

A Systematic Review of Homeopathic Pathogenetic Trials

- Context.
- The popularity of Homeopathy
- The importance of HPTs in developing the knowledge base of Homeopathy
- Previous reviews of the literature

- **Gathering the evidence for this review**
Inclusion criteria. Included studies
- **Issues and dilemmas.**
- **Findings of this review**
- **Recommendations**

Context. The popularity of Homeopathy

- The World Health Organisation estimate that 500 million people worldwide use homeopathy (WHO 2005)
- In the UK it is estimated that 15% of the population use and trust Homeopathy (TGI 2008).
- Homeopathy has also always been a part of the state funded National Health Service in the UK (since it began in 1948)
- There are currently four homeopathic NHS hospitals receiving 55,000 referrals a year
- 400 General Practitioners practise homeopathy, treating 200,000 patients per year with homeopathic medicine within primary care. (British homeopathic Association 2009).

The importance of HPTs to Homeopathy

- HPTs (often referred to as provings) remain one of the major sources of knowledge and data for the practice of homeopathic medicine
- Homeopathy is based on the idea of similars, that 'like cures like'.
- For 200 years, researchers have tested homeopathic medicines on healthy persons, observing symptoms which follow and using those observations as the basis for using the same medicines in those who are ill.

Are HPTs reliable?

- From the perspective of much of modern science and of health research, homeopathy appears implausible.
- From a critical perspective the symptoms observed in HPT's might be due to various sorts of bias rather than being genuine pathogenetic effects, 'caused' by the medicine.
- Many published HPTs appear to attribute all symptoms that are reported by participants during a trial to pathogenetic effects of the medicine.

Possible sources of bias in HPTs

- The absence of a control group (due to temporal effects and/or regression to the mean)
- The absence of random allocation
- The absence of blinding
- The inclusion of trivial and pre existing symptoms
- The lack of a definition of a healthy volunteer
- The use of well known friends as volunteers
- The sudden prohibition of all medicinal drugs and foodstuffs.

Existing reviews of HPTs

Dantas et al reviewed the quality of HPT's in a paper published in Homeopathy entitled "*A systematic review of the quality of homeopathic pathogenetic trials published from 1945 to 1995*". The paper was not published until 2007

(Homeopathy 2007 96)

They highlighted the poor methodological quality of most HPTs and the results of this. For example two trials of the same medicine showed a 5000% difference in the number of symptoms reported, the difference seemingly related to a significant difference in quality.

I aimed to update and expand on this work by looking at quantitative as well as qualitative data

Title and aim of the review

To determine whether the effects of homeopathic substances (ultra molecular dilutions) on human subjects differ from the effects of placebo in homeopathic pathogenetic trials. (HPTs)

Inclusion criteria for this systematic review

- This review only included studies with the following features
- Participants -Adults aged 18+
- Interventions - The ingestion of one or more doses of homeopathic substances (ultra molecular dilutions).
- Comparators - Studies which reported comparing homeopathic medicines to identical placebo medicines.
- Outcomes -any outcome relating to symptoms experienced at any point in the duration of the trials. Methods for recording symptoms include the daily completion of an unstructured diary by participants, structured diaries and specially developed proving questionnaires.
- Study Designs - RCTs

Searching the literature 1 - Databases

Database	Date Range
OID MEDLINE	Jan 1996-May 2009 (wk 4)
AMED	Jan 1996-May 2009 (wk 4)
EMBASE	Jan 1996-May 2009 (wk 4)
CINAHL	Jan 1996-May 2009 (wk 4)
HOMINFORM	All dates
LILACS (English language only)	Jan 1996-May 2009 (wk 4)

Included studies

- Title and abstracts identified and screened - n = 503
- Excluded - n = 487
- Full copies retrieved and assessed for eligibility - n = 17
- Additional studies identified after contact with experts - n = 1
- Excluded – not relevant design - n = 6
- Excluded – no outcomes - n = 1
- Publications meeting inclusion criteria - n = 11
- **Number of studies included in the review - n = 15**

