Review Article

Qualitative systematic review of homeopathic outcome studies in patients with HIV/AIDS

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ABSTRACT

Background and aims: Systematic reviews of high-quality randomized controlled trials (RCTs) are crucial in evidence-based medicine (EBM). The aim of the present review was to investigate whether there is enough evidence on the efficacy of homeopathy in individuals with HIV/AIDS based on clinical trials. **Methods**: The present is a criteria-based systematic review of cumulative research, and assessment of the methodological quality of published studies. The quality of the trials was evaluated using a list of validated and predefined criteria, and their outcomes were interpreted based on their quality. The main outcome measure was the methodological quality of the studies in terms of the threats to external, internal, construct, and statistical conclusion validity. **Results**: Among the 6 clinical outcome studies located, 3 were open-label, non-randomized, non-controlled trials, 2 were RCTs, and one was a single-set replication study. The trials were too few in number, and did not exhibit very high quality. The results showed a positive trend regardless of the quality of the trials, or the variety of homeopathic treatment used. The results of the present review may be complicated by publication bias. **Conclusion**: The currently available evidences do not suffice to infer definitive conclusions. Therefore, further evaluation of homeopathic treatment by means of appropriate RCTs with high methodological quality is required.

Keywords: Homeopathy, HIV/AIDS, clinical trials, literature review

Introduction

A systematic review is a survey of the literature focused on a research question to identify, appraise, select, and synthesize all the high-quality evidences relevant to that question. Systematic reviews of high-quality randomized controlled trials (RCTs) are crucial in evidence-based medicine (EBM) [1]. An understanding of systematic reviews and how to implement them in practice is becoming mandatory for all healthcare professionals. In addition to health interventions, systematic reviews may assess clinical tests, public health interventions, social interventions, adverse effects, and economic evaluations [2,3]. Systematic reviews often, but not always, use statistical techniques (meta-analysis) to combine the results of the eligible studies, or at least score the levels of evidence based on the methodology used. Systematic reviews apply objective and transparent approaches to the analysis of studies to minimize bias. While many systematic reviews are based on an explicit quantitative meta-analysis of the available data, qualitative reviews adhere to standards for gathering, analyzing, and reporting evidence [4].

Formulated originally by Samuel Hahnemann, homeopathy is a system of medicine based on the principle of therapeutic similarity ("similia similibus curantur"), according to which, agents that induce in healthy individuals complaints resembling the ones in patients can cure the latter. Nevertheless, the claims made for the clinical efficacy of homeopathy are controversial, due to its use of drugs in high dilutions (HD). HD above 24x/12cH are traditionally considered very unlikely to contain one single molecule of the starting substance [5], whereas according to homeopathic theory, higher dilutions exert stronger effects compared to the lower ones, allegedly as a function of the 'biological activity' they exhibit following dilution and agitation beyond Avogadro's number [6]. In the selection of the most similar medication, unusual symptoms that do not fit with the syndromes recognized by conventional medicine may eventually be more important than the regular ones. This is why homeopathy is a highly individualized therapy, and different medications are prescribed to patients who would receive identical treatment in conventional medicine [5].

Few therapies have attracted more debate and controversy than homeopathy [7]. Proponents have quoted seemingly rigorous trials that suggest efficacy, while critics have little trouble in citing equally rigorous studies that imply the opposite. Although one approach to overcome such contradictions is to conduct systematic reviews and meta-analyses [7], following their superb meta-analysis from1997, Linde *et al* commented that no single clinical condition was identified in which homeopathy was clearly superior to placebo [7-10].

Aims

The aim of this review was to investigate whether there is enough evidence on the efficacy of homeopathy in patients with HIV/AIDS based on RCTs.

Materials and methods

A survey of the literature was performed in the following databases: National Library of Medicine (Medline/ via PubMed), The Cochrane Library, Centralized Information Service for Complementary Medicine (CISCOM), British Homeopathic Library (Hom-Inform), Central Council for Research in Homeopathy (CCRH), India and cross-referencing between published papers. The search terms used were "homeopath…","homeopath… clinical trials on HIV/AIDS", "HIV and homeopathy", "AIDS and homeopathy", "meta-analysis in homeopathy", "systematic review in homeopathy", etc. Articles published from January 1990 to August 2012 were searched for. Only the bibliography of full articles published in peer-reviewed journals was scanned for further relevant references. Systematic reviews (with or without meta-analysis) of both controlled and non-controlled trials and clinical outcome studies on homeopathy involving patients with HIV/AIDS were included. All the articles were evaluated by the authors. All forms of homeopathic interventions were included, from classical single-remedy homeopathy to 'same formula in all patients' [11].

