The 2005 Lancet review proved superior quality of homeopathy trials

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More than 30 years ago I started medical practice as a General Practitioner without any knowledge of homeopathy. It appeared that many patients had poor results with my conventional therapies, because complaints frequently returned. Then some patients came to tell me that homeopathy cured what conventional therapies could not cure. And I became intrigued; first of all because it would be arrogant not to be intrigued after my failure.

The only thing I knew about homeopathy was that it could not work because of the dilutions. Giving it some second thought I realised that this only meant that it could not work like conventional medicines, and, indeed, patients told me that it worked differently. Of course, I realised, this could be the reason that homeopathy worked after conventional medicine failed, it works differently! How important is a theoretical explanation? The famous Polish scientist Nicolaus Copernicus (1473-1543, figure 1) followed his own observations and showed that theory can be totally wrong. Rejecting homeopathy on theoretical grounds would lead science back to the Middle Ages. Anything that works is worth investigating. There is so much we don't know, especially about living nature.

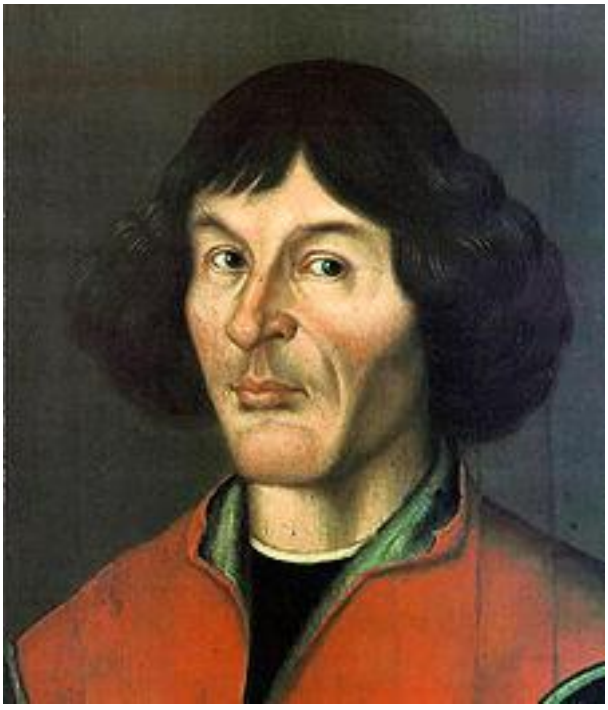

Figure 1: Nicolaus Copernicus (1473-1543)

The first thing to investigate was the assumption that homeopathy is a placebo effect. The gold standard for such research is the Randomised Clinical Trial (RCT). After a sufficient number of RCTs this proof can be analysed by meta-analysis.

Subjectivity

But even in the utmost gold standard of science in medicine, the meta-analysis (systematic review) of RCTs, subjectivity is involved. After analysing a large number of reviews from the worldwide Cochrane database Ezzo concluded: *"The number of reviews indicating that the modern biomedical interventions show either no effect or insufficient evidence is surprisingly high. Interrater disagreements suggest a surprising degree of subjective interpretation involved in systematic reviews"*.[1]

Apparently the shining of our gold standard depends on the light that is thrown on it. The renowned epidemiologist professor Jan Vandenbroucke stated in 2001*: "A reflection of the scientific behaviour of adherents of conventional medicine toward one form of alternative medicine – homeopathy – teaches us that physicians do reject seemingly solid evidence because it is not compatible with theory"*.[2]

At the moment four large meta-analyses have been published:
1991: Kleijnen et al.[3] 105 trials
Conclusion*: "The amount of positive evidence even among the best studies came as a surprise to us. Based on this evidence we would readily accept that homeopathy can be efficacious, if only the mechanism of action were more plausible... the evidence presented in this review would probably be sufficient for establishing homeopathy as a regular treatment for certain indications"*

1997: Linde et al.[4] 186 trials, 89 suited for analysis.
Conclusion: *"The results were not compatible with the hypothesis that the effects of homeopathy are completely due to placebo"*

2000: Cucherat et al.[5.] 184 trials
Conclusion: Chance that homeopathy is merely a placebo effect, based on 17 'best' trials (2.001 patients) $p<0{,}001$, but quality is too low.

2005 Shang et al.[6] 110 Homeopathy trials compared with 110 matched conventional trials.

All four meta-analyses concluded that the overall result is comparable with conventional medicine. The second and third analyses conclude that the result is still positive in good quality trials, the third that quality of the trials is low.

Re-analysis

The last analysis got by far the most publicity. Was it because it concluded negative for homeopathy? Anyway, it is the most interesting analysis because it was performed by a team led by a very competent opponent of homeopathy, professor Matthias Egger. Few people know that Egger in fact analysed homeopathy twice. He asked for, and received, Linde's source data and plotted them in British Medical Journal in 2001,[7] and later in his re-analysis in the Lancet in 2005. The two plots are shown in Figure 2.

