Pharmacoeconomic Study of Homeopathic Medicines: A Critical Appraisal of Methods and Conclusions Shows Serious Cause for Concern

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In March 2024, a paper titled 'Prescriptions of homeopathic remedies at the expense of the German statutory health insurance from 1985 to 2021: scientific, legal and pharmacoeconomic analysis' was published by Leemhuis & Seifert in Naunyn Schmiedeberg's Archives of Pharmacology.[1] The authors' overarching conclusion was that *'In aggregate […] abolition of reimbursement of homeopathic medicines in Germany at the expense of the [Statutory Health Insurance] system is well justified'*.

I write to express my concern that this paper misrepresents the evidence for homeopathic medicines and reaches an unfounded conclusion. The aim of this letter is to critically appraise the methods used by Leemhuis & Seifert and assess the impact on the paper's findings. Commenting on the legal aspects of marketing and regulation of homeopathic medicines is beyond the scope of this letter.

In their paper, Leemhuis & Seifert use the terms homeopathic 'remedies' and 'medicines' interchangeably, which arguably is misleading. Instead, a clear distinction has been made in this letter such that 'homeopathic medicines' refers only to clinically prescribed branded medicinal products, rather than homeopathic remedies that are given as part of individualised homeopathic treatment. No inferences can be made from Leemhuis & Seifert's study about the cost or effectiveness of remedies prescribed during individualised homeopathic treatment: only non-individualised homeopathic medicines were considered.

The Paper Did not Use a Recognised Economic Assessment Method

Leemhuis & Seifert claim to have used *'stringent pharmaco–economic and pharmacological criteria'* in their analysis of homeopathic medicines prescribed through the German Statutory Health Insurance (SHI).[1] However, no recognised economic method was used. Specifically, when the paper is assessed against the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist,[2] the methods do not meet the criteria for any of the main types of cost analysis, such as Cost Benefit Analysis, Cost Effectiveness Analysis, or Cost Utility Analysis.[3]

The closest method could arguably have been a Cost Minimisation Analysis, where the cost of one medicine is compared directly to the cost of another medicine, but this is only informative if both medicines have demonstrated therapeutic equivalence and very similar safety profiles: this is unfortunately rarely the case even in conventional medicine[3,4] and Leemhuis & Seifert are clear in their *a priori* belief that homeopathy is a placebo, not an equivalent treatment.[1,5]

The absence of a rigorous economic evaluation method severely limits the paper's usefulness for stakeholders and policy makers faced with economic decisions in public health.

The Paper Omitted all Cost Effectiveness Studies of Homeopathy

It is noteworthy that Leemhuis & Seifert neglected to cite the most recent systematic review on the cost effectiveness of homeopathy by Ostermann et al[6] and omitted every primary cost/clinical study included therein. In so doing, Leemhuis & Seifert created an inaccurate picture of what is known on the topic and neglected to discuss where their paper sits within this body of evidence. It was therefore not made clear that 'Leemhuis & Seifert 2024'[1] is in fact the only paper to date to reach a definitively negative conclusion that homeopathy is both ineffective and costly; the other 21 studies all show that homeopathy has similar or better clinical effectiveness compared to control groups, with an overall trend towards cost effectiveness.[6]

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The 'Pharmacoeconomic' Assessments are Selective and Rudimentary

In the absence of a recognised economic analysis method, the pharmacoeconomic assessments of Leemhuis & Seifert[1] appear to be selective and rudimentary.

The Abstract claims that: *'Homeopathic remedies are on average significantly more expensive than their rational pharmacological alternatives…. costs have continued to rise over the years analyzed'*. To reach this conclusion, Leemhuis & Seifert identified 16 homeopathic medicines listed at least once in the German annual drug reports (AVRs) from 2005 to 2022. These drug reports represent a summary of the top 3,000 medicines prescribed per year by registered doctors in outpatient clinics, dispensed and paid for by public pharmacies, allowing their respective costs to be tracked. The unit of cost used by Leemhuis & Seifert was chiefly the Defined Daily Dose (DDD), which is a statistical measure of drug consumption based on the assumed average maintenance dose per day for a drug used for its main indication in adults.[7]

Costs Over Time

Leemhuis & Seifert presented both total and average DDD costs from 1985 to 2021 for the 16 included homeopathic medicines. The authors themselves stated that only 7/16 medicines had consistent data across this extended time-period (i.e., the dataset is incomplete), that the data were heavily influenced by a high number of prescriptions for *Meditonsin* (i.e., the dataset is skewed), and that from 2004 onwards SHI reimbursement for homeopathy prescriptions became largely paediatric. This suggests that certain homeopathic medicines should not be trackable in the AVRs after 2004: for example, *Sinuselect* contains 30% alcohol and should only be prescribed for adults, and yet *Sinuselect* was included in the list of 16 medicines and allegedly provided data up to 2011.