For inclusion in the present study, the articles had to meet the following criteria: (1) be written in English; (2) use a homeopathic intervention for a HIV/AIDS-related clinical condition; (3) assess the intervention outcomes using an empirical measure of some type; (4) be prospective; and (5) have sufficient information for scoring in a scale of threats to validity.

Each article was reviewed using established and previously validated criteria for judging threats to the characteristics and quality of empirical research. We also investigated whether the primary outcome was improved, unchanged, or made worse by homeopathic treatment. The reliability and accuracy of the present review were checked by another author (MM) neutral in regard to homeopathy. All the criteria were scored based on whether the high-quality items were present and adequate, or missing or inadequately met. Finally, we considered the number and percentage of the threats to external, internal, construct, and statistical conclusion validity in all the included studies [11-15] (Table 1).

Table 1: Scale to measure threats to validity

	A. Threats toexternal validity	**3**	**2**	**1**	**0**
1	Sample size weightage points	≥100	50-99	25-49	<25
		1		***0***	
2	Characteristics of patients	Adequately described		Inadequately described	
3	Matching	Performed		Not performed	
4	Intervention	Completely described		Incompletely described	
5	Interaction with other forms of therapy	No interaction; no reporting bias		Interaction might be present; chances of reporting bias	
6	Interaction of testing and treatment	No		Yes	
7	Generalizability	Adequate measurements		Restricted approach to measurements	
8	Sampling bias	Absent		Might be present	
9	Interaction of setting and treatment	Evidence present		No evidence	
10	Interaction of history and treatment	No interaction		Chances of interaction	

	B. Threats to internal validity	**1**	**0**
1	Randomization	Correct	Pseudo or no randomization
2	Blinding	Double blinding	Single or no blinding
3	Study setting	Multicenter	Monocentric
4	Replication studies	Present	Absent
5	Attrition rate	Properly reported	Not properly reported
6	History	Sequentially correct	Not correct
7	Maturation	Performed	Not performed
8	Testing	Sensitive measures tested	Measures are not known to be sensitive
9	Instrumentation	Use of properly calibrated instruments	Poorly or non-calibrated instruments
10	Statistical regression	No	Yes
11	Mortality	<30%	>30%
12	Interaction with selection	No	Yes
13	Ambiguity of cause	No	Yes
14	Diffusion of treatment	No chance	Chances
15	Compensatory equalization	No	Yes
16	Compensatory rivalry	No	Yes
17	Resentful demoralization	No	Yes

C.	Threats to construct validity	1	0
1	Inadequate explication	No	Yes
2	Mono-operation bias	Absent	Present
3	Mono-method bias	No	Yes
4	Hypothesis guessing	Not applicable	Chances
5	Evaluation apprehension	Not probable	Chances
6	Experimenter bias	Absent	May occur
7	Confounding constructs	Range restriction present	Absent

D.	Threats to statistical conclusion validity	1	0
1	Low statistical power	High power of statistical test	Low power
2	Violated assumption	Not applicable	May occur
3	Fishing/error rate	Performed	Not performed
4	Reliability of measures	Not applicable	May be present
5	Reliability of treatment	No	Yes
6	Random irrelevancies	No	Yes
7	Representative of random heterogeneity	Effort is evident as regards heterogeneity of sample	Effort is not evident
8	Data presentation	Amenable to review	Not amenable
9	Effect measurement	Yes	No

Various methodological criteria to assess the threats to validity were considered in the scale:

1. Threats to external validity (maximum score = 12): included sample size weightage point (≥100: 3, 50-99: 2, 25-49: 1 and <25: 0), description of the patients' characteristics (symptoms, duration, severity, etc.), matching of comparable baseline characteristics and potential variables, description of intervention (dose, duration, method of manufacture, etc.), interaction with other forms of therapy, interaction of testing and treatment (evidence that testing might be related with treatment so that the subjects test different after treatment), generalizability (due to limited measurement approach), sampling bias, interaction of setting and treatment (evidence(s) suggesting that treatment works in all settings), and interaction of history and treatment (evidence that the length of the study might have an impact on the findings).