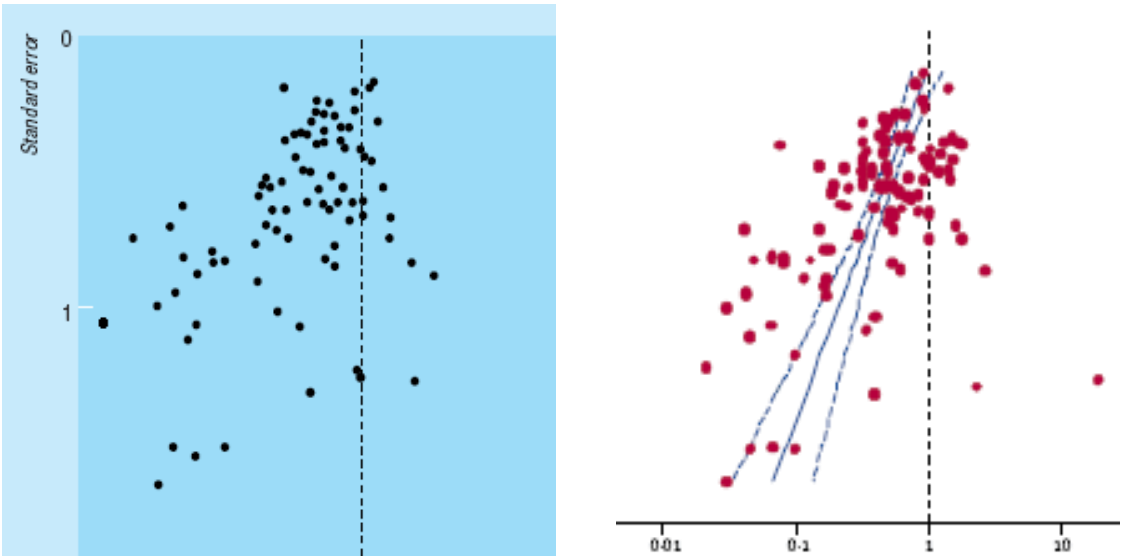

Figure 2: two analyses of homeopathy trials by Egger, left 2001 (source: Sterne, Egger, Smith; BMJ 2001;323:100-105) regarding 89 'Linde studies', right 2005 (source Shang, Egger et al; Lancet 2005;366:726-732) regarding 110 studies

In these plots the dots left of the dotted vertical line represent the positive trials, the effect of the homeopathic medicine is stronger than placebo. The dots right of the vertical line represent the trials where placebo works stronger than the real medicine. In the lower part of the plot are the smaller trials, with few patients. The largest trials are in the top of the plots. The left plot is made by Egger in 2001, the right in 2005. Something strange happened with the right plot. It contains, of course, more trials (110) because it adds later data then the 89 in Linde's analysis. However, four very positive trials in the upper left quadrant of the 2001 plot disappeared in the 2005 plot. According to the post-publication data 'no matching trials' could be found for these trials.[8, 9, 10, 11] The result, however, is a more asymmetric plot. Moreover, Egger hypothesises that large trials are better, but not everybody agrees on that point.

Because of the subjectivity of meta-analyses the Cochrane Collaboration warns: *"Reliable conclusions can only be drawn from analyses that are truly pre-specified before inspecting the trials' results"*.[12] The leader of the 2005 analysis of homeopathy was familiar with most of the trials beforehand. Why was the 2001 analysis not mentioned in the 2005 paper? It was also surprising to see that out of the six best trials in Linde's analysis four were not qualified as good. These four trials were published in leading medical journals.

The left plot in Figure 2 was based on the analysis by Linde in 1997. Based on the same analysis Vandenbroucke challenged his audience in the 175th anniversary lecture of the Lancet: *"Let us imagine that this funnel plot was not about homeopathy, but about something we believe in - our favourite disease and our favourite drug which we are certain works. If the funnel plot looked exactly like this plot, what would we say? We would look at the funnel plot and we would admit: "Yes, we know that the literature is always somewhat optimistic, but even if you leave out the outliers, a sizeable effect remains, doesn't it? And if you look especially at the high quality trials, the effect is still there. And what of the few largish trials with no effect? These were done by people who do such large but sloppy trials, they did not use the right dosage, or the right timing, and they failed to exclude properly patients with contraindications. And, now that we think of it, we can explain those outliers: this must be a subpopulation of patients with more severe disease, and that is why they are apart. The drug*

is more effective among them; you can see it. They have their own little funnel plots". Does this sound familiar?".[13]

In short: any plot of trials can be criticised, even regarding the best medical therapies, and interpretation is subjective. Vandenbroucke questions the quality of large trials.