Included studies

- Brien S, Lewith G and Bryant T (2003) S. Brien, G. Lewith, T. Bryant, Ultramolecular homeopathy has no observable clinical effects. A randomized, double-blind, placebo-controlled proving trial of Belladonna 30C *British Journal of Clinical Pharmacology* 2003;56(5): 562-568
- Dominici G et al (2006) Double blind, placebo controlled homeopathic pathogenetic trials: symptom collections and analysis *Homeopathy* 95,123-130
- Goodyear K Lewith G and Low JL (1998) Randomised Double blind, placebo controlled trial of homeopathic proving for Belladonna C30 *Jrnl of the Royal Society of Medicine* 91 579-582
- Fisher P and Dantas F (2001) Homeopathic pathogenetic trials of Acidum Malicum and Acidum Ascorbicum *British Homeopathic Journal* 90 118-125
- Mollinger H Schneider R and Walach H (2009) Homeopathic pathogenetic trials produce specific symptoms different from placebo *Forsch Komplementmed* 16 105-110
- Signorini A et al Classical and new proving methodology: provings of Plumbum metallicum and Piper methysticum and comparison with a classical proving of Plumbum metallicum. *Homeopathy*. 2005 Jul;94(3):164-74.
- Vickers A McCarneyR Fisher P and Van Haselen R (2001) Can homeopaths detect homeopathic medicines? A pilot study for a randomised double blind placebo controlled investigation of the proving hypothesis. *British Homeopathic Journal* 90 126-130
- Walach H et al (2001) the effects of Homeopathic Belladonna 30CH in healthy volunteers – a randomised, double blind experiment. *Jrnl of Psychosomatic Research* 50 155-160
- Walach H et al (2004) Homeopathic proving symptoms result of a local non local or placebo process? A blinded placebo controlled pilot study *Homeopathy* 93 179-185
- Walach H et al (2008) Homeopathic pathogenetic trials produce more specific symptoms than non specific symptoms: results from two double blind placebo controlled trials. *Jrnl of psychopharmacology* 22(5) 543-55

Issues and dilemmas

- Idiosyncratic symptoms or those known in Homeopathy as 'strange rare and peculiar' are thought to be very significant in HPTs, and to provide strong clues for prescribing.
- They occur in few or no volunteers in small HPTs and may be discounted in studies which focus on exclusively quantitative statistical analysis.

Issues and dilemmas

- On the one hand symptoms which occur during an HPT in only one or a small number of participants may be chance occurrences, attributable to what might be termed 'background noise'.
- On the other hand such rare symptoms may be genuine pathogenetic effects. Homeopaths believe that such symptoms are often subsequently shown to be very reliable prescribing indicators in practice.
- Kaptchuk (1996) has concluded that "homeopathy *still has no clear answer to the question of rare symptoms versus chance symptoms in provings*".

Issues and dilemmas

- Homeopathic theory suggests that only people who are sensitive or susceptible to a particular homeopathic medicine will respond to it – the idea of individualising.
- This is true in clinical practice and also in HPTs
- Evidence from the trials included in this review suggests that proving reactions and pathogenetic effects are unlikely to occur in more than 14% of a random sample of the population. (see also Goodyear 1998)

Issues and dilemmas

- Levels of nocebo symptoms in any random sample of the population are likely to be at least at the same level.
(Kaptchuk 1996, Green 1964)
- Therefore HPTs which involve random samples of the population are unlikely to show quantitative differences between placebo and intervention groups.

Key findings

- Only 3% of studies located met the inclusion criteria
- None of the studies that met the criteria used any screening procedures for selecting participants for sensitivity to the medicine being tested.

Findings – proving reactions

- A number of researchers adopted the strategy of pre-defining a proving reaction and then assessing how many participants demonstrated this.
- Defined as e.g 2 true symptoms on 2 consecutive days and no false symptoms.
- Results according to proving reactions were as follows

<u>Study</u>	<u>Participants showing a proving reaction</u>
• Vickers and Van H	4/52 (8%) verum 1/52 (2%) placebo
• Goodyear	5/20 (25%) verum 1/27 (3.%) placebo
• Brien	14 /101(13.9%) verum 15/105 (14.3%) placebo

Meta analysis

- Pooling of the heterogeneous outcomes from the three trials showed no significant differences

Figure 3.11 Meta analysis (fixed effects model) Participants showing a proving reaction.

