Proving non-conventional methods: A paradigmatic paradox

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Abstract

Originally, it was thought that Evidence-Based Medicine (EBM) would supplant decision-making based on intuition or plausibility. Later, it appeared that the gold standard in EBM, the Randomised Controlled Trial (RCT), was not as 'hard' a reference point as had been supposed, and an assessment of credibility was needed. After some decades, 'credible' RCT-centred EBM has led to the dismissal of therapies deemed to be implausible, such as Homoeopathy. Nevertheless, such therapies remain widely appreciated by patients who use them alongside conventional medicine. Nearly two hundred RCTs of Homoeopathy showed no difference in efficacy between Homoeopathy and comparable conventional trials. There is no proof that conventional trials are of better quality and there is no proof of harm by Homoeopathy. However, selective analysis of evidence shows statistically insignificant results, then interpreted as unscientific 'confirmation' of the hypothesis that Homoeopathy is a placebo. As a result, the use of Homoeopathy instead of antibiotics in acute respiratory tract infections has been discouraged, despite the absence of evidence of the efficacy of antibiotics for this indication and an established risk of harm. Complex statistical interpretations of RCT evidence lead to impractical and even harmful advice. Credible proof is actually based on many subjective (often continuous) variables. As an endpoint for EBM, Bayesian probabilities, based on more than RCT evidence, would provide a more practical and personalised type of advice for patients, and would develop the diagnostic process into a prognostic framework, offering alternatives if one particular solution was to fail.

Keywords: Bayes' theorem, Credibility, Evidence-based medicine, Homoeopathy, Hypothesis testing, Paradigm

'No number of sightings of white swans can prove the theory that all swans are white. The sighting of just one black one may disprove it'.

- Karl Popper.

Introduction

In 1992, the Evidence-Based Medicine Working Group (EBMWG) stated: '*Medical practice is changing, and the change, which involves using the medical literature more effectively in guiding medical practice, is profound enough that it can appropriately be called a paradigm shift*'.[1] This paradigm shift refers to Kuhn.[2] The EBMWG stated: *'Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research'.*

Criticism of evidence-based medicine (EBM) has gradually increased and is, according to some, evolving into a crisis.[3] Greenhalgh, among others, commented on the inappropriate influence of vested interests, statistical significance, management (and neglect) of patient-centred care and multimorbidity. Most clinicians will find it impossible to interpret the vast amount of existing information or to assess its credibility. Reviews are meant to guide clinicians, but at the beginning of this century, there were more than 100 systems available to rate the quality of research; there was extensive disagreement between these and none appeared to be particularly useful for clinical practice.[4] Since 2004, the GRADE guidelines have been accepted as the method of choice to assess the credibility of evidence. Although the GRADE guidelines are meant to prevent different conclusions being drawn from the same information, the interrater reliability of GRADE is assessed variously as 'low' to 'considerable' by different authors.[5]

For the last quarter of a century, the *Journal of Evaluation in Clinical Practice* has been active in encouraging the leaders

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of EBM to embrace authentic scholarship and to engage properly with their critics.[6] Its main criticism of the current interpretation of EBM is its reductionistic approach which makes it inadequate for chronically ill patients and those with multimorbidity. EBM recognises the need to integrate patients' values and preferences, but it is not clear how to do this. Furthermore, a considerable number of patients make choices that appear contradictory to the fundamental beliefs of many practitioners.

A clear example is the use of complementary and alternative medicine (CAM). Patients who have derived inadequate benefit from conventional medicine, especially those with chronic complaints, seek alternatives such as CAM.[7] Patients who use both conventional medicine and CAM appear to value both and tend to be less concerned about their medical doctor's disapproval than about his or her inability to understand or incorporate CAM therapy.[8] Most patients do not disclose their use of CAM to their conventional doctors, who may particularly disapprove of methods such as acupuncture and Homoeopathy because these are implausible according to their paradigm or pathophysiologic rationale. Nevertheless, these two are the most frequently used therapies of more than 700 CAM modalities.

Basing an acceptance of CAM methods on evidence may be more complicated than was originally expected. In 1993, the Dutch Health Board recommended that CAM methods should be recognised after 'repeated' evidence.[9] Gaining such evidence, however, turned out not to be straightforward; in 2005, Ioannidis stated that most published research findings in medicine were false.[10] 'Evidence' was replaced by 'credible evidence,' and since then, most evidence has been discarded. The pathophysiologic rationale is, however, a large part of the existing paradigm and this strongly influences what is perceived as credible. Kuhn stated (page 78): *'... scientists fail to reject paradigms when faced with anomalies or counterinstances. They could not do so and still remain scientists'*.

The European Academies Science Advisory Council (EASAC) stated, after examining 176 randomised controlled trials (RCTs), that Homoeopathy *'may pose significant harm to the patient if incurring delay in seeking evidence-based medical care and that there is a more general risk of undermining public confidence in the nature and value of scientific evidence'*, because *'authoritative and impartial bodies, state that a placebo effect may appear in individual patients, but there is no robust, reproducible evidence that homoeopathy is effective beyond the placebo effect'*.[11]

In recent decades, the existing interpretation of EBM has not brought about a paradigm shift that brings CAM and conventional medicine closer together. On the contrary, the current EBM questions the judgement of large numbers of patients who use both Homoeopathy and conventional medicine, as well as that of the very many doctors who apply both methods. This raises certain questions: Is it possible to prove beyond doubt that a CAM method is not a placebo, and how relevant is it to try to do so? Why do patients keep on using CAM? This article is based on the existing literature and the personal experience of doctors trying to understand and reconcile a particular paradigm with patients' preferences for using both Homoeopathy and conventional medicines. This means understanding the patient's perspective, how a doctor's belief in Homoeopathy can change, and why CAM therapy can be effective after conventional treatment has failed.

