, instead of 'whole population' (as used in LR calculation), a subpopulation of 'patients suffering from a particular disease or condition' is considered. Hence, instead of seeking prevalence of one symptom in 'whole population', prevalence of a symptom in 'disease population' is calculated.[7] The symptoms present in cured patients and the medicines given make the 2 × 2 table wherein the total patients suffering from condition 'X' are considered in the denominator. However, it should be kept in mind that in subgroups defined by conditions is only valid for these subgroups, but we must still be aware of the influence of this selection. If we select a subgroup on condition, we inherently also select a subgroup of medicines that are related to that condition. These medicines are all related to the condition, but some more than others. If we compare these medicines by LR, we can get LR values below unity because some medicines are less than average related to the condition. This low LR means nothing more than that the medicine has less relationship to the condition than the other selected medicines (but still more than many not selected medicines), but it works contra-intuitively because LR <1 is associated with a contraindication for that medicine.

In the underlying research, the LR was not confined by a specific condition, but by the availability of data. The limited availability of data was possibly related to the applied method of medicine selection: If the symptom was not mentioned in the available materia medica or if the eligible medicine was not in the repertory-rubric, it was not checked. Hence, we cannot know the prevalence of the symptom in the populations where it was not checked. In proper prospective PFR, each symptom should be checked in every new patient. Besides, a mean of a symptom of different medicines' prevalence will not render the same result as the prevalence of the symptom in the remainder of the population both in general LR research and in confined LR. In future, during further estimation of general LR on the same symptoms, we should check whether it fits within the 95% confidence interval or not.

In terms of LR, Homoeopathy is experiencing a transition from the notion of 'important' symptom to the LR-weighted symptoms based on modern epidemiological principles. The task is enormous; in return, we get more reliable instruments. Symptoms can be seen as diagnostic instruments and the LR as an indication for optimal use. This may be a solution to shortcomings of the repertory, for example, handling rare remedies and vagueness of reporting. Furthermore, the new data will be based on evidence instead of intuition. Moreover, this is becoming possible with the least possible interference with day-to-day practice.[6] A computer repertory can easily produce a graph that shows the increase of probability that a medicine will work with the corresponding LR. Small symptom rubrics will be difficult to assess in prospective studies because they relate to infrequently occurring symptoms.[4] In future, computer programmes may show the symptoms with the highest LR(+) to confirm a medicine, or the lowest LR(−) to exclude it.[6]

Conclusion

Of the total 166 general symptoms evaluated of 29 medicines under this CV programme of CCRH during 2005–2010, medicines having LRs and confined LRs >1.5 were identified for 6 and 49 symptoms, respectively; much were under-reported and kept for calculation in future. Thus, in spite of the substantial limitation of study design and considerable caveats in the recorded data, this paper provides the first insight into the prevalence and LRs of general symptoms of some less frequently prescribed homoeopathic medicines. Further research of this kind is warranted, but with enhanced methodological rigor.

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Conflicts of interest

None declared.

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नैदानिक सत्यापन हेतु 29 कम सामान्य रूप से निर्धारित होम्योपैथिक दवाओं के सामान्य लक्षणों की व्यापकता और संभावना अनुपात का पूर्वव्यापी अनुमान

उद्देश्यः सामान्य रूप से निर्धारित होम्योपैथिक औषधियों में से 29 के सामान्य लक्षणों की व्यापकता और एलआर का अनुमान लगाना।