2. Threats to internal validity (maximum score = 17): included randomization, blinding, study setting, replication studies, reporting of attrition rate (withdrawal and drop-outs), history (repeated measurements without temporal control), maturation (repeated measurements without temporal control on developmentally sensitive outcomes), testing (measurements that are sensitive to the testing process), instrumentation, statistical regression (study of cases selected from extremes without control group), mortality (more than 30% of the sample not completing the study – migration out, refusal, non-compliance, etc.), interaction with selection (evidence that allocation to groups might interact with history, maturation, or testing), ambiguity of cause (an association that might be interpreted in either direction vis-à-vis cause and effect), diffusion of treatment (contact between

experimental and control subjects), compensatory equalization (evidence that the groups have knowledge on the design and might equal things out), compensatory rivalry (evidence that groups have knowledge on the design and might compete with other group members), and resentful demoralization (evidence that one group feels disadvantaged by the allocation process).

3. Threats to construct validity (maximum score = 7): included inadequate explication (evidence that the choice of measurement operations does not represent the construct), mono-method bias (use of only one approach in measurements, e.g. self-report for main outcome), hypothesis guessing (evidence that the subjects might attempt at guessing what the results should be, i.e. absence of appropriate blinding), evaluation apprehension (evidence that the subjects might become anxious during assessments), experimenter bias (absence of controls to keep interested parties from participating in the measurements), and confounding constructs (range restriction in measurement with levels of constructs).

4. Threats to statistical conclusion validity (maximum score = 9): included low statistical power (any group <10 or correlations with fewer than 30 pairs), violated assumption (evidence of non-normal distributions with parametric statistics), fishing/error rate (more than 10 statistical tests without Bonferroni's similar correction), reliability of measures (failure to test, note, or reference information on measures), reliability of treatment (failure to test or note consistently the application of treatments), random irrelevancies (absence of effort to make measurements reasonably consistent), representative of random heterogeneity (absence of effort to ensure that the sample is reasonably heterogeneous), data presentation (data presented in such a manner that analysis might be checked by readers), and effect measurement (sensible, relevant, adequate, reproducible).

Two main outcomes were investigated in the RCTs: 'null hypothesis rejected' and 'null hypothesis not rejected'. The findings of studies in category 'null hypothesis rejected' were classified as 'positive' (i.e. for homeopathy) or 'negative' (i.e. against homeopathy) based on a two-tailed test. Positive trial was one where at least one outcome measure was significantly improved by homeopathy compared to placebo or alternative treatment ($p < 0.05$). Negative study was one where at least one outcome measure was significantly inferior compared to placebo or alternative treatment ($p < 0.05$). 'Null hypothesis not rejected' was the conclusion of studies where no significant intergroup difference in the outcome/s was evident ($p > 0.05$).

Results

A total of five clinical trials, 3 non-controlled, and 2 controlled, a single-set replication study, and one review article [16] evaluating the effects of homeopathic interventions in patients with HIV/AIDS were located. All the studies were published in peer-reviewed journals. Most studies (n=3, 60%) were government funded, and the others (20%) were technically assisted by private foundations.

Both controlled studies reported the age and gender of participants, but none their race or ethnicity. Only one randomized trial was replicated once in 8 different cities of the United States over 8-16 weeks [17]. In all the studies the sample was less than 100.

All the studies were prospective. From the 2 controlled trials, one used placebo [18], and the other used 2 active controls (natural and conventional antiviral therapy) [17]. Both studies used matched control groups. None of these studies described the sampling frame used; however, they considered potentially confounding variables in their design. The threats to validity of these trials are described tables 2 and 3.

Table 2: Scoring of the methodological quality of the trials

Trials (in chronological order)		Consideration of threats to validity					
		External validity (max=12)	Internal validity (max=17)	Construct validity (max=7)	Statistical conclusion validity (max=9)	Total score (max=45)	Score %
1	Bissuel *et al*, 1995	5	13	5	7	30	66.67
2	Rastogi *et al*, 1999	7	14	7	8	36	80
3	Danninger *et al*, 2000	6	9	5	7	27	60
4	Brewitt *et al*, 2000	7	14	5	6	32	71.11
5	Brewitt *et al*, 2002	9	15	6	8	38	84.44

