Quantitative Methods for Validating Human Pathogenetic Trials in Homoeopathy

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Background:

Homoeopathy is a unique form of drug therapy which is capable of stimulating the body's own power of self healing in a special way. In order to understand what symptoms potential Homoeopathic medicines can provoke in healthy individual, Homoeopaths conduct 'Drug proving or Human pathogenetic Trials .They are the pillars of Homoeopathy. Hahnemann was one of the first to give medicines to healthy people in order to understand its effects in the sick. He was not the first, however to have had the idea. Albrecht von Haller, a Swiss doctor advocated it in1771 and Anton Storck, Head of a Viennese Hospital experienced with pharmaceutical substances on himself. But what was unique about Hahnemann was his systematic approach. In the beginning, Hahnemann used mainly mother tinctures and low potencies for drug proving, he later switched on to centesimal Potencies and many of his followers did the same. In modern HPTs, the substances have been given in the form of ultra high succussed dilution, avoiding any risk of toxicity. The question of whether HPTs using ultra high succussed dilution, yield symptoms which differ from placebo is unresolved.

Considering the great importance of Human pathogenetic Trials in Homoeopathic theory and practice, it is surprising to see that very little scientific work has been done on the particular subject. This is a weak point in research which has already taken up by critics of Homoeopathy. The debate has to focus on the weakness of traditional proving methods and steps to reform it.

Table – 1 Methodological flaws in Hahnemannian Drug proving:

Methodological flaws	**Consequences**
Absence of Control group	Prover's symptom + Random symptom + Medicine symptom
Use of well known friends as provers.	Placebo effect to please master prover.
Provers were informed about medicine.	Expectancy + conditioning effect.

Recording of all symptoms & signs.	Medicine symptoms + Naturally occurring symptoms.
Absence of masking provers & supervisors.	Selective perception + investigators effect.
Close supervision & daily recording of symptoms.	Hawthorne effects.
Sudden prohibition of tea, coffee etc.	Effects of abstinence & surfacing of hidden symptoms.
Vague definition of healthy provers.	Symptom related to prior & current disease.

HPT versus Clinical trials:HPTs have certain similarities to phase I trials for new pharmaceutical products, they are conducted on healthy volunteers, but there are key differences. HPTs are clinical trials designed to investigate the effect of the exposure of human volunteers, good in health, to potentially toxic or pathogenetic substances, diluted and serially agitated according to homoeopathic pharmacopoeial methods.

Table – 2 HPT versus Clinical trials: Differences

HPT	**Phase I clinical trial**
Use of ultra molecular doses of drugs.	Use of defined pharmacological dose
Expecting more subjective & objective symptoms.	Close monitoring of objective changes (Lab tests)
The more reliable symptoms, the better.	The fewer symptoms, the better.
High level of detail for every reported symptom.	Raw symptoms
Tendency to produce type-B reactions, but without potential serious effects.	Apt to produce type – A reactions.

HPT versus Clinical trials: Similarities

a) Non – patient volunteers.

b) Observation of subjective & objective changes.

c) Multiple or more specific end points.

d) Controlled experiments.

e) Small number of subjects (20 – 100).

Current trends in HPTs:

Necessity of placebo controls:

For more than 100 years proving have been done without placebo control. The Placebo control in a HPT is only useful, if introduced as an intra – individual control, i.e, a crossover design. Parallel – group designs are of no value in HPT. There are so many variables which govern the variance of individual symptoms that in parallel – group designs only very large numbers (several 100 or so) may give a chance of controlling them by randomization. But if we use intra – individual control, we have to be aware of carry over effects. If there are carry over effects, the design is compromised, and only the first half of the experimental period can be used. So the crossover design with all its inherent difficulties remains the candidate of choice, but it is vital to control the carry-over effect either by a washout period. (1)

Methodological Quality Index for HPTs:

A Methodological Quality Index is introduced to assess the reliability of HPTs. It is based on key components of methodological quality including internal and external validity items. The MQI includes aspects such as randomisation, inclusion and exclusion criteria, blinding and criteria for selection of pathogenetic effects with values ranging from 1 to 4 for each component, giving arrange from 4 to 16.Scoreweredivided into 4 methodological classes, where class I is the worst and class IV is the best, with arbitrary cutoff points (< 6 for class I, 7-10 for class II, 11-13for class III, > 14 for class IV).