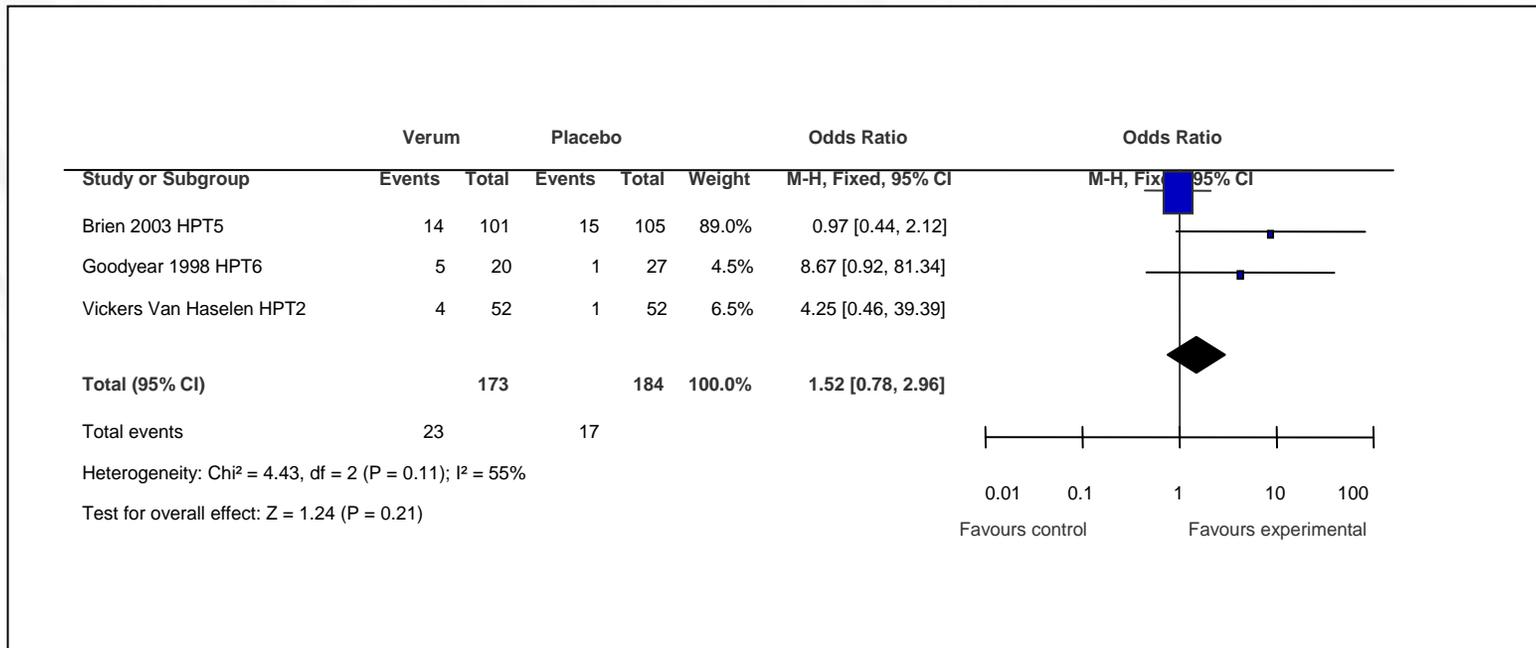
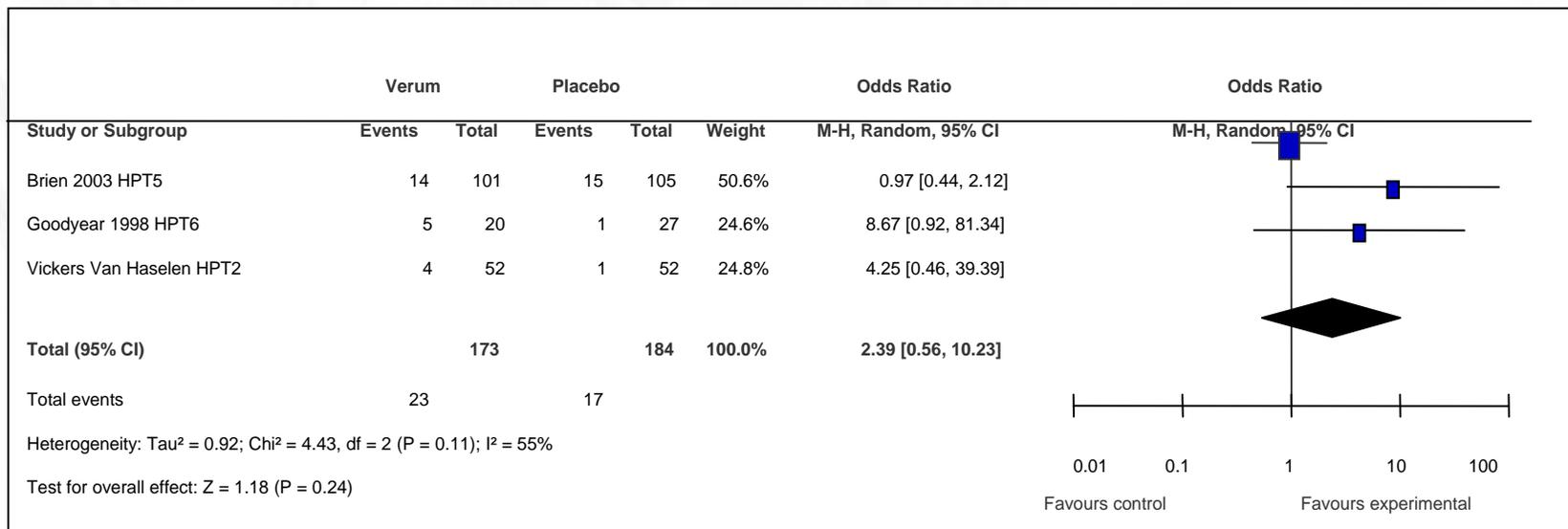