Table 3: Characteristics and results of trials

Trials & Investigators		Methodology score %	Indication	Intervention	Results
Non-controlled trials	Bissuel *et al*, 1995	66.7	Desensitization of hypersensitivity to prophylactic trimethoprim-sulphamethoxazole (TMP-SMX) therapy in HIV-infected patients	TMP-SMX 9 or 15 cH	positive
	Danninger *et al*, 2000	60.0	Decrease of circulating immune complexes (CIC) in healthy research subjectsand HIV-positive patients, with significant increase of CD4 lymphocytes, CD4/CD8 ratio and improvement of HIV-related symptoms	Lysate of *Staphylococcus aureus* strain Cowan I 12cH	positive
	Brewitt *et al*, 2000	71.1	Physical, immunologic, neurologic, metabolic, and quality-of-life benefits from homeopathic growth factors in patients with HIV/AIDS	Combination of IGF-1, PDGF-BB, TGF β1, and GM-CSF 30cH, 200cH, and/or 1000cH	positive
Randomized controlled trials	Rastogi *et al*, 1999	80.0	Holistic approach to patients with HIV/AIDS anddecreased CD4 and/or CD8 count	Single individualized homeopathic remedy	positive
	Brewitt *et al*, 2002	84.4	Physical, immunologic, neurologic, metabolic, and quality-of-life benefits from homeopathic growth factors in patients with HIV/AIDS	Combination of IGF-1, PDGF-BB, TGF β1, and GM-CSF 30cH, 200cH, and/or 1000cH	positive

Most of the studies reported on the reliability of measures, but failed to report the response rates, i.e. the number of patients screened compared to the number who entered the study. One single study reported the attrition rate.

All the studies reported statistically significant improvement as a result of treatment. However, the probability of positive outcomes was significantly lower when random allocation was performed compared to lack of randomization (χ^2=7.71, p=0.0055).

Significant threats to validity occurred in all the analyzed studies [19 – 21], especially in regard to the external validity, as all the studies had small samples, and none was multicenter, nor replicated. Therefore, the results are difficult to generalize beyond the study sample. Surprisingly, the scores of internal, construct, and statistical conclusion validity were not very low, indicating that homeopathic research is not appreciably inferior in regard to control of bias and systematic error.

Discussion

In trials with limited numbers of participants, there is no guarantee that randomization will divide the known and unknown confounders equally among the experimental and control groups. In addition, publication bias may be less likely in studies with large numbers of participants [6]. Other major criteria of methodological soundness are randomization and double-blindness. When prognostic factors of the illness other than the intervention under study are insufficiently known, random allocation to the contrasted treatments is useful to ensure comparable prognoses. Double-blindness is important to keep the intervention exactly the same in the contrasted groups except for the homeopathic treatment, and to ensure unbiased assessment of the effects. This is especially important in regard to the relief of subjective symptoms, as it is often the case in homeopathic treatments [6].

The overall quality of the homeopathic trials was unsatisfactory. Homeopathic clinical research is clearly in its childhood, as most studies use poor sampling and measurement techniques, few subjects, single sites, virtually no replication, and practically no overlap in the investigated conditions. Many of these problems might be corrected, even in the case of a so-called 'holistic' paradigm given sufficient research expertise, support and method. To build credibility within the medical research community, multiple replications and/or extensions using the same or similar approaches to the treatment of same or similar medical conditions are necessary. Multisite research with larger sample sizes is essential to improve the confidence level and generalizability of the findings [11].

The comprehensive clinical interviews and long-term follow up commonly included in the homeopathic management of cases increase the patient-doctor interaction, and are likely to enhance expectancy and placebo effects. These factors might hinder the detection and isolation of the effects induced by homeopathic drugs when they occur. Combined with the small sample sizes, these factors might falsely increase the report of negative studies. Therefore, the effect of the homeopathic clinical procedures should be studied separately from the investigation of the eventual specific (non-placebo) effects of homeopathic drugs. The former should be assessed in pragmatic randomized trials comparing homeopathic to standard treatment, and the latter by means of simple laboratory or clinical models easy to repeat by independent investigators [11].

The lack of appropriate frameworks to conduct large trials with homeopathic drugs is one, but not the only challenge posed to high-quality research. Critical systematic reviews of studies are able to identify the areas those need to be improved. Quality guidelines for research in homeopathy have already been published. More

critical peer-review of homeopathic studies complying with those and other guidelines might improve the quality of research. The methodological pitfalls of homeopathic trials ought to be carefully addressed by investigators if the quality, credibility, and usefulness of research in homeopathy are to improve [11].

Due to problems with the external validity, the results of the analyzed studies are not likely to be generalizable beyond the study population. However, the scores of internal validity quality were not always appreciably worse compared to conventional therapy [11].

More rigorous trials in homeopathy are associated with smaller effect sizes compared to non-randomized, non-controlled trials. The overall effect becomes even more insignificant when possible publication bias is also taken into account, or only high-quality trials are included in reviews or analyses [7-10, 22].