The Patient's Perspective

The median 12-month prevalence of all use of Homoeopathy worldwide is 3.9% (range, 0.7%–9.8%).[12] Many patients suffer long-lasting complaints before consulting a homoeopathic practitioner (Witt *et al.*'s study: 79%, average duration of 8.8 ± 8 years).[13] Disease severity decreased significantly during and after homoeopathic treatment ($P < 0.001$) between baseline and 24 months (adults from 6.2 ± 1.7 to 3.0 ± 2.2; children from 6.1 ± 1.8 to 2.2 ± 1.9). People frequently seek homoeopathic treatment after other treatments have failed (Güthlin *et al.*'s study: 70%).[14] Patients also value the longer consultations which are a necessary feature of Homoeopathy.[15]

The fact that a considerable number of patients do not respond well to conventional medicine, even if there is good evidence for it, is a disquieting reality.[16] RCT evidence using a placebo control shows that the verum works for more patients than the placebo does, not that it works for every patient. Patients who do not fit the inclusion criteria for a RCT are even less likely to benefit. RCT evidence is also absent or insufficient for many conventional treatments. Patients may prefer to avoid the use of antibiotics or may have experienced that antibiotics failed to work for their complaint. The Cochrane Collaboration states that there is no evidence of benefit from antibiotic use in the common cold or for persisting acute purulent rhinitis in children or adults, and there is evidence that antibiotics cause significant adverse effects.[17] There is insufficient evidence for the use of antibiotics as a means to reduce the risk of otitis or pneumonia in children, but nevertheless, acute respiratory tract infections (ARTIs) remain responsible for 75% of the total amount of prescribed antibiotics in high-income countries.[18] The number needed to treat (NNT) to prevent one serious complication in ARTI and otitis media using antibiotics is over 4000.[19] Recurrent acute otitis media occurs more frequently in children previously treated with amoxicillin.[20]

Doctors Practising Homoeopathy

There are homoeopathic doctors in more than 70 countries worldwide and more than 280,000 in India.[21,22] Many doctors prescribe both conventional and homoeopathic medicines. They begin as conventional doctors, because it is rare to find any instruction in Homoeopathy in universities. These doctors are well aware of the plausibility problem with homoeopathic medicines: extreme dilutions cannot produce any drug–receptor interactions. However, the vigorous shaking between dilution steps is believed to create a new substance.[23]

History shows that even phenomena once thought impossible, such as quantum mechanics, do not completely overturn the existing physicochemical knowledge base. The EBMG stated: *'The study and understanding of basic mechanisms of disease are necessary but insufficient guides for clinical practice. The rationales for diagnosis and treatment, which follow from basic pathophysiologic principles, may in fact be incorrect, leading to inaccurate predictions about the performance of diagnostic tests and the efficacy of treatments'*.[1]

A scientific attitude should not prevent doctors from making their own observations. Scepticism gradually fades away after numerous observations of unexpected cures and hearing remarkable stories from their patients. They value the complementary possibilities which Homoeopathy offers, and they are able to use fewer antibiotics in ARTI (odds ratio [OR]: 0.43 and 95% confidence interval [CI]: 0.27–0.68)[24] and in otitis media.[25] Antimicrobial resistance (AMR) is expected to become the principal cause of death in a few decades and already costs over 700,000 lives each year.[26] Doctors also value the safety of Homoeopathy: Posadzki *et al*. found only four deaths possibly related to the use of Homoeopathy in the literature in all languages over 34 years.[27] Serious problems caused by delay in seeking conventional treatment were found in only 16 cases. However, medicines containing high doses of toxic natural ingredients can at times be falsely labelled as 'homoeopathic'.[28] Homoeopathic medicines should be of guaranteed safety and manufactured to high standards.

It is unlikely that our knowledge of physics and chemistry is complete. One of the factors which counters the belief that medicines can only work via molecular interactions is that the effect of Homoeopathy in chronic or multiple complaints differs considerably from conventional medicines: it builds up gradually and the effect of one medicine extends over different complaints. Homoeopathy appears to be useful in chronic complaints and multimorbidity after conventional therapy has failed. Another experience that confirms the difference between conventional medicines and Homoeopathy is the fact that a homoeopathic medicine cannot be prescribed on the diagnosis of a condition alone. The choice of the homoeopathic medicine, say *Belladonna,* must be based on a match between the patients' symptoms and the consensus among prescribers regarding which symptoms and characteristics indicate this medicine, for example, in otitis media:

- Ear pain less in a half-sitting position
- Perspiration during fever
- Grinding the teeth during sleep.

On the other hand, *Belladonna* could also be used in other conditions, such as respiratory tract infections, ADHD or migraine. Doctors who practise both Homoeopathy and conventional medicine do not dismiss RCT evidence, but they value the reliable manner in which Homoeopathy can offer rational options after the failure of conventional therapy. When choosing alternative options, reproducibility provides a more scientific basis than simple intuition or personal experience. Patients prefer CAM to be practised by medically qualified doctors, citing safety reasons.

To prescribe homoeopathic medicines successfully requires an extensive knowledge of a large number of medicines, with hundreds of characteristics per medicine. For a single indication such as otitis media, homoeopathic practitioners must choose between more than 10 medicines. RCT evidence by Steinsbekk *et al*. may demonstrate that the untrained use (self-treatment) of Homoeopathy with only three different remedies shows no difference between Homoeopathy and placebo,[29] but of course, this finding may well have other causes, such as the inefficacy of the homoeopathic method.

Evidence for Homoeopathy

In 1991, Kleijnen *et al*. concluded that although there was more RCT proof for Homoeopathy than expected, this might be caused by publication bias.[30] A meta-analysis by Linde *et al*. in 1997 then proved that publication bias was an unlikely cause of the positive outcome for Homoeopathy.[31] A meta-regression analysis by Linde *et al*. in 1999 showed a smaller effect in higher-quality studies, but there was no linear decline of effect with better quality: the mean OR of trials with the highest Jadad score was 2.00 (95% CI: 1.37–2.91).[32] Vandenbroucke stated that the funnel plot of Homoeopathy trials was comparable to the best conventional results.[33] Shang *et al*.'s hypothesis[34] was that quality in Homoeopathy, especially in smaller trials, would be lower than in conventional trials, but the outcome was the opposite: 21 out of 110 (19%) higher-quality trials in Homoeopathy, 9 out of 110 (8%) in conventional medicine; there were 13 smaller, higher-quality trials in Homoeopathy versus 3 in conventional medicine.[34] The median sample sizes and effect sizes were similar.