Hypothesis: asymmetry and quality bias

Egger formulated his hypothesis about the positive results of homeopathy in 2001 (BMJ). He stated that poor quality could have caused exaggerated effects, and that for quality bias another method of analysis should be used: meta-regression analysis. In meta-regression analysis you draw a regression line through the plot and extrapolate it towards the largest trials (see Figure 3, left part). If the plot is asymmetric and the line inclines towards zero effect in the top this could mean that the largest trials render no effect. But you have to be careful because asymmetry in the plot is not always caused by bias.

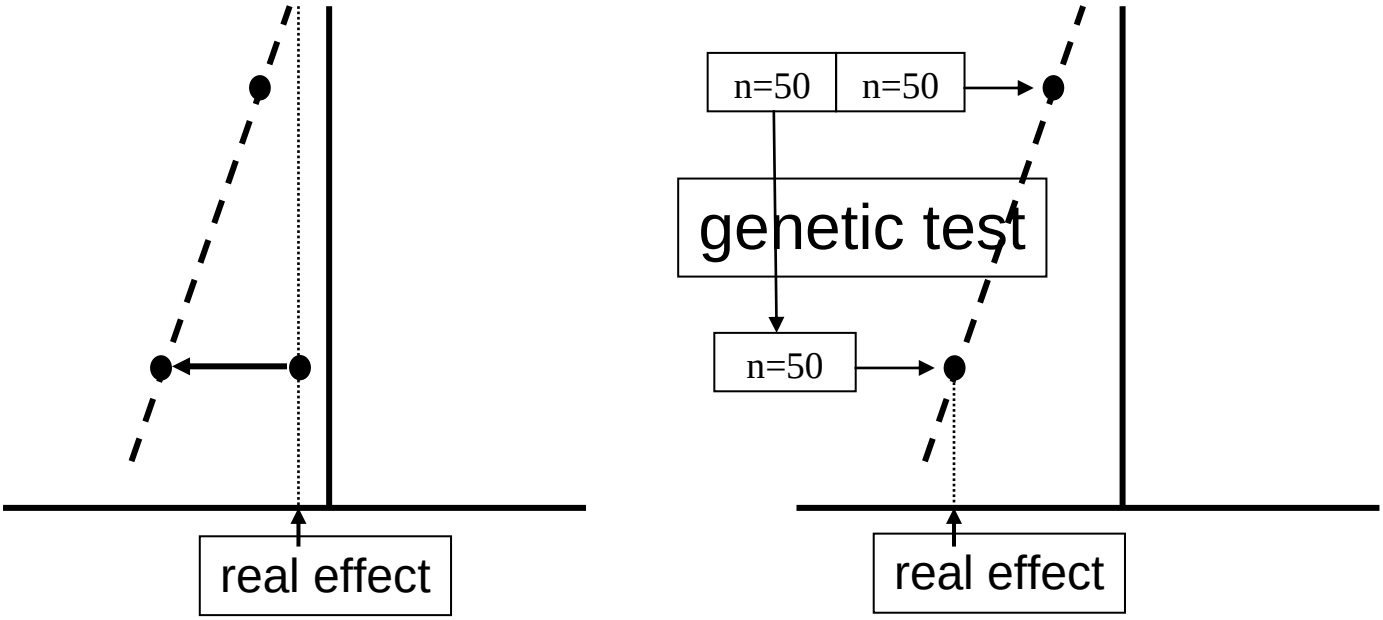

Figure 3: difference between high quality and low quality. Left: in low quality exaggerated effects, that diminish in larger trials; therefore extrapolation towards largest trials to estimate effect. Right: in high quality studies stronger effect is explained by better selection of patients, and therefore real effect.

Why can smaller studies rightfully show stronger effects and cause an asymmetric plot? Suppose you want to test a conventional medicine for hypertension on 100 patients. It is known that genetic factors can influence the effectiveness of this kind of medication. Now suppose that you have a genetic test for selecting the 50% of the patients that will respond better to this medicine. Then you have a stronger effect in a smaller group of 50 patients, see right part of Figure 3. The same goes for homeopathy: homeopathic medicines should be carefully selected to fit the patient.

On the other hand, if you have a low quality trial where you give the patients that receive the placebo odd numbers and the verum patients even numbers (bad allocation concealment), the doctors will recognise the patients by their numbers. It is, however, not clear if allocation concealment affects smaller trials more.

So, meta-regression analysis should only be performed on low quality trials. In his 2001 analysis of homeopathy Egger concluded that meta-regression of Linde's trials did not prove that the apparent benefits of homeopathy were due to bias, but he suspected a combination of publication bias and inadequate methodological quality.