विधिः अध्ययन बहु–केंद्रित, खुला एवं अवलोकन आधारित था। रोगियों को पूर्व–निर्धारित पात्रता मानदंडों के अनुसार नामांकित किया गया। साथ ही, शिकायतों, सामान्य लक्षणों को औषधि देने के दौरान ध्यान में रखा गया। सेंटेसिमल पोटेंसी में औषधियां निर्धारित की गई। सामान्य लक्षणों की एलआर गणना नैदानिक प्रस्तुत किए गए परिणामों पर आधारित थी, जो प्रस्तुत शिकायतों के लिए 'सुधार' और 'सुधार नहीं' के रूप में थीः इन्हे तीन खंडों में विभाजित किया गया थाः सबसे पहले, जब एक लक्षण का प्रसार साहित्य से उपलब्ध था, तो एलआर की गणना उत्तरदाता नमूने में उस लक्षण की व्यापकता का आकलन करके की गई; दूसरा, ऐसा न होने पर, गणना का मतलब केवल अध्ययन के नमूने (सीमित एलआर) से प्रचलित डेटा को सीमित करना था और तीसरा, 'सीमित एलआरएस' की गणना उन लक्षणों के लिए नहीं की गई थी जिनकी व्यापकता कम से कम 5 दवाओं के लिए दर्ज नहीं की गई और भविष्य में अनुमान के लिए रखी गई थी।

परिणामः 29 औषधियों के 166 सामान्य लक्षणों में से, एलआर और सीमित एलआर > 1.5 क्रमशः 6 और 49 लक्षणों के लिए प्राप्त किया गया।

निष्कर्षः काफी विरोध के बावजूद, यह कम प्रयुक्त होम्योपैथिक औषिधियो के सामान्य लक्षणों की व्यापकता और एलआरएस में पहली अंतर्दृष्टि है। आगे शोध की आवश्यकता है।

Estimation rétrospective par vérification clinique des rapports de prévalence et de vraisemblance des symptômes généraux de 29 médicaments homéopathiques prescrits moins fréquemment.

Objectif: Estimer les rapports de prévalence et de vraisemblance des symptômes généraux de 29 médicaments homéopathiques prescrits moins fréquemment.

Méthodes: L'étude était polycentrique, ouverte et observationnelle. Les patients ont été inscrits selon des critères d'éligibilité prédéfinis. Les symptômes présentés par les patients ainsi que les symptômes généraux ont été pris en compte au moment de la prescription. Les médicaments ont été prescrits dans des dilutions centésimales. Le calcul du RV des symptômes généraux était basé sur les résultats évalués par les médecins et classés en groupes « améliorés » et « non améliorés » et il a été divisé en trois catégories : d'abord, lorsque la prévalence d'un symptôme était disponible dans la documentation, le RV a été calculé en évaluant la prévalence de ce symptôme dans l'échantillon des participants ; deuxièmement, en l'absence de mention dans la documentation, le calcul a été limité aux données de prévalence moyenne obtenues de l'échantillon étudié (« RV restreint ») ; et troisièmement, les « RV restreints » n'ont pas été calculés pour les symptômes dont la prévalence n'a pas été enregistrée pour au moins 5 médicaments et ont été conservés pour une estimation ultérieure.

Résultats: Sur les 166 symptômes généraux de 29 médicaments, les RV et les RV restreints > 1,5 ont été obtenus pour 6 et 49 symptômes respectivement.

Conclusion: En dépit de mises en garde considérables, la présente étude offre un premier aperçu des rapports de prévalence et de vraisemblance des symptômes généraux des médicaments prescrits moins fréquemment. De plus amples recherches sont nécessaires.

Estimación retrospectiva de la prevalencia y el cociente de probabilidad de los síntomas generales de 29 medicamentos homeopáticos menos prescritos, verificados clínicamente

Objetivo: Estimar la prevalenciay el cociente de probabilidad (CP) de los síntomas generales de 29 medicamentos homeopáticos menos frecuentemente prescritos.

Métodos: El estudio fue multicéntrico, abierto y observacional. Los pacientes se incluyeron conforme a los criterios de elegibilidad preseleccionados. Durante la prescripción, se tuvieron en cuenta tanto las molestias presentes como los síntomas generales. Los medicamentos se prescribieron en potencias centesimales. El cálculo del CP de los síntomas generales se basó en los parámetros valorados por el médico como "mejora" o "no mejora" de las molestias presentes y se dividió en tres secciones: en primer lugar,cuando se disponía de la prevalencia de un síntoma en la literatura, el CP se calculó evaluando la prevalencia de ese síntoma en la muestra respondedora; en segundo lugar, en ausencia de la misma, el cálculo se limitó a los datos de la prevalencia media de la muestra de estudio ("CP confinado") y, en tercer lugar, no se calcularon los "CP" en síntomas cuya prevalencia no se había registrado en al menos 5 medicamentos y se dejaron para un estimación en el futuro.