The systematic review by Shang[34] is the only comparison of homoeopathic and conventional RCTs. The funnel plots showed no difference in effect [Figure 1]. Meta-regression of results was originally proposed by the authors to extrapolate effects, on the assumption that smaller trials were of lower quality. However, it is not valid to compare two methods by meta-regression if one has a better quality of smaller trials, because small trials will naturally show stronger effects because of better selection of patients.[35]

This comparative analysis is often cited as proof of the inefficacy of Homoeopathy, but the conclusion 'weak evidence for Homoeopathy, but strong evidence for conventional medicines' was based on undisclosed subsets of eight Homoeopathy and six conventional trials. After disclosure, the pooled Homoeopathy subset (OR: 0.88, 95% CI: 0.65–1.19) of 'larger, higher-quality trials' proved to be highly heterogeneous with respect to indications [Table 1], and only two out of the eight trials were compared with conventional trials. The confidence interval of larger and better Homoeopathy trials overlaps with that of larger and better conventional trials (OR: 0.58, 95% CI: 0.39–0.85): note that a difference in statistical significance is not a statistically significant difference.

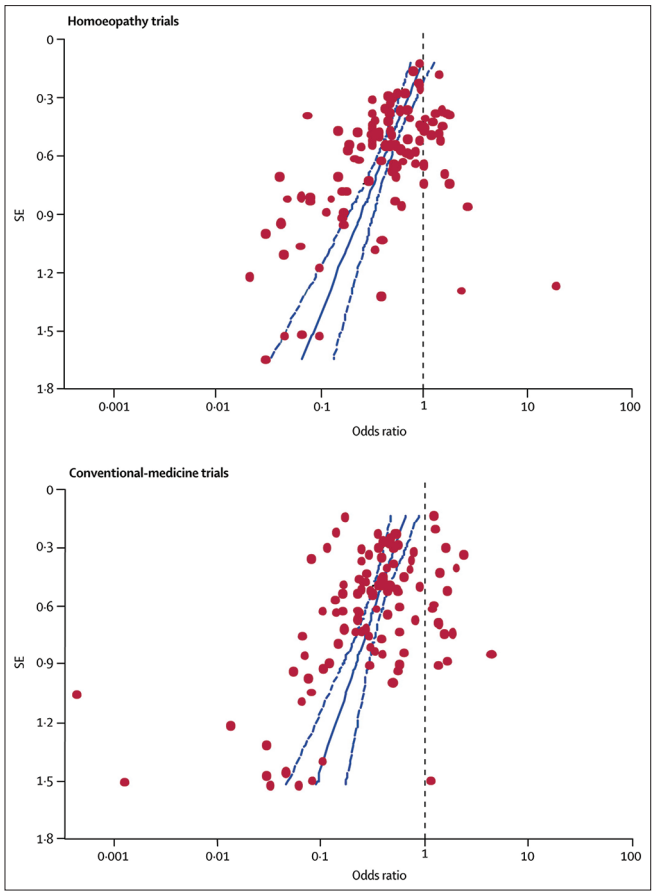

Figure 1: Funnel plots of 110 Homoeopathy trials (above) and 110 conventional trials (below). Source: Shang *et al*

Table 1: Subset of eight 'larger,' higher-quality Homoeopathy trials in Shang's review. (*n* = sample size) Two (Jacobs, Papp) were compared with conventional trials

Indication	Homoeopathy
Diarrhoea	Jacobs (*n*=116)
Treatment of influenza	Papp (*n*=334)
Prevention of influenza	Rottey (*n*=501)
Plantar warts	Labrecque (*n*=162)
Weight loss	Schmidt (*n*=208)
Muscle soreness	Vickers (*n*=400)
Headaches	Walach (*n*=98)
Sinusitis	Weiser (*n*=104)

In this case, the definition of 'larger trials' was unusual: 'with standard error in the lowest quartile'. The more usual definition of 'sample size above median' would almost have given a significant positive outcome for Homoeopathy (OR: 0.82, 95% CI: 0.71–1.02).[36] One single indication (muscle soreness after marathon running) was the main cause of the loss of statistical significance. A meta-analysis of four trials based on this indication gave a nearly significant negative effect (OR: 1.30, 95% CI: 0.96–1.76).

Reviews which draw negative conclusions are all based on selections of fewer than 10% of all trials.[37] Many different criteria are used for these selections, e.g., the National Health and Medical Research Council (NHMRC) of Australia uniquely chose a minimum sample size of $n = 150$. The way in which selection leads to different outcomes is illustrated by the evidence for Homoeopathy in ARTIs:

- Shang (2005)[34]: Pooling of eight trials showed *'a substantial beneficial effect (OR 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'*
- NHMRC (OPTUM, 2013)[38]: *'no reliable evidence that homoeopathy is as effective as the other therapies for the treatment of upper respiratory tract infection'*. This conclusion was based on *'...* especially *one medium-sized, good-quality trial (251 participants) did not detect a difference between homoeopathy and placebo'*
- Hawke *et al*. (Cochrane, 2018)[39]: '*Pooling of two prevention and two treatment studies did not show any benefit of homoeopathic medicinal products compared to placebo on recurrence of ARTI or cure rates in children'*.

The first review pooled eight trials, showing a positive effect. The latter two reviews concluded that Homoeopathy should not replace conventional therapies, such as *'anti-inflammatory drugs, antibiotics or other therapies'*, in ARTI. The NHMRC did not pool trials, while Hawke restricted the analysis to children and pooled in pairs of two. Hawke did not pool the primary outcome 'disease severity' of different trials because of different outcome measures.

The evidence for Homoeopathy may be inconclusive, but it is no worse than in comparable conventional studies – the conclusions reached depend heavily on the selection of trials.

Credibility

Patients who find that a CAM therapy has worked for them after conventional medicines have failed, complain that conventional doctors question their credibility. They try to convince their doctor by citing remarkable results which would not usually be seen in conventional practice. Some doctors may be intrigued by this, and if they try the method themselves, they may then see it confirmed; they then start to doubt their former beliefs, especially if they also obtain remarkable results. The response to remarkable cases is paradoxical, however, it can work in both directions: while the observer may be led to doubt their prior beliefs, their own objectivity may then be doubted by others. Similarly, carrying out a RCT in Homoeopathy poses a danger for the credibility of the researchers: they must be biased, because it is assumed that Homoeopathy cannot work.[40] Demanding credible RCT evidence from CAM researchers, thus, also becomes a contradiction.