In the 2005 analysis Shang, Egger et al compared 110 homeopathy trials with 110 conventional trials matched on diagnosis. Their conclusion that homeopathy was a placebo effect and that conventional medicine was, however, based on a comparison of 8 homeopathy trials with 6 conventional trials. How is this difference in numbers possible in an analysis that was qualified by the authors as "a comparative study of carefully matched trials"?

Normal science?

Looking back at the course of events we ask ourselves: is this normal science? Is it normal science that authors repeatedly refuse to supply essential data to support their conclusion? The steering committee for this analysis criticised in the final report the authors regarding this point the 24th of April 2005, [14] but in the Lancet publication four months later (August 27) these data were still missing. After the publication people asked for this information by telephone, but this was refused. In the reply to letters to the editor of the Lancet (December 17) only the 8 homeopathy and the 6 conventional studies that were used for the conclusion were supplied.[15] December 23d the rest of the data were supplied, but the authors supplied no Odds Ratios (ORs) or Confidence Intervals (CIs), only graphs. Therefore, the ORs and CIs had to be reconstructed from the original articles, a time-consuming process.

Because of the missing data no adequate response was possible shortly after the Lancet publication, we could only ask questions like:
- was this really a comparative analysis?
- the influence of subjective choices; which easily leads to cherry picking to get desired results?
- influence of ineffective treatments?

Is it normal publishing policy that the Lancet published a paper with so much impact that did not comply with the QUOROM statement that meta-analyses should supply essential data? Is it fair that, within the given time, no adequate response could be given because data were still not supplied? Is it fair that a response after reconstructing the data in June 2006 was immediately rejected by the Lancet? This response was published by the Journal of Clinical Epidemiology in October 2008, after extensive review.[16]

Matching and comparability

Even after the critics the authors maintained that their conclusion was based on ".. a comparative study of carefully matched trials". This was not true, the conclusion was based on a subgroup where matching was lost. The comparability of the homeopathic and conventional trials was flawed from the beginning because the homeopathy group comprised 16 (15%) unpublished trials and the conventional group none. It is well known that in conventional medicine unpublished trials have less positive outcome. According to Chan et al the odds of publishing results in conventional medicine are greater if results were significant (pooled odds ratio 2.4, 95% CI 1.4 to 4.0).[17]

The authors of the Lancet analysis started with a comparison of quality and went on with comparison of effect in subsets where matching was lost. The degrees of matching in the most relevant groups were:

110 homeopathy - 110 conventional	100%
Trials with n<100	82%
Trials with n<66 (median)	65%
'higher quality'	19%
Conclusive subset	37.5%

Another difference between the two groups was safety. Homeopathy appears to be safe in trials and in practice and the authors admitted that they did not consider safety. We will show this influence later.

Subjective choices

Were subjective influential choices made, in other words: was cherry picking involved? The first striking choice was mentioned before: a new definition of quality that caused 4 out of 6 Linde's best trials not to be regarded as good. These trials were at the time of publishing regarded as top-quality by top-journals. Table 1 shows the four best quality trials according to Linde that were discarded by Shang et al.

First author	Indication	Sample size	OR	95% CI of OR
de Lange-de Klerk[18]	Upper respiratory tract infection	170	0.85	0.47 to 1.53
Reilly[19]	Pollinosis	144	0.43	0.22 to 0.85
Hofmeyr[20]	Childbirth	122	1.03	0.40 to 2.64
Reilly[21]	Asthma	24	0.08	0.02 to 0.40

Table 1: The four best studies according to Linde et al, arranged by sample size.

The inclusion of the four trials would have had little influence on the effect of all good trials, Odds Ratio would shift from OR=0.76 (95% CI 0.59-0.99) for 21 trials towards OR=0.74 (95% CI 0.59-0.94) for 25 trials. But we will see that there is a definite influence on the conclusive subgroup.

The second striking choice was the definition of 'larger trials'. Semantically this seems straightforward: smaller or larger is a dichotomy, so the cut-off value should be the trial with median size. So, larger trials are trials with sample size above median, in this case n>65, including 14 good quality trials.

The authors, however, defined 'larger' as “Trials with Standard Error in the lowest quartile”, including 8 high quality homeopathy trials. This striking choice gave a striking difference. 'Above median' rendered the best, significantly positive, result for homeopathy, the author's choice gave the worst, not significantly positive, result for homeopathy. Despite the importance of Standard Error (SE), the authors did not provide SE in their post-publication data.

These two choices constituted the subgroup 'Larger higher quality trials', shown in Table 2.

