

Building quality research evidence in Homoeopathy

Homoeopathy remains a popular choice of treatment worldwide, with more and more people choosing it for holistic and individualised treatment. The recent surveys suggest many people integrate, use and value Homoeopathy as a complementary treatment option.^[1-3] It is estimated that there are more than 200 million users of Homoeopathy worldwide.^[4]

With growing popularity of Homoeopathy comes the necessity to build upon the scientific evidence. Consequently, there is increasing pool of evidence for the scientific and plausible understanding of the mechanisms of homoeopathic medicines; several clinical trials have been published in indexed journals showing the effectiveness of Homoeopathy, along with systematic reviews and meta-analysis.^[5,6] Studies have revealed that homoeopathic remedies contain nanoparticles of source materials;^[7] they act by modulating biological function of the allostatic stress response network^[8] and by stimulating hormetic adaptive systems rather than by linear pharmacological effects.^[9-11] Several research organisations worldwide are focusing on building the evidence base for Homoeopathy. Recently held breakthrough seminar,^[12,13] ‘New Horizons in Water Science – The Evidence for Homeopathy’, had the scientific community including Nobel Laureates talking about electromagnetic signals and quantum theory with respect to Homoeopathy,^[14] citing studies which state that electromagnetic signals can be transduced in highly diluted aqueous solutions originally containing some bacterial or viral DNA.^[15]

The WHO Traditional Medicine Strategy 2014–2023 document also endorses the clinical education and research in the complementary and alternative medicine (CAM) including Homoeopathy to ensure safety, efficacy and quality of traditional medicines. Further, keeping in view the resolution on traditional medicine adopted by the World Health Assembly in 2003, and the outcomes of the WHO Global Survey of Traditional Medicine (2005), the WHO aims to provide technical support to the Member States in the development of an appropriate framework for research, with guidelines and methodologies for research and evaluation, to ensure the quality, safety and efficacy of traditional medicine in order to facilitate the integration of traditional medicine into the broad health sectors.^[16]

RESEARCH EVIDENCE

Despite the growing popularity and evidence, Homoeopathy continues to face criticism for its plausibility, safety, efficacy, etc. The reasons for this could be many; the current research evidence may not be sufficient with reluctance of many practitioners to engage in evidence-based practices, lack of appropriate training to conduct high-quality research,

inadequate or poor funding for researches, etc. Multiple barriers exist for the conduct and application of research in CAM.^[17] The review indicated barriers in terms of access to high-quality research (poor access to high-quality systematic reviews, limited qualitative studies, lack of CAM including Homoeopathy journals in mainstream databases, few opportunities for research education and research in CAM, etc.) and competency of practitioners in conducting research (insufficient research experience, limitations in interpreting the results accurately, lack of knowledge regarding research methodologies). Further, ‘bias’ is found to be an important barrier, as innate negative perceptions about CAM, specifically Homoeopathy, are there.^[18] Another significant barrier was found to be complexities of CAM including Homoeopathy. The individualistic nature, homoeopathic principles and philosophy, nature of treatment, etc., are not completely reflected in the conventional research framework, thus it is difficult to capture the true effect of Homoeopathy.

RANDOMISED CONTROLLED TRIALS AND SYSTEMATIC REVIEWS

Randomised controlled trials (RCTs) are generally considered as ‘gold standard’ for establishing how well an intervention works, and also for their ability to reduce bias and confounding factors that could otherwise influence both group assignment and prognosis.^[19]

Although the explanatory trials that assess the research hypothesis under ideal study circumstance have strong internal validity—we can depend on the results of a given trial—such trials may have limited external validity: we may not be able to apply the results to routine clinical practice.^[20] The pragmatic trials seek to know, if the particular intervention work under usual conditions and have high generalizability.

Even with many benefits, the shortcomings such as difficulty in recruiting sufficient patients, missing out on concerned/reference population due to the exclusion criteria and concerns with information and consent^[21] in existing clinical trials have been reported. RCTs come under criticism for the following reasons namely, the behaviour of the principal investigator could—from the design of the study alone—be altered by his/her expectations (Rosenthal effect). The individuals involved are aware of this difference and possibly behave differently (Hawthorne effect for study participants).^[22] Further, there is difficulty in blinding, providing true placebo group, reporting the complexities, etc., which hamper the quality of trials.

RCTs in Homoeopathy are considered to have several limitations such as low statistical power, less sample size

and inadequate reporting.^[23] There is debate that RCTs in Homoeopathy are mostly done to show the effect of Homoeopathy versus placebo only. On the contrary, it is also argued that research conducted to show the effectiveness of Homoeopathy is not what is done in day-to-day practice, as treatment is provided to individual patient, not the disease.^[24]

The RCTs are the raw material for the systematic reviews and meta-analysis. The systematic reviews are on the top of the evidence hierarchy. There are many systematic reviews and meta-analyses of Homoeopathy; however, outcomes of some of these are used for tarnishing the image of Homoeopathy. Empirical studies show that inadequate quality of trials may distort the results from systematic reviews and meta-analyses.^[25] Thus, it is essential that good quality, better designed RCTs are conducted in order to develop the evidence base that can decisively provide reliable effect estimates of homoeopathic treatment.^[26]

Despite the advantages of doing a meta-analysis, there are certain limitations. The bias in the meta-analyses must be reduced through proper systematic review; examination of heterogeneity must be done and addressed adequately using appropriate statistical tool and publication bias. Limitations also are due to arbitrary selection of studies, selection of relevant outcome, methods of analysis, interpretation of heterogeneity and generalization and application of results. Many times, there are methodological flaws in the clinical trials, low-quality studies leading to systematic reviews and meta-analysis against Homoeopathy.^[27] There are various tools that can be used for conducting the meta-analyses,^[28] assessment of risk of bias, quality of trials, etc.