The RCT as a method now enjoys lower credibility than was the case 25 years ago.[41] Credibility depends on statistical issues (such as power, false positives or negatives), methodological choices, reporting, financial and other interests and prior

beliefs. Methodological choices and vested interests can undermine the credibility of individual RCTs. No objective and consistent quality criteria have yet been established, and this is also true of GRADE. Criteria such as a large sample size, highly valued by NHMRC, are disputable. As an example, a study showed that adding Homoeopathy to usual treatment produced a higher survival rate 6 months after severe sepsis (75.8% vs. 50.0%, $P = 0.043$).[42] This is highly relevant to clinical practice, despite the sample comprising only 70 patients. Insisting upon large sample sizes is therefore ethically questionable.

Experts in Homoeopathy may have different views of the quality of trials from those who lack such expertise. For example, the Steinsbekk trial, which investigated the effect of just three medicines chosen by parents, is low-quality Homoeopathy, but this trial is regarded as being of high or moderate quality by non-experts (NHMRC, Hawke). For the NHMRC, this trial was considered to be the only one acceptable for ARTI. For Hawke, it was one of the two acceptable trials for 'prevention' of ARTI. Unlike in former reviews, the ARTI trials were divided into 'prevention' studies and treatment studies. In practice, only patients who have previously had infections come for homoeopathic treatment, so this is not real prevention, and they are then treated both during and between episodes. It would also be interesting to have a Cochrane review which was not restricted to children, such as Keneally's Cochrane review for antibiotics in ARTI.[17] Homoeopathy is of especial value to patients and practitioners when it is used as an addition to conventional medicine, e.g., in multimorbidity. Neither this added value nor the safety aspects are considered in reviews.

Shifting quality standards makes it difficult to design study protocols that continue to hold good into the future. The trial by Lange-de Klerk (1994) was conducted by one of the Holland's best research institutes in an Amsterdam university hospital; in 1997, it was regarded as one of the best Homoeopathy trials, but it is now considered to be of low quality. Credibility is inevitably a subjective matter – the recognition of Homoeopathy would create a considerable emotional upset for many – and this makes it difficult to combine with 'hard' criteria such as statistical significance or $P < 0.05$. Shang found a statistically significant effect in ARTI with no quality bias, but claimed that this was not credible because of biases 'shown in our study'. However, their research actually showed that there was less bias in the Homoeopathy trials.

Falsification

Despite 176 Homoeopathy RCTs, it still seems impossible for the research community to acknowledge Homoeopathy, even though the quality of these RCTs and the effect sizes shown are no different from comparable conventional RCTs. Even if there is a problem with the credibility of RCTs in general, there is no evidence that Homoeopathy RCTs are themselves less credible. The pathophysiologic rationale is always given as the reason for the low *a priori* belief in Homoeopathy. In 1993, a small number of RCTs seemed sufficient to cause a paradigm shift, but then the credibility of the RCT itself came into question. At present, insufficient credible proof is regarded as actual proof that Homoeopathy is a placebo effect. However, the absence of evidence of an effect is not evidence of the absence of an effect (the *argumentum ad ignorantiam* fallacy).[43] The editor of the Lancet, based on an undisclosed subset of 8 out of 110 trials, proclaimed: *'Now doctors need to be bold and honest with their patients about homoeopathy's lack of benefit'*.[44] The result was, in fact equivocal, positive, but not statistically significant: OR, 0.88 and 95% CI, 0.65–1.19. These eight, highly heterogeneous trials were pooled with the aim of confirming the placebo hypothesis, while the same heterogeneity was considered a reason to avoid pooling the results in other reviews.

The NHMRC[45] states: *'there are no health conditions for which there is reliable evidence that homoeopathy is effective'*. This is a hasty generalisation from the results obtained by selectively sampling the evidence base; the NHMRC selected 5 out of 176 Homoeopathy trials for 61 conditions. It is no surprise that a failure to pool results should lead to an inconclusive outcome, and the generalisation to all other conditions cannot be valid. The negative outcome in ARTI was based on a single trial involving self-medication, while Shang (2005) reported a strong effect with no quality bias based on eight trials. The NHMRC advises: *'Homoeopathy should not be used to treat health conditions that are chronic, serious, or could become serious'*. This is a straw man fallacy: in reality, many patients with chronic, or even serious, conditions that do not respond to conventional therapy find relief from Homoeopathy. For them, Homoeopathy is a therapy with reproducible results, and this is a more scientific stance than relying on simple intuition or unsystematic clinical experience.

There are four possible outcomes of a RCT: placebo works better, statistically significant or not, and verum works better, statistically significant or not. An outcome which is not statistically significant is inconclusive. However, many reviews regard any outcome that is not 'statistically significant positive' as positive evidence that Homoeopathy is a placebo. Antonelli found that 25 out of 61 reviews concluded that Homoeopathy is a placebo.[46] Many of those, like Shang's (OR: 0.88 and 95% CI: 0.65–1.19), are positive but not statistically significant, i.e., inconclusive. Moreover, inconclusive outcomes are seen only in subsets based on various arbitrary definitions of quality and homogeneity.

According to Popper, any attempt to confirm a hypothesis such as 'all swans are white' is unscientific, and similar hypotheses such as 'Homoeopathy is a placebo effect' can only be falsified.[47] Recall that a funnel plot of all Homoeopathy trials was similar to a comparable conventional plot [Figure 1], but with higher quality in the Homoeopathy trials; this is not consistent with subgroup reviews which appear to confirm the placebo hypothesis. Shang's finding in ARTI is not consistent with those of the NHMRC and Hawke. Does restricting trials to those in children support the conclusion that Homoeopathy

is a placebo in ARTI? Does the higher credibility of negative ARTI reviews confirm the inefficacy of bad Homoeopathy, the placebo hypothesis or uncertainty about the interrater reliability (validity) of the GRADE guidelines? It is indeed uncertain whether fewer than 5% of infinite repetitions of the one or two trials on ARTI selected as credible would show no effect above placebo; does this fact justify the conclusion that antibiotics should be used and Homoeopathy should be avoided in ARTI?