Indication	homeopathy	conventional medicine
Diarrhoea	Jacobs[22] **N=116**	Kaplan[23] **N=256**
Treatment of influenza	Papp[24] **N=334**	Nicholson[25] **N=319**
Prevention of influenza	Rottey[26] **N=501**	de Flora[27] **N=248**
Plantar warts	Labrecque[28] **N=162**	
Weight loss.	Schmidt[29] **N=208**	
Muscle soreness	Vickers[30] **N=400**	
Headaches.	Walach[31] **N=98**	
Sinusitis	Weiser[32] **N=104**	
Stroke (venous)		Horn[33] **N=454**
Post operative infection		Crowley[34] **N=273**
Pollinosis		Möller[35] **N=146**

Table 2: Larger higher quality studies, according to Shang et al

Looking at table 2 it is obvious that this was not a 'comparison of carefully matched trials'; only three out of eight homeopathy trials were matched with conventional trials. The fact that the eight homeopathy trials were about eight different indications is contrary to the Cochrane recommendation that *"Meta-analysis should only be considered when a group of trials is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary"*.

Matching of trials could have been improved by including Reilly's trial on pollinosis with a sample size of 144 and regarded as top-quality by the Lancet in 1986. In that case even the cut-off value for 'larger trials' chosen by the authors would have given a more positive result for homeopathy, because for Reilly's trial OR=0.43 (95% CI 0.22-0.85).

The influence of one out of 16 indications

In reply to the letters to the editor of the Lancet of December 17th, Shang, Egger et al had two answers. The first was that the comparison was carefully matched. We refuted this above. The second answer was: *"Why did this (no result in the conclusive subgroup) not happen in the case of conventional medicine?"*. The answer to this would have been clear if a sensitivity analysis regarding the role of different indications were included. Egger warned earlier *"Opinions will often diverge on the correct method for performing a particular meta-analysis. The robustness of the findings to different assumptions should therefore always be examined in a thorough sensitivity analysis"*.[36] The answer lies in selective inclusion of one out of 16 indications in the group 'good quality trials', see Figure 4.

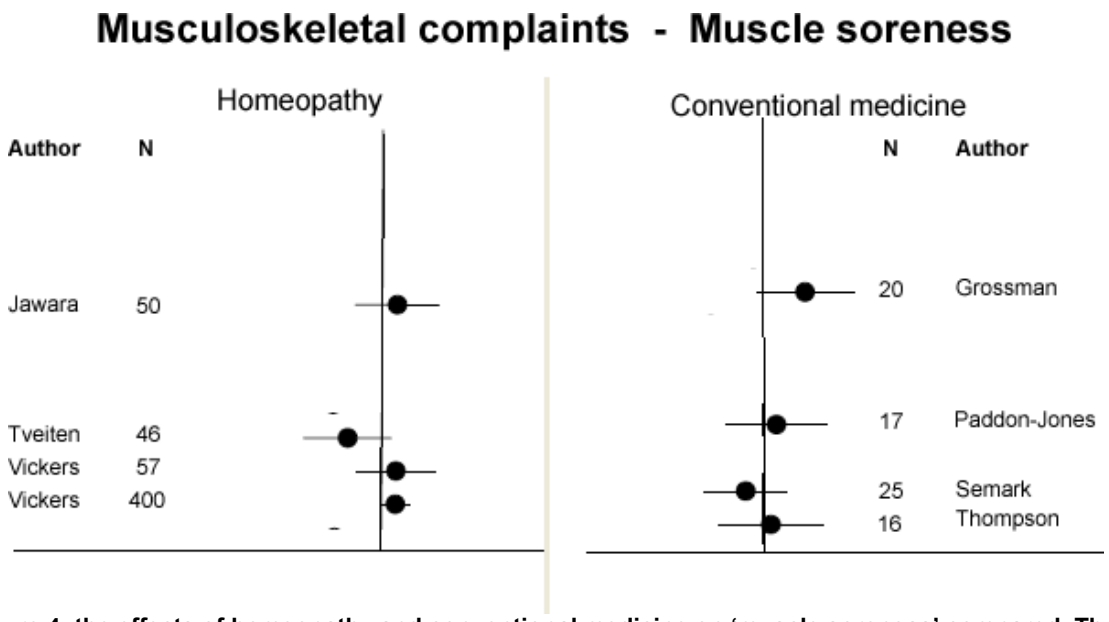

Figure 4: the effects of homeopathy and conventional medicine on 'muscle soreness' compared. The other trials in the group 'Musculoskeletal complaints' are disregarded. The four studies concerning muscle soreness for both methods are indicated by author names. N = trial size. Source www.ispm.ch.

The indication 'Muscle soreness after marathon' is attractive from an organisational point of view, but we must realise that we are dealing with very healthy people in this case. It is quite possible that medicine cannot 'cure' in this case because there is nothing to cure. And indeed, neither homeopathy, nor conventional medicine were effective for this indication: three out of four trials gave negative results for homeopathy as well as for conventional medicine. But the four homeopathy studies were regarded as good quality studies and all conventional studies were not. All homeopathy studies were also larger than the conventional studies. This means that the homeopathy studies are higher in the right plot in figure 1 and cause more asymmetry.