Key issues that must be addressed in future homeopathic studies include the research question posed, its associated trial design, and the outcome measures chosen. Non-placebo-controlled designs may adopt measures of 'quality of life'. Placebo-controlled trials should take acute medical conditions into consideration (as opposed to chronic conditions, where the selection of treatment according to various homeopathic schools is based on the patients so-called 'constitutional' character), where prescribing might be relatively simpler due to the narrower range of indicated remedies, and the effects quickly and more accurately ascertained. Testing the effects of homeopathy as adjuvant to conventional medication is also another option currently being considered by investigators. Equivalence trials offer another promising way forward [23, 24].

Conclusion

The hypothesis that any homeopathic remedy induces clinical effects in patients with HIV/AIDS significantly different from placebo, or superior to other control interventions is not adequately supported by systematic reviews. There is a dearth of high-quality studies supporting their effectiveness and safety. Until more compelling results are available, homeopathy cannot be viewed as an evidence-based form of therapy in HIV/AIDS. However, homeopathic outcome studies may represent respectable endeavors to clarify the effects of homeopathic care by producing quantifiable, reproducible and/or constructive data, provided research is performed more rigorously and systematically than up to the present time.

New trials of homeopathic medicines against placebo are no longer considered a research priority [25]. The question whether ultra-molecular dilutions might exhibit any measurable physical/biological effect based on electromagnetic waves [26] or 'conglomerates'/'aggregates' of nanoparticles retaining encrypted information of the starting substance in the interfacial water [27-30] is best tackled by means of advanced materials science concepts and complex experimental tools. However, there is still a role for pragmatic trials comparing the effect and cost effectiveness of orthodox and homeopathic treatments [25].

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Revisão sistemática qualitativa de estudos de desfecho do tratamento homeopático em pacientes com HIV/AIDS

RESUMO

As revisões sistemáticas de estudos randomizados controlados (RCTs) são essenciais na medicina baseada em evidências (MBE). O objetivo deste estudo foi estabelecer se há evidência suficiente a favor da eficácia da homeopatia em pacientes com HIV/AIDS a partir de ensaios clínicos. Trata-se de uma revisão sistemática da pesquisa acumulada baseada em critérios, com avaliação da qualidade metodológica dos estudos publicados. A qualidade dos estudos foi avaliada mediante uma lista de critérios validados e predefinidos e os resultados foram interpretados a partir de sua qualidade. O desfecho principal analisado foi a qualidade metodológica dos estudos nos termos das ameaças a sua validade externa, interna, de construto e conclusão estatística. Dos 6 estudos clínicos informando resultados que foram localizados, 3 eram ensaios abertos, não randomizados e não controlados, 2 eram RCTs e um era um estudo de replicação com um único grupo. O número de ensaios clínicos localizados foi muito pequeno e de qualidade não muito alta. Os resultados apontaram uma tendência positiva independentemente da qualidade dos ensaios e do tipo de tratamento homeopático utilizado. Os resultados desta revisão podem sofrer de viés de publicação. As evidências disponíveis atualmente são insuficientes para conclusões definitivas. Portanto, o tratamento homeopático ainda precisa de maior avaliação, através de RCTs adequados e de alta qualidade metodológica.

Palavras-chave: Homeopatia, HIV/AIDS, ensaios clínicos, revisão da literatura

Revisión sistemática cualitativa de estudios de resultado del tratamiento homeopático en pacientes con VIH/SIDA

RESUMEN

Las revisiones sistemáticas de estudios controlados aleatorizados (ECC) son esenciales en la medicina basada en evidencia (MBE). El objetivo de este estudio fue evaluar si hay evidencia suficiente a favor de la eficacia de la homeopatía en pacientes con VIH/SIDA a partir de ensayos clínicos. Se trata de una revisión sistemática basada en criterios de la investigación acumulada, con evaluación de la calidad metodológica de los estudios publicados. La calidad de los estudios fue evaluada mediante una lista de criterios validados y predefinidos y los resultados fueron interpretados a partir de su calidad. El principal resultado medido fue la calidad metodológica de los estudios expresa como amenazas a su validez externa, interna, de constructo y conclusión estadística. De los 6 estudios clínicos de resultados localizados, 3 eran ensayos abiertos, no aleatorizados y no controlados, 2 eran ECC y uno un estudio de replicación con un único grupo. El número de estudios clínicos localizados fue muy bajo y su calidad no muy alta. Los resultados indican una tendencia positiva independiente de la calidad de los estudios y el tipo de tratamiento homeopático efectuado. Los resultados de esta revisión pueden adolecer de sesgo de publicación. La evidencia actualmente disponible no permite inferir conclusiones definitivas. El tratamiento homeopático necesita mayor evaluación mediante ECC adecuados y de alta calidad metodológica.

Palabras clave: Homeopatía, VIH/SIDA, estudios clínicos, revisión de la literatura

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