Bayes' Theorem

Bayes' theorem is used to explain why RCT evidence for Homoeopathy is not seen to justify an acknowledgement of Homoeopathy.[48] However, Bayes' theorem is about updating beliefs after consecutive observations, not a statement about truth, especially not after one observation. It describes how our beliefs change after an observation:

Posterior odds = LR × prior odds.

LR = Likelihood ratio = (prevalence of an observation in a target population)/(prevalence of the observation in the remainder of the population).

Similar considerations can be applied to diagnostic tests in rare diseases: a positive test outcome increases the chance that the patient has the disease, but this chance could still be very low. It would be a mistake, however, to disregard the test result simply because of this low posterior chance – confirmation by other tests or symptoms could increase the probability step by step. The rate at which posterior chance increases after a few further tests or symptoms may appear surprisingly fast to people not used to handling odds.[49] The essence of Bayes' theorem is probabilistic reasoning, with the adjustment of the probability after each new observation. It describes how we learn from the past experience.

Bayes' theorem also offers the possibility of comparing the likelihood of different hypotheses, using another variant of the formula:

$$P(H_i|E) = \frac{P(H \cap E)}{P(E)} = \frac{P(E|H_i) * P(H_i)}{\sum_{all\ hypotheses} P(E|H_i) * P(H_i)}$$

Where H_i is a certain hypothesis (i) and E is the evidence. Expressing this equation in words: the probability of hypothesis i, given evidence E, is the probability of evidence E, given hypothesis i, times the probability of hypothesis i, divided by the sum (for all possible hypotheses i) of the probabilities of the evidence, given each hypothesis, multiplied by the probability of each hypothesis.

A famous example of (mis) using Bayes' theorem in this way can be found at the trial of OJ Simpson (OJS), who was suspected of murdering his wife. The finding of DNA material from OJS at his wife's home was explained by his lawyers as having been planted by the police. Using this formula, they compared the probabilities of different hypotheses: (1) OJS left his DNA at the murder site; (2) the DNA belonged to someone else; and (3) the DNA was planted. Putting this into Bayes' formula gives us Table 2.[50]

The outcome of this Bayesian comparison of hypotheses in OJS' case was that the existing evidence mostly supported the hypothesis that the evidence had been planted ($P = 0.94$). Adducing the hypothesis that the DNA was planted then reduces the probability of OJS's guilt to $P = 0.06$. Intuitively, such a conclusion makes us feel uneasy. The catch lies in the subjective nature of the prior chance estimate, the weakest point in Bayesian reasoning when it comes to hypothesis testing. Why should this prior chance be so low? In this case, because it was based on the assumption that OJS could have been anywhere in the US at that time. If that assumption is wrong, the prior chance of OJS being at the murder site is also wrong.

Something similar happens in scientific disputes: if the assumption that there is no possible mechanism of action other than molecular interactions is wrong (the assumption is a *reductio ad absurdum*), the extremely low prior chance attributed to Homoeopathy is wrong. The real issue here is the ability to estimate a prior chance objectively or a willingness to accept the observations of others. Are the observations of a doctor who has experience of both Homoeopathy and conventional medicine less credible? Did looking through a telescope make someone less credible in the debate about the Copernican worldview? If this credibility depends on the assumed prior chance we are caught in circular reasoning. Bayes' theorem, however, performs well in an expert system which advises users how to interpret their observations; the system then becomes data driven, rather than theory driven.

Diagnosis/Prognosis

The greatest advantage of Bayesian reasoning is that it describes expectations based on previous experience as probabilities, rather than as binary, true-or-false options. Beliefs shift after

Table 2: The defence's Bayesian comparison in the OJ Simpson trial of chances that his DNA was at the crime scene because OJ Simpson was there (H1), or the DNA was not his (H2), or the DNA was planted. The prior chance of H1 was supposed to be very low and the likelihood that the DNA was OJ Simpson' very near 100%. The joint probability of H1 and its likelihood is the product of both. The posterior chance of each hypothesis is the joint probability divided by the sum of joint hypotheses

Hypothesis H	Prior P (H)	Likelihood P (E|H)	Joint P (H∩E)	Posterior P (H|E)
H_1: OJS	$6.25* 10^{-8}$	1	$6.25* 10^{-8}$	0.06
H_2: Other	≈1	$0.588* 10^{-8}$	$\approx 0.588* 10^{-8}$	0.00
H3: Planted	$\approx 10^{-6}$	1	$\approx 10^{-6}$	0.94
		P (E)	$\approx 106.9* 10^{-8}$	

OJS: OJ Simpson

a series of new observations, and this also reflects the natural process of diagnostic reasoning in medicine.[51] Maximising the probability of a diagnosis remains the core skill of medicine. The hypothesis that a medicine works no better than placebo is a null hypothesis, a proxy for the hypothesis that the medicine works. This enables falsification, but it is not real falsification in the Popperian sense (the first black swan), because all it actually indicates is that the chance of a false-positive outcome is 5% or less.[52] The expected chance that the therapy will improve the patient's condition would be a more informative parameter than the chance that this is not a placebo effect. There are good reasons to extend diagnostic reasoning to prognostic reasoning.[53] Prognostic reasoning in Homoeopathy shows how similar the two can be, as shown in Figure 2. The step-by-step increments in probability of the diagnosis/prognosis can be explained by Bayes' theorem: the LRs of symptoms are greater than unity because the symptoms occur more frequently in patients with pneumonia or in patients who respond well to *Belladonna*. This hypothetical case shows how the homoeopathic medicine *Belladonna* could be chosen if symptoms indicating *Belladonna* are present. The medicine would be expected to work only if sufficient indicating symptoms were presented by this particular patient. The wider the knowledge which the practitioner has of different medicines, the more patients he or she will be able to help. The estimates of the accumulating chances in this case are based on expert opinion and consensus. Such estimates can be made more accurate by research into diagnostic/prognostic factors, not only for diagnostics tests, but also for symptoms such as 'rapid breathing' in pneumonia.[54] Similarly, we can also assess the prognostic relationship between a medicine such as *Belladonna* and symptoms such as 'grinding the teeth during sleep'.[55]

The existing EBM framework will not support a patient's choice of therapy if there is no 'credible' RCT evidence, or if there is multimorbidity, or if there is no effect despite evidence that there could be. Bayesian statistics can give an actual probability that a therapy will work, given the patient's particular characteristics. Bayesian reasoning complements frequentist reasoning; it is less suited to the falsification of hypotheses, but better suited to making individual prognoses. Prognostic factor research (PFR) can assess all the relationships between personal factors and future outcomes.[56] In the case of AMR, or if existing treatments offer no personal benefit, a prognosis of, say, 60% that a specific medicine will work is more relevant than any degree of certainty that this is not a placebo effect. Advice based on PFR is also better than relying only on intuition or personal experience.