Figure 5 shows how great the influence of this single indication was on results. We calculated cumulative effects starting with the two largest trials and successively adding trials in descending order of patient numbers. Below the horizontal line the effect is positive. The left-hand plot is the original set of 21 trials with 'muscle soreness' included, the right-hand is without the indication 'muscle soreness', but including Linde's four high quality trials. Adding these four trials did not change overall results, but discarding 'muscle soreness' made a big difference: homeopathy was significantly effective in most combinations.

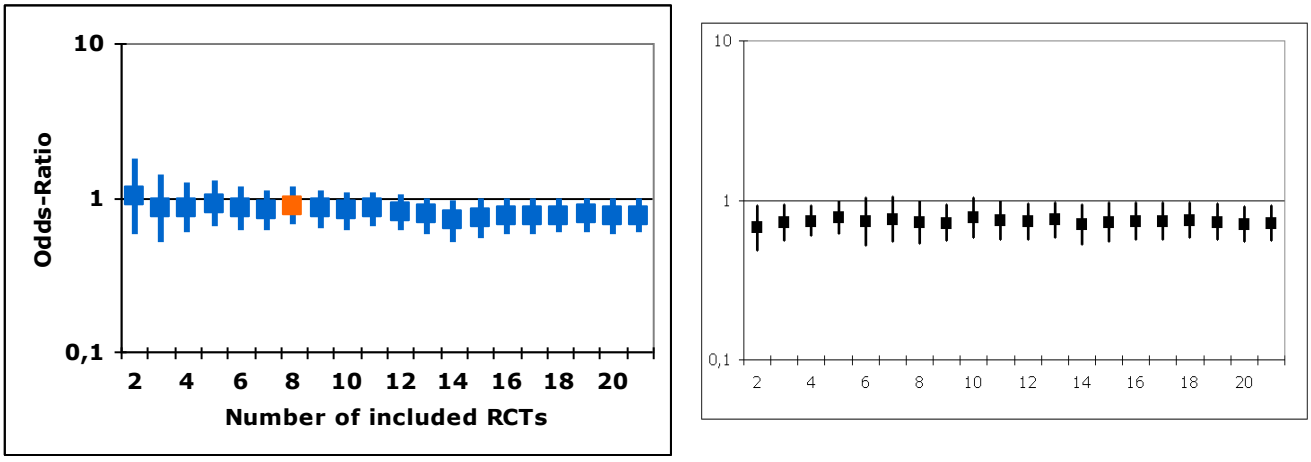

Figure 5: plots of overall ORs (random effects analysis) and CIs, against the number of included trials, successively drawn from the high quality trials in order of sample size. Left including the indication 'muscle soreness' (4 trials), left excluding 'muscle soreness', but including Linde's 4 best trials

We conclude that the conclusion of Shang, Egger et al was based on a sequence of 8 disputable choices:
1. discarding larger positive trials
2. new quality criteria discarding 4 out of 6 top-trials
3. incomparability by disrupted matching
4. incomparability because of different quality
5. different publication bias and safety
6. strange definition of 'larger trials'
7. selective inclusion of one ineffective therapy
8. heterogeneity: 8 trials on 8 indications

But, even then …

We showed that a number of disputable choices were made to arrive at the conclusion that homeopathy is a placebo effect. But, even then …. Was this conclusion rectified?

Let us follow Vandenbroucke's challenge and look at the result as if it were about a generally accepted conventional therapy.

The conclusion for homeopathy was based on OR=0.88 (CI: 0.65-1.19), the total sample size n=1923.

World-wide many billions of dollars are spent on statin treatment. In a meta-analysis of statin treatment and the occurrence of haemorrhagic stroke Vergouwen et al found an effect of OR=0.88 (CI:0.78-0.99).[37] This is the same OR as in Shang's final subset, but the 95% Confidence Interval did not include 1.0 because the sample size was much larger.

If we increase sample size for homeopathy by including all good quality trials as defined by Shang, Egger et al (also 'muscle soreness') sample size grows to n=2651. Although this sample size is much smaller than the statins example we get a statistically significant result: OR=0.76 (CI:0.59-0.99).

All textbooks on epidemiology warn for this pitfall: the type II error or false negative conclusion based on insufficient sample size.

Cherry picking

What happens if we take another standpoint? We respect existing quality criteria that top-journals applied to accept trials for publication, we define 'larger' semantically correct as 'above median sample size', and we perform the sensitivity analysis Egger recommended and exclude the indication 'muscle soreness'. The result for the selection of 'larger good quality trials' would be OR=0.76 (95% CI 0.57-0.97, p=0.0273).

