Homeopathy (2015) 104, 328–332

http://dx.doi.org/10.1016/j.homp.2015.05.003, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Controlled clinical studies of homeopathy

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Introduction: **Observations about controlled clinical trials expressed by Max Haidvogl in the book *Ultra High Dilution* (1994) have been appraised from a perspective two decades later. The present commentary briefly examines changes in homeopathy research evidence since 1994 as regards: the published number of randomised controlled trials (RCTs), the use of individualised homeopathic intervention, the 'proven efficacy of homeopathy', and the quality of the evidence.**

Methods: **The commentary reflects the details of RCTs that are available in a recently published literature review and by scrutiny of systematic reviews of RCTs in homeopathy.**

Results: **The homeopathy RCT literature grew by 309 records in the 18 years that immediately followed Haidvogl's article, with more than a doubling of the proportion that investigated individualised homeopathy. Discounting one prior publication, the entire systematic review literature on homeopathy RCTs post-dates 1994. A total of 36 condition-specific systematic reviews have been identified in the peer-reviewed literature: 16 of them reported positive, or tentatively positive, conclusions about homeopathy's clinical effectiveness; the other 20 were negative or non-conclusive. Reviews typically have been restricted in the strength of their conclusions by the low quality of the original RCT evidence. Three comprehensive systematic reviews concluded, cautiously, that homeopathy may differ from placebo; a fourth such review reached negative conclusions. A recent high-quality meta-analysis concluded that medicines prescribed in individualised homeopathic treatment may have small, specific, effects.**

Conclusions: **Despite important growth in research activity since 1994, concerns about study quality limit the interpretation of available RCT data. The question whether homeopathic intervention differs from placebo awaits decisive answer.** *Homeopathy* (2015) **104**, 328–332.

Key words: Clinical research evidence; Haidvogl; Homeopathy; Meta-analysis; Randomised controlled trial; Systematic review

Introduction

In his contribution to the book *Ultra High Dilution*, published in 1994, Max Haidvogl summarised his chapter on clinical studies of homeopathy as follows: "*Numerous controlled clinical studies have proved the efficacy of homoeopathic remedies, but most of them could not meet sufficient methodological quality. However, specially (sic) homoeopathic studies have to show a maximum in scientific standard because they have to withstand much more criticism than pharmacological studies relating to the common paradigmas (sic) of clinical medicine. Clinical studies on homoeopathy should be planned in co-operation between homoeopathic practitioners and university clinics, because this allows for a maximum methodological standard and also for the possibility of publication in distinguished journals with a high impact factor, which usually are not available for homoeopathic practitioners. Controlled clinical human studies in the field of homoeopathy are only useful if they take into account the characteristics of homoeopathic drug prescription, i.e. the person-specific, individual choice of the remedy.*"[1]

Haidvogl based these observations importantly on the contemporary comprehensive review of randomised controlled trials (RCTs) of homeopathy by Kleijnen and colleagues (who, from today's perspective, misleadingly

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Received 27 February 2015; revised 12 May 2015; accepted 20 May 2015

termed their study a 'meta-analysis').[2] Of the 105 trials with interpretable data, 81 indicated positive results, which included RCTs that received high-quality ratings for randomisation, blinding, sample size, and other methodological criteria. Kleijnen came to the conclusions: 'Based on this evidence we would be ready to accept that homoeopathy can be efficacious, if only the mechanism of action were more plausible'; 'the evidence presented in this review would probably be sufficient for establishing homoeopathy as a regular treatment for certain indications'. It is apparent, therefore, that Haidvogl provided a reasonable summary of the clinical research evidence that existed at the time.

The present paper briefly addresses the following: Since 1994, what has happened to the RCT evidence as regards: the number of published studies; the use of individualised homeopathic intervention; the 'proof of efficacy' (including systematic review and meta-analysis data); the quality of evidence, including the peer-reviewed status of the publications?

