Introduction

A meta-analysis is a statistical evaluation study based on a certain number of clinical trials. For several years, these studies have nourished the debates on scientists’ capacity to evaluate homeopathy and on the determination of homeopathic circles to do so.

In 1991, J. Kleijnen et al published an encompassing study\textsuperscript{15} that was the result of meticulous processing of 107 clinical trials.

In 1996 and 1997 two other important meta-analyses were published. First of all the study by J.P. Boissel et al\textsuperscript{23}, made public by the European community, analyzed 184 trials of which a group of 17, ranked as among the best studies, found that homeopathic treatment was better than placebo. The study by K. Linde et al\textsuperscript{26}, which analyzed 89 clinical trials all carried out in double blind versus placebo, estimated that these results "are not compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo."

Even if these studies show that homeopathic research is perfectible, they do demonstrate that this therapeutic method has undergone experimentation, and that the related findings that can no longer be disqualified as a whole.

In this way, dozens of clinical trials have been conducted. For a small number of them, non-significant results were obtained. However, most of them obtained statistically-significant and positive results. In a few cases, trials with positive findings were repeated and their results came out positive again. About one third of the clinical trials concerning the use of homeopathic medicines, for a given disease, did not obtain positive and statistically-significant results. Among these, very few took into account all of the requirements of homeopathic prescribing methods: one of them will be examined here in order to describe the conceptual biases that hampered it.

As more and more clinical trials came to exist, they were assessed according to various meta-analysis procedures. It is encouraging to note that in less than a decade the controversy over the true therapeutic effect of homeopathy has moved from notable skepticism to acknowledgement of an effect that is strong enough to be incompatible with a placebo effect, for homeopaths and non-homeopaths alike who examined this topic.
In a 1991 overview published in the British Medical Journal, three Dutch epidemiologists, J. Kleijnen, P. Knipschild and G. Riet evaluated the methodological quality of 107 controlled clinical trials dealing with the activity of homeopathic treatments, representing 96 different publications. The paradoxical statement of the authors was: "Most trials seemed to be of very low quality, but there were many exceptions."

After three years of investigation, the authors concluded: "It is also often stated that homoeopathy has not been evaluated using modern methods – that is, controlled trials… [This] is certainly not true." The overall results do effectively show a positive trend, whether this is due to the quality of the trials or to the types of homeopathic prescribing used. Among the 107 tests with interpretable results, most of them (81 versus 24) obtained positive results.

The findings of this meta-analysis can nonetheless be complicated by possible publication biases, especially in such controversial subjects as homeopathy. For the time being, "the evidence of clinical trials is positive but not sufficient to draw definitive conclusions."
Six years after the British Medical Journal’s publication by J. Kleijnen et al., a comparable study was carried out on request by the European parliament: "Overview of data from homeopathic medicine trials: report on the efficacy of homeopathic interventions over no treatment or placebo."

In this report, the authors present the work of a study group that examined 184 clinical trials out of 377 bibliographic references. 115 of the 184 cases had been randomized (69 had no randomization or else unreliable randomization). Among these 115 trials, 32 had one main specific criterion. And among these 32 trials, 20 of them corresponded to curative interventions, 6 to preventive interventions, and 6 were comparisons between allopathy and homeopathy.

The authors analyzed the 20 trials which all had the following characteristics: correct randomization, definition of a specific main criterion, curative interventions. After eliminating trials where there was not sufficient data for all of the author-planned statistical analyses, 17 comparisons were retained for analysis, corresponding to 15 different publications and 2,001 patients.

The authors consider that, under these conditions, all of the comparisons aim at answering a single question: "Does homeopathy have an effect?" As a consequence it is possible to combine the $p$ values in order to obtain a single value in answer to the question. The null hypothesis for the significance test is that there is no significant difference in efficacy between the two compared treatments. The alternative hypothesis is that homeopathy does indeed have an effect - defined as a rejection of the null hypothesis - which is superior to placebo in at least one trial. After analysis the authors state: "For the 17 eligible comparisons, for each method used, the result is a $p$-value far below 0.001. This means that, in at least one trial, the null hypothesis of the absence of effect of homeopathy can be rejected.

This namely means that, in at least one trial, the homeopathy-treated patients had more beneficial effects than the placebo-treated patients, assuming that none of the pooled trials were biased in any way. This does not mean that homeopathy had an effect in all the analyzed trials. It simply means that the number of significant results is probably not due to chance alone. It is possible that some results are due to an effect of the studied treatment, but it is impossible to identify them."

* See glossary page 103.
In this publication, K. Linde and W. B. Jonas (Director of the evaluation division of alternative medicines of the National Institutes of Health, U.S.A.) examined the existence of 186 clinical studies on homeopathic therapeutics. Among these, they analyzed 89 trials centered on the study of what they call "classical homeopathy". This covers trials in which the prescribing of one or several medicines is done while remaining as close as possible to the actual criteria of the therapeutics.

The authors concluded that "The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homoeopathy is clearly efficacious for any single clinical condition. Further research on homoeopathy is warranted provided it is rigorous and systematic."

The results of this meta-analysis have not only distinctly affirmed the superiority of homeopathy in comparison to placebo (Odds ratio* = 2.45) [see Figure 1], but also the authors included a page discussing potential "classical" objections ahead of time, before they were actually raised.

**There are two types of objections:**

**Publication bias**

After nearly every clinical trial in homeopathy, it is usual to hear this type of polemic (except when the results are negative): that the authors of these homeopathic clinical trials tend to suppress negative information and willingly communicate the positive findings.

**The quality of proof**

The authors point out that the overall quality of their analyzed trials is very much comparable to the overall quality of any series of clinical tests concerning a disease or therapeutic method. They also note that if the studied trials are segmented by level of quality, this does not modify the positive outcome of the observed results in any group. They observe that the group of high-quality clinical trails is situated in the top layer of recognized quality (for this type of obser-

* See glossary page 103.
Objections

Publication of this meta-analysis in *The Lancet* was accompanied by comments by two adversaries of homeopathy.

- Professor J.P. Vandenbroucke (Department of Clinical Epidemiology, University of Leiden, the Netherlands) stated that homeopathy is no more than a placebo and that in total this meta-analysis is just a matter of "placebo versus placebo". According to him, the major difference denoted between the placebo subgroup and the homeopathy subgroup is not scientific and merely constitutes "an event". He concluded: "events become 'facts' when they are invoked to back up a theory".

- Professor M. J. S. Langman (Medical School, University of Birmingham, United Kingdom) considers that irrespective of the qualities of this meta-analysis and of the clinical trials that it evaluates, "**scientists must question whether the diversion of significant resources to conduct these trials can be justified as long as a rational basis for choosing homeopathy, or one of its specific modalities, is lacking**." K. Linde, W. B. Jonas and their team members had replied to this type of reasoning, as soon as their article came out: "**Between 30 and 70% of patients in developed countries use supplementary, alternative or non-conventional medicine, even if there is scarcity of high-quality scientific research on these practices.**"

The two reviewers nonetheless congratulate Linde, Jonas and colleagues for the quality of their research.

References