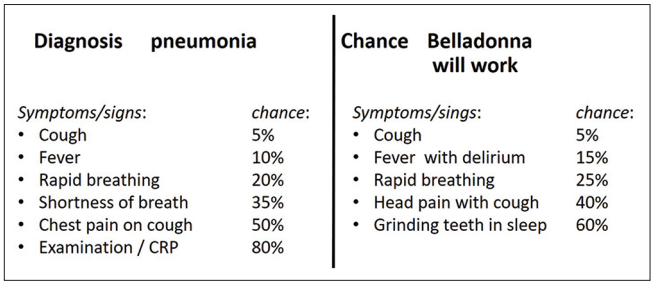

Figure 2: Hypothetical comparison of a diagnostic procedure and a prognostic procedure in Homoeopathy. Chances are estimates by experts

Discussion

Based on nearly two hundred RCTs, the current state of EBM has led medical authorities to conclude that Homoeopathy is a placebo and its use could be harmful. Antibiotics should be preferred over Homoeopathy in ARTI. EBM, however, simultaneously indicates that antibiotics may do more harm than good in ARTI: The NNT for antibiotics is over 4000 and there are over 700,000 yearly deaths caused by AMR. Despite all this, ARTI remains the prime indication for prescribing antibiotics.[18] There is no proof that Homoeopathy does any harm, nor does RCT evidence demonstrate that Homoeopathy is any less effective than comparable conventional medicine. The conclusions which have been drawn from various meta-analyses of trials of Homoeopathy in ARTI vary from a strong effect to no effect over placebo, depending on the manner in which trials are pooled for analysis. Apparently, 'insufficient' evidence is regarded as a contraindication for non-conventional therapies, outweighing the established inefficacy and harm of conventional therapies.

The authorities policing the use of EBM and users of Homoeopathy appear to inhabit different worlds. EBM is concerned that patients suffering chronic complaints will neglect EBM using Homoeopathy, while users of Homoeopathy have already experienced the limitations of EBM before trying Homoeopathy. It seems that these two worlds do not communicate well and this contributes to a paternalistic attitude by EBM. Cooperation between experts in non-conventional methods and those who lack such expertise is conspicuously absent.

If there exists a similarly insufficient level of evidence for two therapies for the same disease (ARTI) and demonstrable harm from only one of them, a preference for the harmful therapy cannot be right. Logical fallacies may be involved and a chain of these could lead to the choice of antibiotics rather than Homoeopathy: (1) *reductio ad absurdum*, molecular interaction is the only possible mechanism of action; (2) *argumentum ad ignorantiam,* absence of evidence of an effect is evidence of absence of an effect and (3) *straw man fallacy,* use antibiotics rather than Homoeopathy in ARTI.

Fallacies may be obscured by complex, biased reasoning, e.g., by combining frequentist (hypothesis testing) and Bayesian (probabilistic) reasoning. We can use Bayesian prior belief to explain how we update our belief, but the correct Bayesian outcome is a rapid strengthening of this belief after repeated observations, not a frequentist lack of statistical significance after the first observation.[49] How credible a proof appears depends on belief, which in turn is influenced by a large number of (often continuous) variables. This results in a variety of possible choices based on unvalidated and therefore arbitrary

criteria, leading to a range of statistical significance values, each with an unknown probability. The outcome becomes nothing more than, e.g., 'if the selection of these two trials is credible enough, the chance of a false-positive outcome is more than 5%. If we select these eight trials, the chance of false-positive outcome is below 5%'. The first option leads to the rejection of an implausible method, but would the second choice lead to acceptance? Or do we just avoid the second choice? Bias in RCT evidence became apparent in conventional RCTs, but this was then considered to be an explanation for the unexpectedly positive outcomes of Homoeopathy RCTs. This constitutes the first step away from falsification – the original goal of RCT – towards confirmation, the unscientific use of evidence.

Plausibility becomes less relevant to patients when plausible therapy fails. For practitioners, plausibility is much more relevant because the pathophysiologic rationale is fundamental to their knowledge. However, a scientific attitude requires that this rationale is considered in the light of observations. For a few CAM methods, there is an extensive body of shared experience between patients and practitioners, allowing a consensus to be reached about prognostic factors for specific interventions.

In their daily practice, medical practitioners apply Bayesian reasoning to update their beliefs with respect to diagnosis and prognosis, based on their own experience. Is medicine a Popperian science anyway? Treatment starts with the Bayesian probability of a diagnosis, built up by consecutive symptoms and tests which are relevant to that particular patient. It then goes on to assume a 'certainty' about therapy, which is not a real certainty at all, but a frequentist $P < 0.05$ value relating to a proxy outcome (not better than placebo), applicable to an undefined subset of patients; credibility considerations then add a probability distribution to the *P* value. Neither diagnosis nor the results of treatment are dichotomous variables; a prognostic framework is needed in which probability-based decisions can be arrived at.[53]

Introducing the notion of credibility into hypothesis testing presents a spectrum of probabilities of statistical significance. With so many nuances of credibility existing across 'proven' and 'unproven' therapies, hypothesis testing in medicine has become a broad spectrum of shades of grey in the Popperian white swan. The end result is a subjective choice which varies according to the position of the observer.