Does this prove that homeopathy works? No, we would be accused of cherry picking because we used a selection of 21 trials. Well …, that was precisely what we wanted to prove: the conclusion of Shang, Egger et al was based on cherry-picking. Or, to put it more scientifically:

The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials

By-the-way: this conclusion is valid for most meta-analyses in medicine! Conclusions based on subgroup-analyses can always be disputed.

What is new in the 2005 analysis?

We filled in some missing data in the 2005 analysis by Shang/Egger et al and we showed that conclusions based on subsets can easily be qualified as cherry picking. That is actually no news and proof for homeopathy is still comparable to proof for conventional medicine. Former analyses showed that homeopathy worked even if only good quality trials were analysed. The negative conclusion of the 2005 analysis was cherry-picked by a new definition of quality, a disputable definition of 'larger trials', heterogeneity and a false negative conclusion.

So, was there anything useful in this analysis? Then we have to go back to the original hypotheses:
1. Bias is larger in homeopathy than in conventional medicine
2. This bias is more likely to affect small studies

The outcome of the first hypothesis was in the Lancet paper: 21 (19%) of the homeopathy trials and 9 (8%) of the conventional trials were of good quality, The first hypothesis was falsified (p=0.03).

Curiously, the second hypothesis was not considered in the Lancet paper. For the second hypothesis we have to choose a cut-of value for 'smaller trials'. We chose n<100 because it was near the cut-off value of Shang, Egger et al and because matching on indication was still 82% with this cut-off value. For smaller trials homeopathy had 14 good quality trials and conventional medicine 2. Therefore, hypothesis 2 was also falsified (p=0.003).

Suppose that the outcome was the opposite: quality of homeopathy lower, especially in smaller trials. Then we could say "yes, the plots of homeopathy and conventional medicine are similar, but that is caused by low quality of smaller homeopathy trials and meta-regression analysis proves that homeopathy does not work". But in reality we have the opposite situation, where regression analysis is meaningless.

Meta-regression analysis

Despite the meaninglessness of regression in good quality trials the Lancet paper showed a suggestive figure where meta-regression lines of the homeopathy trials and conventional trials were compared. The regression line for homeopathy inclined more, but not significantly, towards zero effect. According to the authors this supported the hypothesis that homeopathy is a placebo effect, see Figure 6.

There are several objections against this conclusion. First there is selection bias. Earlier we showed that four trials in the left-upper quadrant of the homeopathy trials (upper part of Figure 5) were missing, because "no matching trials could be found". For one of them this is unexpected because it was a trial on rheumatoid arthritis.

4 Spots missing in Shang, e.g. Wiesenauer, Rheumatoid arthritis, n=176 (no matching trial)

Homeopathy: 16 (15%) unpublished trials
Conventional: 0 unpublished trials

Homeopathy: 21 (19%) good quality
Conventional: 9 (8%) good quality

Strongest influence:
1. Influenza vaccine - influenza, n=1358
2. Piroxicam - muscle soreness, n=1282
   Contraindicated (EMEA 2006)
3. Deladumone - breastfeeding, n=450
   Contraindicated (FDA 1989)
4. Dexfenfluramine - obesity, n=133
   Contraindicated (FDA 1997)