Leemhuis & Seifert also claimed that the cost of homeopathic medicines has *'continued to rise'* over time, but it is unclear how the authors arrived at this conclusion: no account appears to have been taken of inflation and the data were not compared to any concomitant changes in conventional medicine costs. Additionally, the DDD does not necessarily represent actual costs of prescribed medicines as it is calculated from summarised data per drug component: for mixed homeopathic medicine combinations the DDD becomes complex.

Further, the context in which these claims are stated is not made clear. On close inspection of the annual total DDD costs for homeopathic medicines from 1985 to 2021 Leemhuis & Seifert's data showed that the total costs have actually declined, with 2021 representing the lowest total annual DDD cost in the dataset. Leemhuis & Seifert also failed to note that the total cost of homeopathic medicines on the SHI is only approximately 0.01% of the total expenditure.[8] Within this fuller context, it is difficult to see how homeopathy can be deemed expensive and causing rising costs to the SHI overall.

Taken together, these anomalies raise serious concerns about the extent of selective reporting by Leemhuis & Seifert, and its impact on the accuracy of their conclusions.

Cost Comparison

It is important to note that a central finding of the paper—that homeopathic medicines are allegedly *'significantly more expensive'* than conventional medicines—seems to be based on a purely descriptive comparison of two boxplots. Specifically, the average DDD cost for the homeopathic medicines was compared to the average DDD cost for author-selected *'rational pharmacological alternatives'*, for the year 2021 only.

In other words, the cost comparison analysis simply placed the price of daily medicines alongside each other, with no consideration for clinical outcomes, and whether the homeopathic medicines were prescribed in addition to, or instead of conventional medicines. Unfortunately, it is also not clear which medicines were included in either of these datasets (a concern in itself regarding replicability, explored further below). As noted above, this approach does not conform to any recognised cost assessment method and appears over-simplified.

Furthermore, the DDD data appear skewed towards lower costs with some high-cost outliers, which would disproportionately impact calculation of a mean *('on average')*. Indeed, the range of costs in both datasets is broad and the homeopathy costs are entirely within the full range of costs for the conventional medicines: a statistically significant difference is unlikely. Also, on this point, no statistical analysis was done anywhere in the paper, which means that the alleged 'significance' of the cost comparison findings is unsubstantiated. Despite these obvious shortcomings, Leemhuis & Seifert claimed that higher costs for homeopathy was *'astonishing'*.

The Cost Analysis is Non-Replicable

In addition to appearing rudimentary and flawed, the cost analysis is non-replicable, raising concerns about transparency of reporting in the paper.

In their Methods section, Leemhuis & Seifert state that: *'the following analysis based on data from the Scientific Institute of the General Local Health Insurance Fund (WIdO) (https://www.wido.de, as of 16 August 2023), the DDD, DDD costs, and total sales of 16 homeopathic medicines from 1985 to 2021 were examined'*.

When accessing the WIdO via the link provided, users are directed to the publicly available PharMaAnalyst database,[9] which is populated with data from the AVRs. The database provides information on the number of packs or daily doses prescribed, the absolute net costs, the net costs per prescription, or the net costs per daily dose; these data can be accessed for named drugs, active ingredients, or groups of active ingredients. The PharMaAnalyst database was thus assumed to be the data source referred to by Leemhuis & Seifert and was used to replicate their findings.

However, this online database covers prescriptions from 2012 to 2022 only, and 7 of the 16 homeopathic medicines included by Leemhuis & Seifert do not appear to be listed (i.e., *Sinuselect, Sinusitis Hevert, Monapax, Tonsilotren, Spascupreel, Zappelin*, and *GrippHeel*). This raises the question of where, precisely, the authors got their data from.

