Comment on blog by Edzard Ernst on systematic review

13.11.2023, Harald J. Hamre, Klaus von Ammon, Anja Glockmann, Helmut Kiene

Background

Our publication[1] of a systematic review (SR) of meta-analyses (MA) of randomised placebo-controlled homoeopathy trials for any indication was addressed in a blog[2] by Edzard Ernst (also reprinted at the end of this document). We are happy to clarify and correct a number of wrong, misleading or unsubstantiated statements in this blog:

Wrong, misleading or unsubstantiated statements

"…who would want to do an SR of MAs (a most peculiar exercise)… bizarre approach"

Wrong: SRs of MAs are neither peculiar nor bizarre, there are plenty of them. A Google Scholar search for the exact phrase "systematic review of meta-analyses" yields 7,510 hits, a full Google search ca 835,000 hits.

"…by pooling the MAs, they generated a positive result… this strategy (which in effect multiplies the results of many primary studies by factor 6)"

Wrong: We have not pooled any results. Pooling of several results into one effect estimate is done in MAs, this was an SR of existing MAs without any new meta-analytic pooling.

Wrong: There was no multiplication of any results whatsoever. We have followed standard procedures for SRs, grouping results and other features of the 6 MA together, and assessing the confidence in the cumulative evidence according to the detailed GRADE framework[3] (presented in Additional file 3).

"…about the 'efficacy' (actually it should be effectiveness)"

Wrong: The scope of our SR was MAs of placebo-controlled trials, which evaluate efficacy not effectiveness.

"…the 6 MA included more or less almost the same primary studies"

Wrong: As described in the Trial Characteristics section of our SR, the 6 MA comprised 310 trials or trial comparisons, thereof 182 different trials. Thus only 41.3% ((310-182)/310) of trials overlapped.

"The 6 included MAs are marginally positive…"

Misleading: In the GRADE framework, the term "marginally positive" corresponds to "imprecision" (significantly positive effect estimates with confidence intervals close to the threshold for 'no significant difference[4]). The blog comment suggests all six MA had imprecise results, which was not the case: The primary outcome of our SR comprised 9 effect estimates from the six MA, of which 6 showed a significant and "more than marginally" positive effect of homeopathy, compared to placebo; 2 estimates showed a significant and "marginally" positive effect (see Additional file 3, section 1.4); and 1 estimate showed a positive but not significant effect.

"…(mainly due to publication bias and other artefacts)"

Unsubstantiated: This is essentially a reiteration of the assumption of the Shang 2005 MA[5] ("*effects… could be explained by a combination of methodological deficiencies and biased reporting",* p.730) without further substantiation. We have assessed the possible impact of publication/nonreporting bias as well as other forms of bias and confounding in all six MA (see Additional file 3, sections 1.1-1.8 and Additional file 2). Further information can be found in our assessment of risk of bias in the Shang 2005 MA in Additional file 1, pp. 11-15 and our comment on the circular logic underlying the above-mentioned assumption in the Discussion (p. 21).

"One of the two MAs by Mathie et al excluded primary studies that reported positive findings (i.e. mine and the one by Walach et al)".

Wrong statement: Contrary to the statement by Ernst, the two trials in question (White 2003[6] with Ernst as last author, Walach 2000[7]) did not report "positive findings", i.e. significant positive effects of homeopathy, compared to placebo. For both trials, no significant nor relevant between-group differences in main outcomes were reported.

Wrong trial: Walach 2000 was an open-label long-term follow-up analysis of the primary double-blind trial Walach 1997.[8] Hence, Walach 1997 not Walach 2000 was the primary candidate for the Mathie 2014 MA[9], which is in question here.

Unsubstantiated: Three of the six MA, including Mathie 2014, presented data on trials included in the SR section of their analysis but excluded from the MA, because they did not have results extractable for meta-analytic data pooling. In Mathie 2014, Walach 1997 and White 2003 as well as eight other trials were included in the SR section but excluded from the MA for this reason. Ernst does not substantiate any other reason for his disapproval of the two exclusions apart from the trial results.

Citations without credit to the original authors and source

This blog contains only 15 full sentences by the author, the rest are verbatim citations from our SR, only in part marked as such (cf. the CC BY 4.0 license). Thus the reader might think the first five paragraphs summarising the SR to have been written by the blogger, while they were actually copied from our abstract.

Conclusion

The 15 original sentences of this blog by Edzard Ernst contain a number of statements that are wrong (7 times), misleading (1x) and unsubstantiated (2x).

References

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A new systematic review of homoeopathy reported a positive result – but I can't take it seriously!

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Since 1997, several meta-analyses (MAs) of placebo-controlled randomised efficacy trials of homoeopathy fo any indication (PRETHAIs) have been published with different methods, results and conclusions. To date, a formal assessment of these MAs has not been performed. The main objective of this systematic review of MAs of PRETHAIs was to evaluate the efficacy of homoeopathic treatment.

The inclusion criteria were as follows: MAs of PRETHAIs in humans; all ages, countries, settings, publicatio languages; and MAs published from 1 Jan. 1990 to 30 Apr. 2023. The exclusion criteria were as follows: systematic reviews without MAs; MAs restricted to age or gender groups, specific indications, or specific homoeopathic treatments; and MAs that did not assess efficacy. We searched 8 electronic databases up to 14 Dec. 2020, with an update search in 6 databases up to 30 April 2023.