Methods

This commentary has been informed by an analysis of the RCT records detailed in the text and the appendices of a recent major literature review[3] and by close scrutiny of the systematic review literature.[4,5]

Results

Number of RCTs and individualisation

Up to and including 2011, there had been a total of 489 published records of RCTs in the peer-reviewed and non-peer-reviewed literature; 95 of them were repeat publications.[3] From an analysis of these RCT records, it is apparent that 180 (37%) of the 489 would have been potentially available to Haidvogl (i.e. published up to the end of 1993); the RCT literature therefore grew by 309 records in the interim period. It is also apparent that, up to and including 1993, only 26/180 (14%) RCTs had studied individualised homeopathy; for the years since then, the figure increased to 114/309 (37%). Before 1994, the large majority (87%) of RCTs were placebo-controlled; during the intervening years to 2011, the corresponding figure was little changed (83%).[3]

In 1994, homeopathy was rightly described as a 'new field' of clinical research investigation; indeed, the 15 years from 1997 witnessed a sharp increase in research activity to an average of 10−12 RCT papers per annum, compared to 2−6 per annum in the 15-year period up to 1991.[3] The marked increase in RCT research on individualised prescribing might reflect the homeopathy research community's response to Haidvogl's encouragement to investigate that key facet. The lack of change in the proportion of placebo-controlled trials, however, suggests that conventional study design has prevailed over Haidvogl's expressed concerns about appropriateness and ethics of double-blinding.

Systematic reviews and quality of evidence

Haidvogl's recognition that poor-quality studies dominated the research literature contrasts with his associated summary conclusion about 'proven efficacy'. Nevertheless, the main text of his article clarifies that low methodological quality does seriously undermine the reliability of evidence. Focus on reliable evidence as a critical arbiter of efficacy or clinical effectiveness has not been considered sufficiently in reviews during the years since 1994, though this matter is being rectified in a new series of systematic reviews of homeopathy RCTs.[6,7] The latter programme of research is also reflecting evidence solely from peer-reviewed journals, whose relative contribution to the total RCT literature in homeopathy increased strikingly from 1997 onwards.[3]

Every systematic review or meta-analysis of homeopathy for a specific medical condition, or for a group of diagnoses, has been published since Haidvogl's article in 1994. At the time of writing the present article, the peer-review literature comprised 36 such systematic review papers, 16 of which reported clearly or tentatively positive conclusions on homeopathy's effectiveness; 11 reviews reported clearly or tentatively negative conclusions; nine were non-conclusive either way. All 36 references, together with those that reported a more comprehensive review of homeopathy RCTs, are listed in Table 1.

Detailed consideration of RCT quality is intrinsic to all systematic reviews in the Cochrane Library, and seven reviews on homeopathy have been published there; four of the seven included meta-analysis, an approach that has seldom been applied for disease-specific reviews outside the Cochrane context. None of those seven reviews reached a clearly positive conclusion about homeopathy's effectiveness (Table 1).[8−14] Two of the reviews highlighted some positive meta-analysis findings, but which were undermined by the low quality of the available evidence. Mathie et al. (2012) reported that, 48 h after the start of treatment for influenza, the homeopathic medicine Oscillococcinum® produced a statistically significant absolute risk reduction of 7.7% in the frequency of symptom relief compared with that of placebo (mean risk ratio = 1.86).[13] In meta-analysis of two RCTs of participants with irritable bowel syndrome, Peckham et al. (2013) found a statistically significant difference in global improvement between *Asa foetida* treatment and placebo at two-week follow-up: 73% of patients in the homeopathy group improved, compared to 45% in the placebo group (mean risk ratio = 1.61).[14]

Following Kleijnen,[2] there have been four further comprehensive systematic reviews of RCTs in homeopathy; each of them included meta-analysis data. Three of those systematic reviews of RCTs reached the cautious conclusion that homeopathy differs from placebo.[15−17] Boissel et al. undertook meta-analysis on the primary outcomes of 15 strictly selected trials, and obtained a pooled significance value of $P = 0.0002$; they concluded 'there is evidence that homeopathic medicine is more effective than placebo', but 'the strength of this evidence is low