RESEARCH DESIGNS IN HOMOEOPATHY

Having understanding of difficulties and challenges in the existing approaches, several new methods to conduct scientific research are being undertaken. Researchers are rethinking clinical trial designs, even the mainstream researchers are focusing on personalised medicine.^[29] New tools for assessing the model validity of RCTs of Homoeopathy are available in the form of Model Validity of Homeopathic Treatment.^[30] Model validity reflects the concordance between the trial study design and the 'state-of-the-art' practice for the intervention under investigation. Further, a set of guidelines specific to reporting of Homoeopathy trials (Reporting data on homoeopathic treatments: a supplement to Consolidated Standards of Reporting Trials^[31]) must be unvaryingly followed to address the issue of disparities in reporting.

Trials within Cohorts

Trials within Cohorts^[32] are one or more RCTs within cohorts. The advantages of the design are that the cohort serves as a representative pool from which eligible people can be selected and approached for trial participation and a platform in which multiple interventions can be tested simultaneously (efficient use of control patients,

improved comparison between different interventions), and contamination between study arms is minimised.

PROGnosis REsearch Strategy

The PROGnosis REsearch Strategy^[33] series developed by an interdisciplinary team of conventional researchers is a framework of four interlinked prognosis research themes which provides examples from several disease fields to show why evidence from prognosis research is crucial. Prognostic factor research aims to identify factors associated with subsequent clinical outcome in people with a particular disease or health condition. In Homoeopathy, this can prove to be very significant, as it assesses the prognostic relationship between symptoms and personal characteristics and outcome of treatment.^[34]

N-of-1

N-of-1^[35] or single-subject clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side effect profiles of different interventions.^[36] The ultimate goal of an n-of-1 trial is to determine the optimal or best intervention for an individual patient using objective data-driven criteria. Thus, this design will provide new possibilities in Homoeopathy, where individual treatment effects are to be investigated.^[36] Such trials can leverage study design and statistical techniques associated with standard population-based clinical trials, including randomisation, washout and crossover periods, as well as placebo controls.

OBSERVATIONAL STUDIES

Evidence generated from the observational studies must be utilised as they have shown the benefits patient got after receiving homoeopathic treatment. Observational studies are often used when there are methodological limitations in conducting RCTs, or address issues which are not addressable by RCTs. Other strength areas are when multiple outcomes are to be examined (cohort), single disease of interest (case-control), etc. An observational study to assess the effect on quality of life in chronic urticaria is discussed in this issue.^[37] Further, we publish another prospective, single arm, pre-post comparison, nonrandomised, open-label, observational trial on individuals of 5–18 years of age presenting with nocturnal enuresis showing potential benefit of homeopathic treatment.

In this issue, we publish a RCT to assess the effectiveness of Homoeopathic Constitutional remedy and Homoeopathic Constitutional + Organ remedy in comparison to Placebo (PL) in cases of benign prostatic hyperplasia.^[38] The study found the effectiveness of Homoeopathy compared to PL; however, a pragmatic long follow-up study to assess the objectives has been recommended. Another randomised trial in the issue, done on patients with gingivitis, that showed significant effect of homoeopathic medicine *Plantago* compared to the PL group is shared with readers.^[39]

Two reviews are included in this issue; one is literature review of role of Homeopathy in the treatment of cancer. The author reported various studies that show the effect of homeopathic treatment in the management of cancer pain, as supportive or palliative treatment, after radiotherapy, chemotherapy, etc. Furthermore, studies showing the proposed mechanism of action of homeopathic medicines through immunomodulation are included in the review.^[40] The other review is compilation of results of experimental pharmacological findings of homeopathic medicines, both *in vitro* and in animal models.^[41] These reviews can be used for undertaking further studies in these areas. We are also publishing physicochemical data of the drug, *Blatta orientalis* with the readers which can be used as standard for authentication, quality assurance and quality control process of the commercially available drug. Diabetic foot is the most crippling complication of diabetes mellitus; its management is challenging to physicians and costly to patients with an increased risk of amputation. A case of diabetic foot ulcer is discussed in the issue, where homeopathic medicine improved the patient.^[42] A book dealing with the art of prescribing 'Politics of Prescribing' by Dr. L. M. Khan is reviewed in the issue.^[43]

Recently, we lost a friend, a mentor, Dr. Peter Fisher, President of the Faculty of Homeopathy, Director of Research at the Royal London Hospital for Integrated Medicine (RLHIM) and Editor-in-chief of the journal '*Homeopathy*'. He has been a guiding force in developing quality homeopathic publications. We pay homage to homeopathic legend in the Obituary note.^[44]

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