Bayesian reasoning can offer a rational personalised therapy, based on shared experience, which can further be improved by PFR. The weakness of research based only on consensus and observation is that it cannot prove causality and is more liable to bias; it can only be used to improve medicine, to get better results. Other incentives, such as academic recognition or financial profits deriving from patents, are liable to introduce bias. However, is not financial profit one of the main problems with the credibility of RCT evidence as well? PFR helps doctors to form their own opinions about CAM, and they can test how reproducible Homoeopathy is by prescribing a homoeopathic medicine if they encounter a patient with recognisable signs/symptoms.

Conclusion

If the credibility of evidence is to be defined by medical authorities, the current application of EBM risks becoming authoritarian; this will estrange patients, result in simplistic decisions and lead to prejudice towards CAM users and researchers. This prejudice is already evident in the unscientific 'confirmation' of the placebo hypothesis with respect to Homoeopathy. In cases of ARTI, this leads to the perpetuation of the harmful use of antibiotics in preference to Homoeopathy because of 'insufficient' evidence. The current application of EBM is becoming untrue to its principle of data-driven science because medical authorities decide subjectively which data are 'credible'. Patients and practitioners who provide data that do not fit within existing paradigms are denied influence. To demand that evidence is provided by researchers who are simultaneously refused, is an absurdity, particularly when the credibility of this evidence is based on existing beliefs.

Hypothesis testing in EBM is irrelevant to many patients, as it gives no real predictions about which treatments will be effective for the individual patient. EBM should acknowledge the reality that many patients fail to respond to conventional medicine, even when the placebo hypothesis is falsified. These patients also need advice about the expected benefits and possible harm of alternative treatments. Like diagnosis, prognosis is based on probabilities, not certainties. In clinical practice, prognostic reasoning is the natural extension of diagnostic reasoning, and prognostic research is more informative for more patients.

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गैर–पारंपरिक पद्धति प्रमाणित करनाः एक उदाहरणस्वरुप विरोधाभास

मूल रुप से, यह सोचा गया था कि साक्ष्य आधारित चिकित्सा (इबीएम) अंतर्ज्ञान या बहुलता के आधार पर निर्णय लेने को स्थान देगी। बाद में, यह दिखाई दिया कि इबीएम में स्वर्णमानक, यादृच्छिक नियंत्रित परीक्षण (आरसीटी) उतना 'कठिन' नहीं था जितना कि माना जाता था, और विश्वसनीयता का आकलन आवश्यक था। कुछ दशकों के बाद, 'विश्वसनीय' आरसीटी–केंद्रित ईबीएम ने होम्योपैथी जैसे अकल्पनीय माने जाने वाले उपचारों को खारिज कर दिया है। फिर भी, ऐसे उपचारों की रोगियों द्वारा व्यापक रुप से सराहना की जाती है जो पारंपरिक चिकित्सा के साथ उनका उपयोग करते हैं।

होम्योपैथी के लगभग दो सौ आरसीटी परीक्षणों में होम्योपैथी और तुलनीय पारंपरिक परीक्षणों के बीच प्रभावकारिता में कोई अंतर नहीं दिखाया। इस बात का कोई साक्ष्य नहीं है कि पारंपरिक परीक्षण बेहतर गुणवत्ता के हैं और होम्योपैथी द्वारा नुकसान का कोई निष्कर्ष भी नहीं है। हालांकि, साक्ष्य का चयनात्मक विश्लेषण सांख्यिकीय रुप से निरर्थक परिणामों को दर्शाता है, और इसी कारण परिकल्पना की अवैज्ञानिक ''पुष्टि'' के रुप में व्याख्या की जाती है कि होम्योपैथी एक कूट भेषज है।

फलस्वरुप, इस संकेत के लिए एंटीबायोटिक दवाओं की प्रभावकारिता के साक्ष्य की अनुपस्थिति और नुकसान के एक स्थापित जोखिम के बावजूद तीव्र श्वसन पथ के संक्रमण (एआरटीआई) में एंटीबायोटिक दवाओं के बजाय होम्योपैथी के उपयोग को हतोत्साहित किया गया है।

आरसीटी सबूतों की जटिल सांख्यिकि व्याख्याएं अव्यावहारिक और यहां तक कि हानिकारक निष्कर्ष को इंगित करती है। विश्वसनीय प्रमाण वास्तव में कई व्यक्तिपरक (अक्सर निरंतर) चर (वेरियेबल) पर आधारित होता है। ईबीएम के लिए एक समापन बिंदु के रुप में, आरसीटी साक्ष्य से अधिक के आधार पर बायेसियन संभावनाएं रोगियों के लिए एक अधिक व्यावहारिक और व्यक्तिगत प्रकार की सलाह प्रदान करेगी और एक विशेष समाधान में विफल होने पर विकल्पों की पेशकश करते हुए निदान प्रक्रिया को एक पूर्वानुमान ढांचे में विकसित करेगी।

Prouver des méthodes non conventionnelles: un paradoxe paradigmatique

À l'origine, on pensait que la médecine basée sur des preuves (MBP) supplanterait la prise de décision basée sur l'intuition ou la plausibilité. Plus tard, il est apparu que l'étalon-or dans la MBP, soit l'essai contrôlé randomisé (ECR), n'était pas un point de référence aussi « difficile » qu'on le supposait et qu'une évaluation de la crédibilité était nécessaire. Après quelques décennies, une MBP « crédible » centrée sur les ECR a conduit à l'abandon de thérapies jugées invraisemblables, telles que l'homéopathie. Néanmoins, de tels traitements restent largement appréciés par les patients qui les utilisent parallèlement à la médecine conventionnelle.

Près de deux cents ECR en homéopathie n'ont montré aucune différence d'efficacité entre l'homéopathie et les essais conventionnels comparables. Rien ne prouve que les essais conventionnels soient de meilleure qualité ni que l'homéopathie est préjudiciable. Cependant, une analyse sélective des preuves montre des résultats statistiquement non significatifs, qui ont été interprétés comme une « confirmation » non scientifique de l'hypothèse selon laquelle l'homéopathie est un placebo.

En conséquence, l'utilisation de l'homéopathie au lieu d'antibiotiques dans les infections respiratoires aiguës (ARTI) a été découragée, malgré l'absence de preuve de l'efficacité des antibiotiques dans ces instances et un risque de préjudice établi.