Additionally, three homeopathic medicines seem to have been missed: an additional *Carum carvi* suppository (from a different manufacturer with different ingredients) and two homeopathic *Euphrasia* eye drop preparations. Overall, 13 homeopathic medicines were identifiable in the PharMa-Analyst database (not 16). Of these 13, 9 were consistently represented every year from 2012 to 2022 and 11 were listed in 2021. DDD costs were extracted for all 13 homeopathic medicines and, for comparison, from 12 representative conventional medicines as suggested by Leemhuis & Seifert[1] (►**Supplementary Table S1**, available online only).

The individual DDD costs for each medicine included in this replication attempt appear stable over 10 years, except for a drop in cost for homeopathic *Contramutan* in 2017 and a rise in cost for the conventional medicine Buscopan (butylscopolamine) from 2020 (►**Supplementary Figure S1**, available online only). Additionally, whilst the summary DDD cost data for each group of medicines in 2021 are similarly skewed towards lower costs with some high-cost outliers, the median cost of homeopathic medicines (€0.85; where the median is a more appropriate measure of central tendency than the mean in a skewed dataset) is actually lower than the median cost of conventional medicines (€1.20) (►**Supplementary Figure S2**, available online only). This difference is not statistically significant (Mann–Whitney U test $p > 0.05$). These observations are in direct contrast to the data presented by Leemhuis & Seifert.

The Choice of Conventional Medicines was Inappropriate

Leemhuis & Seifert inferred that the 16 homeopathic medicines included in their analysis could conceivably be replaced by a total of nine conventional medicines, the most common of which was ibuprofen (11/16 medicine pairs).[1] While generic medicines like ibuprofen and paracetamol are arguably logical for managing minor childhood ailments, more significant concerns are warranted regarding some of the other comparative medicine pairings proposed. For example:

1. Buscopan (butylscopolamine) is an anti-spasmodic drug used for intestinal colic but should not be used in children under the age of 6 years.[10] Yet Leemhuis & Seifert suggested this as a suitable alternative to a homeopathic *Carum carvi* suppository manufactured for babies.
2. For 'nervous disorders and restlessness' in children >1 year (i.e., anxiety and stress) Leemhuis & Seifert compared *Zappelin* homeopathic granules to methylphenidate (Ritalin), which is prescribed for children with a formal diagnosis of attention-deficit/hyperactivity disorder.
3. The nasal decongestant xylometazoline was compared to *Otovowen* homeopathic drops for ear infection and both *Sinuselect* drops and *Sinusitis Hevert* tablets for sinusitis, and yet Leemhuis & Seifert failed to also compare xylometazoline to the homeopathic nasal decongestant spray *Euphorbium compositum SN*.
4. The analgesic and anti-inflammatory medicine metamizole is banned in several countries worldwide (not Germany) due to the risk of agranulocytosis: additional care is thus needed in its use.[11] Yet Leemhuis & Seifert suggested metamizole as an appropriate alternative to 8/16 of the homeopathic medicines for acute respiratory tract infections in children.

This list is not exhaustive, but rather acts as a note of caution that the clinical appropriateness of Leemhuis & Seifert's suggested rational pharmacological alternatives is questionable.

Relevant Clinical Effectiveness Studies were Omitted

In their Abstract, Leemhuis & Seifert concluded that, for the 16 homeopathic medicines included in their study, '*…claims of efficacy go far beyond what can be considered proven in terms of evidence-based medicine and the quality of most clinical studies is poor*'.

It is important to note that this refers to alleged claims of efficacy made by manufacturers on their websites and advertising: this is a very different premise from a systematic review of the clinical effectiveness literature to inform a health economic evaluation and fails to pay due regard to the difference between efficacy and effectiveness. It is therefore not surprising that Leemhuis & Seifert located only 20 clinical studies.

It is surprising, however, that this evidence was then effectively halved: only 11/20 studies were located as full texts for data extraction and covered only 7/16 of the listed homeopathic medicines. Even in the absence of a systematic literature search, relevant PubMed-listed studies have clearly been overlooked for at least three of the homeopathic medicines (►**Supplementary Table S2**, available online only). Thus, basing any conclusions about the effectiveness of homeopathic medicines on incomplete data is clearly unreliable.

Dismissing Observational Studies is Unjustified

In addition to claiming that manufacturers of homeopathic medicines fail to provide evidence of efficacy in accordance with evidence-based medicine (EBM), Leemhuis & Seifert also claimed that manufacturers *'position themselves contrary to evidence-based medicine'*, and go on to ask *'whether the funding of treatments that contradict the principles of evidence-based medicine can still be justified'*.