The primary outcome was the effect estimate for all included trials in each MA and after restricting the sampl to trials with high methodological quality, according to predefined criteria. The risk of bias for each MA was assessed by the ROBIS (Risk Of Bias In Systematic reviews) tool. The quality of evidence was assessed by the GRADE framework. Statistical analyses were performed to determine the proportion of MAs showing a significant positive effect of homoeopathy vs. no significant difference.

Six MAs were included, covering individualised homoeopathy (I-HOM, $n = 2$), nonindividualised homoeopathy (NI-HOM, $n = 1$) and all homoeopathy types (ALL-HOM = I-HOM + NI-HOM, $n = 3$). The MAs comprised between 16 and 110 trials, and the included trials were published from 1943–2014. The median trial sample size ranged from 45 to 97 patients. The risk of bias (low/unclear/high) was rated as low for three MAs and high for three MAs.

Effect estimates for all trials in each MA showed a significant positive effect of homoeopathy compared to placebo (5 of 5 MAs, no data in 1 MA). Sensitivity analyses with sample restriction to high-quality trials were available from 4 MAs; the effect remained significant in 3 of the MAs (2 MAs assessed ALL-HOM, 1 MA assessed I-HOM) and was no longer significant in 1 MA (which assessed NI-HOM).

The authors concluded that *the quality of evidence for positive effects of homoeopathy beyond placebo (high/moderate/low/very low) was high for I-HOM and moderate for ALL-HOM and NI-HOM. There was no support for the alternative hypothesis of no outcome difference between homoeopathy and placebo available MAs of PRETHAIs reveal significant positive effects of homoeopathy beyond placebo. Th accordance with laboratory experiments showing partially replicable effects of homoeopathically p preparations in physico-chemical, in vitro, plant-based and animal-based*

Reading this SR, I got the impression that it was designed to generate a positive result. The 6 included MAs are marginally positive (mainly due to publication bias and other artefacts) and thus very well known to fans of homeopathy. The authors of this paper must therefore have expected that combining them in a review would generate an overall positive finding.

The first question I asked myself while studying this paper was: who would want to do an SR of MAs (a most peculiar exercise); why not at least an SR of SRs which is already an unusual project but would make at least some sense. (An SR is a review that includes all studies that match a set of pre-definied criteria. A MA is a special form of SR where statistical pooling was possible.) The answer is, I fear, simple: this would not have generated a positive result: here are now dozens of SRs of homeopathy and most are not positive (as discussed regularly on this blog)

The authors themselves provide no real justification for their bizarre approach. All they tell us about it is this:

> One approach is to focus on a specifc indication (e.g., depression [4], acute respiratory tract infections i children [5]) while often including open-label trials and observational studies. In this approach, data synthesis is grouped by design, thus yielding information about homoeopathy in patient care. Te opposite approach is to include all indications while restricting study designs to placebo-controlled trial and aggregating results in an MAs, thus yielding information about the specifc efects of homoeopathy beyond those of placebo. A major reason for using this approach has been the claim that 'homoeopathy violates natural laws and thus any efect must be a placebo efect' [6].
> Since 1997, at least six MAs of placebo-controlled homoeopathy trials for any condition have been published [6–11]. These MAs have difered in their methods for trial inclusion, data synthesis and assessment of risk of bias; furthermore, their results and conclusions have been inconsistent. During thi period, there have been substantial advancements in methodology and quality standards for MAs and other SRs [12–15], including SRs of SRs (also called overviews or umbrella reviews) [16–18]. To our knowledge, a formal SR of MAs of randomised placebo-controlled homoeopathy trials for any conditio has not been performed. Herein, we report such an SR.

What the authors actually did is this: they knew of the 6 MA; they also knew that they arrived at cautiously positive conclusions; finally they also were aware of the fact that, obviously, the 6 MA included more or less almost the same primary studies. So, by pooling the MAs, they generated a positive result which was no longer marginally positive but strongly. Anyone looking through this strategy (which in effect multiplies the results of many primary studies by factor 6) must realize that this methods creates a false-positive impression.

My suspicion that this paper is a deliberate attempt at misleading us about the 'efficacy' (actually it should be effectiveness) is strengthened by further facts:

- One of the two MAs by Mathie et al excluded primary studies that reported positive findings (i.e. mine and the one by Walach et al)
- Funding: Open Access funding enabled and organized by Projekt DEAL. Funding specifcally for this SR was provided by Christophorus-Stiftung (No. 393 CST), Stiftung Marion Meyenburg (Date 24.09.2020), Dr. Hauschka Stiftung (Date 16.11.2020) and Gesellschaft für Pluralität im Gesundheitswesen (Dates 11.06.2021, 22.06.2021). General funding for IFAEMM was provided by the Software-AG Stiftung (SE-P 13544). The funders had no infuence on the writing of the protocol or on the planning, conduct and publication of this SR.
- Competing interests: In the past 3 years, HJH has received research grants from two manufacturers of anthroposophic medicinal products (Wala Heilmittel GmbH, Bad Boll/ Eckwälden, Germany; Weleda AG, Arlesheim Switzerland). Anthroposophic medicine is not based on the homoeopathic simile principle or on drug provings, but some anthroposophic medicinal products are potentized. The two manufacturers had no involvement with the present SR. Anthroposophic medicinal products were not part of the intervention in any of the trials evaluated in the MAs of this SR (Suppl. Table 15). DSR has received a development grant from Heel GmbH (manufacturer of homoeopathic products) for online training in case report writing. AG, KvA and HK declare that they have no competing interests.
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Personally, I do not find it surprising that these authors bend over backwards to publish something positive about homeopathy (such things happen in homeopathy all the time). However, I do find it astonishing that an allegedly decent journal passes such pseudoscience for publication as though it is serious science.

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