Table - 3 Methodological Quality Index for HPTs

Component	Score			
	1	2	3	4

Randomisation	Not stated	Only stated	Description of Sequence Generation or allocation concealment	Description of Sequence Generation and allocation concealment
Blinding	Not stated	Single blind	Double blind Without verification	Double blind with post trial verification
Inclusion & Exclusion Criteria.	Not stated	One partially stated	One clearly stated or both partially stated.	Clearly stated
Criteria for selection of effects	Not stated	At least one defined	2 to 4 defined	More than 4 defined

Symptom selection criteria:

A) Nine item pathogenetic index.

In order to judge which symptoms are likely to have been due to treatment, symptoms are assessed by a 3 – stage 'filter'. The first stage is the volunteer's personal judgment concerning the cause of their symptoms; the second stage is the supervisor's judgment, the third stage is 'nine item pathogenetic index'. The Pathogenetic index is adapted from a standard index for judging the causality of possible adverse drug reactions. All such judgments by supervisors or volunteer are made blind. The 'nine item pathogenetic index' yields scores from -6 to +13. Scores from -6 to 0 indicated symptoms unlikely to be associated with medication. Scores from +1 to +4 are considered 'compatible'. Scores from +5 to +8 are 'suggestive' and scores from +9 to +13 are 'highly suggestive'.

Table – 4 Nine item pathogenetic index

Item No.	Question	Yes	No	Don't know
1	Did the symptom appear within seven days of Starting medicine?	+1	-1	0
2	Was the symptom strange or extraordinary to the Volunteer?	+3	0	0
3	Did the volunteer experience a similar symptom in the pre- observation period or the preceding 30 days?	-1	+1	0
4	Are there alternative causes that could have caused the reaction?	-1	-2	0
5	Did the symptom recur when the medicine was readministered?	+2	-1	0
6	Did the volunteer strongly associate the symptom with the trial medicine?	+1	-1	0
7	Did the symptom improve when the trial medicine was discontinued or a specific antagonist was administered?	+1	0	0
8	Did the symptom also occur with placebo?	-2	+1	0
9	Was the reaction more severe with the repetition of the medicine?	+1	0	0

B) Rating of Symptoms: Four Point Scale.

Four point scales for rating symptoms was suggested by Vithoulkas.

Table – 5 Four Point Scale

Scale	Character of Symptom
No Underlining	Vague Symptom
1 Underlining	More clear and intense, But only mentioned when asked.
2 Underlining	Very clear and obvious. Symptoms, when asked for or Mention spontaneously.
3 Underlining	Very strong. Spontaneously mentioned symptoms.

Statistical methods:

Spearman correlation coefficients (r_s) are used to verify relationships between validity and reliability of information from HPTs, including association between Methodological Quality Index and subjective judgments by reviewers. Kappa statistics are used to evaluate agreement between reviewers on judging methodological quality components and to estimate the disagreement on global judgments of quality.

The application of Quantitative Techniques adopts a scientific approach to Human Pathogenetic Trials. The use of proving data in a systematic manner and constructing it into a Materia medica for future use is major function Human Pathogenetic Trials. This processing and manipulating of raw data into meaningful information is the heart of scientific analysis. The aim of the quantitative methods is to improve detected symptoms and gain a finer resolution of observed symptoms by implementing the proving method developed by Hahnemann and his followers. We should combine this phenomenologically accurate method with rigorous methodological standards.

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