The logic behind these statements is difficult to comprehend, especially when Leemhuis & Seifert seem to consider only double-blind, placebo-controlled, randomised controlled trials (DB-RCTs) of efficacy as meeting the criteria of EBM. This is highly questionable given that EBM is the integration of clinical expertise and patient preference with a hierarchy of evidence from pre-clinical studies to systematic reviews.[12]

Leemhuis & Seifert's approach to defining EBM also ignores the fact that DB-RCTs have limited relevance to the

real-world clinical context in which the homeopathic medicines included in their study were prescribed. It is completely inappropriate to dismiss the contribution of observational studies within the EBM hierarchy simply because they are not blinded or randomised, and it is even more inappropriate to suggest that these alleged *'marked scientific deficiencies'* mean that they should not be published at all. Indeed, high impact conventional medical journals frequently publish non-blinded, non-randomised, comparative observational studies: to imply that these have no value is astonishing.

The Paper Misrepresents the Safety of Homeopathic Medicines

Consideration of the safety of homeopathic medicines was not mentioned in the Abstract of Leemhuis & Seifert,[1] but it was included in the Discussion under *'Inconsistency of information in advertisements'*. Here, the impression is created that adverse drug reactions from homeopathic medicines are frequent and potentially serious (including causing bladder cancer) because low dose homeopathic preparations are potentially toxic and use poisonous heavy metals. Experts in homeopathic medicine would argue vociferously that this is inaccurate and inconsistent with the evidence, for the following reasons.

Leemhuis & Seifert failed to mention that, when taken in its entirety, the evidence for homeopathy suggests it is relatively safe, with side effects that are most likely mild to moderate and transient. This position is based upon a total of 12 published studies, where 11/12 reached a supportive conclusion (►**Supplementary Table S3**, available online only). However, Leemhuis & Seifert cited only three of these studies: they misrepresented the findings of two systematic reviews by Stub et al[13,14] suggesting that adverse drug reactions are more frequent and serious than they are; and they selectively reported outlier data from within the only negative study by Posadzki et al,[15] which itself has been discredited by others.[16–19]

It is also concerning to note that five of the eight observational comparative effectiveness studies that Leemhuis & Seifert identified (and dismissed as not being 'EBM') were actually included within the systematic review by Stub et al (2022),[14] and all showed that homeopathy was well tolerated. The studies on *Euphorbium*[20] and *GrippHeel*[21] that were missed in Leemhuis & Seifert's list of effectiveness evidence (noted in ►**Supplementary Table S2**, available online only) were also included in Stub et al's review and showed the comparative safety of homeopathic medicines (►**Supplementary Table S4**, available online only). None of these safety data were mentioned by Leemhuis & Seifert, which raises serious concerns about bias and selective use of studies rather than objective, rigorous analysis.

Leemhuis & Seifert's risk:benefit assessment of homeopathic medicine thus appears highly questionable.

Conclusion

Taking all points described above, the paper by Leemhuis & Seifert is misleading and of inadequate quality. The authors used an unknown, non-replicable method; did not substantiate their key findings in a way that is compliant with EBM; referred selectively to negative homeopathic literature; and made inappropriate and unjustified comparisons with conventional drugs. Stakeholders and policy makers would be better informed by reading the most recent systematic reviews of the cost effectiveness[6] and safety[13,14] of homeopathic medicines that used validated and recognised methods.

Supplementary Material

Supplementary Table S1. Extracted DDD costs for homeopathic and conventional medicines (2012 to 2022).
Supplementary Table S2. Clinical effectiveness studies missed by Leemhuis & Seifert.
Supplementary Table S3. Summary of 12 published safety studies.
Supplementary Table S4. Observational studies with safety data for homeopathic medicines included in both Stub et al and Leemhuis & Seifert.
Supplementary Fig. S1. DDD costs over time for homeopathic and conventional medicines.
Supplementary Fig. S2. Summary DDD costs for homeopathic and conventional medicines in 2021.

Note on Product Names

Mention of homeopathic medicinal product names in this letter is for ease of communication and data handling: it is not intended to imply endorsement of any product in any way. Homeopathic medicinal product names are not stated in the paper by Leemhuis & Seifert but they can be deduced. Prof Seifert was approached by email to confirm the product names, but no response was received.

Conflict of Interest

No funding was received specifically for this work. Data analysis and writing were done independently from other work undertaken as a freelance research consultant within the homeopathy sector and as Editorial Assistant at the journal *Homeopathy*.

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