Figure 3.11 Meta analysis (fixed effects model) Participants showing a proving reaction.



Symptoms typical of the test medicine

- The other approach to measuring outcomes which was typically taken was to pre-define symptoms which would be typical of the test medicine (based on previous trials or other sources of knowledge)
- Nine of the included studies used such measures. Three of these reported significant differences between verum and placebo groups. Only one of these three had statistical data which was suitable for pooling.
- Thus no statistical significance was found on these measures.

Limitations of the study

- Publication bias
- Trial size – 9 of the 15 studies included has less than 50 participants
- Language bias – the study was limited to trials which were fully available in English
- Lack of screening participants for sensitivity to the homeopathic medicine

Recommendations.

- It is recommended that , in order to reduce bias, and to increase the likelihood of distinguishing genuine pathogenetic effects from placebo effects and background noise, study designs for HPTs should include:
- Randomisation, using explicit procedures
- Use of placebo comparator groups
- Blinding of participants and researchers and verification of blinding
- Dealing with loss to follow up and adverse events appropriately.
- Using validated outcomes measures
- Operationalising the definition of health which is used as a standard inclusion criteria for HPTs. The use of the SF36, or some other well validated and widely used measure is suggested.

Recommendations

- It is important that techniques are developed for screening participants for sensitivity/susceptibility to the medicine used in the trial (Vithoulkas 2000, Herscu 2002)
- The REDHOT guidelines (Reporting Data on homeopathic Treatments (RedHot): A supplement to CONSORT, Dean et al 2006)which were specifically developed to improve the conduct and reporting of trials in homeopathy should be updated to include guidance specifically relating to the design, conduct and reporting of HPTs.