Les interprétations statistiques complexes des preuves obtenues par ECR conduisent à des conseils peu pratiques, voire néfastes. Les preuves crédibles reposent en réalité sur de nombreuses variables subjectives (souvent continues). En conclusion pour MBP, les probabilités bayésiennes, basées sur davantage de preuves que les ECR, fourniraient un type de conseil plus pratique et personnalisé aux patients et développeraient le processus de diagnostic dans un cadre pronostique, offrant des alternatives en cas d'échec d'une solution donnée.

Demostración de métodos no convencionales: paradoja paradigmática

En un principio, se creía que la medicina basada en evidencia (MBE) podría reemplazar la toma de decisiones por intuición y verosimilitud. Posteriormente, se vio que el estándar de referencia en la MBE, los ensayos controlados aleatorizados (ECA), no constituía un punto de referencia tan "fuerte" como se había considerado, y que se precisaba una evaluación de la credibilidad. Tras varias décadas, la MBE centrada en ECA "creíbles dio lugar a que se desecharan los tratamientos considerados como implausibles, por ejemplo, la homeopatía. No obstante, los pacientes siguen valorando este tipo de tratamientos y los utilizan junto con la medicina convencional.

Casi 200 ECA de homeopatía demuestran que no diferencias en la eficacia entra la homeopatía y los ensayos convencionales comparables. No hay pruebas de que los ensayos convencionales sean de mejor calidad, ni tampoco hay pruebas de efectos lesivos de la homeopatía. Sin embargo, los análisis selectivos de evidencia muestran resultados estadísticamente no significativos que entonces se interpretan como "confirmación" no científica de la hipótesis de que la homeopatía es placebo.

En consecuencia, se desestimado el uso de la homeopatía, en lugar de antibióticos, en las infecciones agudas del tracto respiratorio (IATR) pese a la ausencia de evidencia de eficacia de los antibióticos en esta indicación y al riesgo establecido de efectos nocivos.

La interpretación estadística compleja de la evidencia por ECA ha llevado a recomendaciones poco prácticas e incluso nocivas. De hecho, la prueba creíble se basa en muchas variables subjetivas (a menudo, continuas). Como parámetro de la MBE, las probabilidades bayesianas, que se basan en más que la evidencia de los ECA, proporcionarían un tipo de recomendación más práctico e individualizado para los pacientes y permitirían desarrollar un proceso diagnóstico dentro de un marco pronóstico, ofreciendo alternativas si una determinada solución fracasase.

Beweisen unkonventionelle Methoden: ein paradigmatisches Paradoxon

Ursprünglich wurde angenommen, dass evidenzbasierte Medizin (EBM) die Entscheidungsfindung auf der Grundlage von Intuition oder Plausibilität ersetzen würde. Später stellte sich heraus, dass der Goldstandard in EBM, die randomisierte kontrollierte Studie (Randomized Controlled Trial, RCT), kein so harter Bezugspunkt war, wie angenommen worden war, und eine Bewertung der Glaubwürdigkeit erforderlich war. Nach einigen Jahrzehnten hat die „glaubwürdige" RCT-zentrierte EBM dazu geführt, dass Therapien wie die Homöopathie als unplausibel abgewiesen wurden. Dennoch werden solche Therapien von Patienten, die sie neben der konventionellen Medizin anwenden, nach wie vor allgemein geschätzt.

Fast zweihundert homöopathische RCT zeigten keinen Unterschied in der Wirksamkeit zwischen Homöopathie und vergleichbaren konventionellen Studien. Es gibt keinen Beweis dafür, dass herkömmliche Studien von besserer Qualität sind, und es gibt keinen Beweis dafür, dass die Homöopathie schädlich ist. Die selektive Evidenzanalyse zeigt jedoch statistisch nicht signifikante Ergebnisse, die dann als unwissenschaftliche „Bestätigung" der Hypothese interpretiert werden, dass Homöopathie ein Placebo ist.

Infolgedessen wurde von der Verwendung von Homöopathie anstelle von Antibiotika bei akuten Atemwegsinfektionen (ARTI) abgeraten, obwohl keine Beweise für die Wirksamkeit von Antibiotika für diese Indikation vorliegen und das Risiko eines Schadens erwiesen ist.

Komplexe statistische Interpretationen von RCT-Befunden führen zu unpraktischen und sogar schädlichen Ratschlägen. Der glaubwürdige Beweis basiert tatsächlich auf vielen subjektiven (oft kontinuierlichen) Variablen. Als Endpunkt für EBM würden Bayes'sche Wahrscheinlichkeiten, die auf mehr als RCT-Beweisen beruhen, eine praktischere und persönlichere Art von Beratung für Patienten bieten und den Diagnoseprozess zu einem prognostischen Rahmen entwickeln, der Alternativen für den Fall bietet, dass eine bestimmte Lösung ausfällt.

驗證非傳統方法：範式悖論

最初，人們認為實證醫學（EBM）將取代基於直覺或合理性的決策。後來，在實證醫學中的黃金標準---隨機對照試驗（RCT）---作為一個參考點的，似乎不像人們想像的那樣「堅實可信」，需要對其可信度進行評估。幾十年後，「可靠的」以RCT為中心的EBM導致了對順勢療法等療法被認為不可信而遭到駁回。儘管如此，這種療法仍廣受使用傳統藥物的患者所歡迎，並與之一併使用。

近200個順勢療法隨機對照試驗顯示，順勢療法和類似的主流實驗之療效沒有差異。沒有證據表明主流實驗的品質更好，也沒有證據表明順勢療法有害。然而，對證據的選擇性分析顯示統計上不顯著的結果，然後就解釋為順勢療法是不科學、是安慰劑的這個假設得到「證實」。

因此，儘管沒有證據表明抗生素治療急性呼吸道感染（ARTI）的有效性，和已確定的危害風險，但仍不鼓勵使用順勢療法代替抗生素。

RCT證據的複雜統計解釋導致了不切實際甚至有害的建議。可信的證據實際上是基於許多主觀（通常是連續的）變數。作為實證醫學的終點，貝氏概率（基於超過RCT的證據）將為病者提供更實用和個人化的建議，並將診斷過程發展為一個預後框架，如果一個特定的解決方案失敗，將提供替代方案。