Resultados: De los 166 síntomas generales de 29 medicamentos, se evidenciaron los CP y los "CP confinados" > 1,5 de 6 y 49 síntomas, respectivamente.

Conclusión: Pese a las considerables limitaciones, este estudio ofrece primeros datos sobre la prevalencia y los CP de los síntomas generales de los medicamentos menos frecuentemente prescritos. Se precisa más investigación.

Retrospektive Abschätzung von Prävalenz- und Wahrscheinlichkeitsverhältnissen allgemeiner Symptome durch klinische Überprüfungvon 29 selten verordneten homöopathischen Arzneimitteln

Ziel: Abschätzung der Prävalenz und der LR allgemeiner Symptome von 29 nicht sehr häufig verschriebenen homöopathischen Arzneimitteln.

Methoden: Es handelt sich um eine offene multizentrischeund beobachtende Studie. Die Patienten wurden gemäß der im Vorfeld festgelegten Zulassungskriterien aufgenommen. Neben der Angabeder Beschwerden wurden bei der Verordnung auch allgemeine Symptome berücksichtigt. Es wurden Centesimalpotenzen verordnet. Die LR-Berechnung der allgemeinen Symptome beruhte auf denvom Kliniker als „gebesserten" und „nicht gebesserten" gezeigtenBeschwerdenund gliederte sich in drei Abschnitte. Erstens: Wenn die Häufigkeit eines Symptoms in der Literatur gefunden wurde, dann wurde LR mittelsHäufigkeit diese Symptoms in der Stichprobeberechnet. Zweitens: Gab es keine Häufigkeit, wurde die Berechnung mangels entsprechender Angaben auf durchschnittliche Prävalenzdaten aus der Stichprobe („begrenzte LR")eingegrenzt. Drittens: „Begrenzte LRs" wurdennicht für Symptome herangezogen, wenn deren Häufigkeit für mindestens fünf Arzneimittel nicht erfasst worden war; sie wurden für zukünftige Schätzungenaufgezeichnet.

Ergebnisse: Von 166 allgemeinen Symptomen von 29 Arzneimitteln wurden LRs und begrenzte LRs> 1,5 für sechs bzw. 49 Symptome hervorgerufen.

Schlussfolgerung: Trotz erheblicher Einschränkungen ist dies der erste Einblick in die Häufigkeitund LR allgemeiner Symptome selten verordneter homöopathischer Arzneimittel. Eine weitere Forschung ist somit gerechtfertigt.

Retrospective estimation of prevalence and likelihood ratios of general symptoms of 29 less frequently prescribed homoeopathic medicines by clinical verification

通過臨床驗證對29種不常處方的順勢療法藥物的全身症狀之發病率和相似比進行回顧性評估

目的：評估29種不常處方的順勢療法藥物的患病率和全身症狀。

方法：這是多中心、非盲的觀察性研究。患者按照預先規定的納入標準登記。在提出不適時，其處方還會考慮到全身症狀。藥物則以C層級處方。基於臨床醫生評定不適結果為「改善」和「未改善」以計算全身症狀的LR，並分為三個部分：第一，如果可從文獻中獲得某一症狀的普遍率，可通過回應者樣本來評估該症狀的流行率來計算LR；第二，如果沒有，計算僅限於研究樣本中平均普遍率數據（「受限的LR」）；及第三，對於少於5種藥物記錄的症狀，其普遍率不會被用以計算「受限的LR」，只將來保留用於估算用。

結果：在29種藥物中的166種全身症狀，>1.5的LR和受限LR分別佔6和49種症狀。

結論：儘管有相當多的限制，但它是首次洞悉非常用處方順勢療法藥物的全身症狀普遍率和LR。有必要進一步研究。