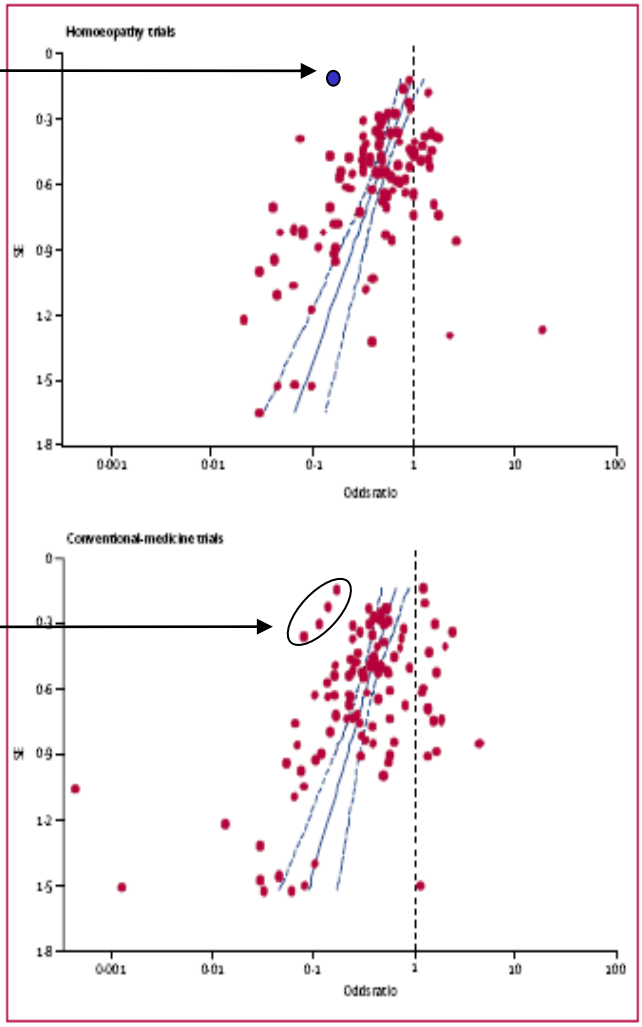

Figure 6: comparison of 110 homeopathy trials (above) and 110 matched conventional trials (below) (source Shang, Egger et al; Lancet 2005;366:726-732).

The comparison of regression lines between homeopathy and conventional medicine (lower part of Figure 6) is meaningless because quality is incomparable, but there is more.

The two methods are also incomparable because of the difference in publication bias. Homeopathy has 16 (15%) unpublished trial and conventional medicine none, so the effect of conventional medicine is over-estimated.

The incomparability of the asymmetry of both plots is also caused by the indication 'muscle soreness'. The three negative trials for homeopathy are higher in the plot because of the larger sample size. This increases the asymmetry, while the lower position of the three negative conventional trials decreases asymmetry.

The last problem with this comparison is safety. Homeopathy is highly valued because of its safety and the authors disregarded this issue. The conventional study on weight loss showed a considerable positive effect of Dexfenfluramine,[38] but Dexfenfluramine for weight loss was withdrawn by the American Food and Drug Administration in 1997 because of serious cardiac complications.[39] Two other larger studies, Deladumone (androgen-estrogen) in breastfeeding

and Piroxicam for soft tissue injury suffered from the same problem.[40, 41] These two treatments were also withdrawn because of adverse effects.[42, 43] There might be other treatments which are hard to compare because of safety, such as Tamoxifen for pre-menstrual syndrome.[44]

Conclusion

A review of data provided after publication of Shang et al's analysis did not support the conclusion that homeopathy is a placebo effect. There was intermingling of comparison of quality and comparison of effects, and thus matching was lost. The comparison of effects was also flawed by subjective choices and heterogeneity. The result in the subgroup from which the conclusion was drawn was further influenced by the choice of cut-off value for 'larger' trials. The comparative meta-regression analysis was meaningless because of selection bias, quality difference in smaller trials, and incomparability between indications and safety. There is no difference between homeopathy and safe conventional therapies. If we confine ourselves to the predefined hypotheses and the part of this analysis that is consistent with the comparative design, the only legitimate conclusion is that quality of homeopathy trials is better than of conventional trials, for all trials ($p=0.03$) as well as for smaller trials with $n<100$ ($p=0.003$).

Evidence based medicine

One of the conclusions of the Lancet 2005 analysis was *"The eight trials of homoeopathic remedies in acute infections of the upper respiratory tract that were included in our sample, the pooled effect indicated a substantial beneficial effect (odds ratio 0·36 [95% CI 0·26–0·50]) and there was neither convincing evidence of funnel-plot asymmetry nor evidence that the effect differed between the trial classified as of higher reported quality and the remaining trials"*. In conventional medicine eight trials is enough for a conclusion by the Cochrane Collaborattion. This conclusion means that homeopathy is Evidence Based Medicine for the most frequently occurring disease in general practice.

The scientific performance of conventional medicine in acute upper respiratory tract infections is rather poor:

- Petersen et al, (BMJ 2007;335:982-4): Antibiotics are not justified to reduce the risk of serious complications of URTI (>3.3 million episodes)
- CDC: over-the-counter cough suppressants have limited efficacy
- CDC: antihistamines and decongestants may relieve cough associated with common cold

After all, the 2005 analysis of homeopathy in the Lancet has a remarkable outcome: the most frequently occurring acute disease in general practice should be treated homeopathically!

What's next?

To our conventional colleagues we want to say: now it is up to you. We have done our scientific job and the epidemiological proof that homeopathy is not a placebo effect is as good as it gets. It is comparable to proof for conventional medicine and that means you can still reject it by making your own selections. But that's the problem of scientific proof, not of homeopathy.

Now you can cling to the opinion that homeopathy cannot not work, or you can specify this opinion to 'homeopathy cannot work like conventional medicines'. This can be regarded as a problem, but also as an opportunity. If it works differently it could be regarded a valuable complement to conventional medicine.

A scientific attitude means 'willingness to know'. Listen to your patient with good results from homeopathy and he will tell you that it works differently. Study how to prescribe homeopathic medicines and try it yourself. You will see that it works differently and it brings you additional therapeutic possibilities.

Acknowledgement
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