Homeopathic Trial Design in Influenza Treatment

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***This paper is currently submitted to and under review at the journal *Homeopathy*, document #HOMP-S-09-00036. The pre-publication version is for private use only, please do not cite or distribute until a published version is available.**

Abstract: This review presents a critical evaluation of methodological quality in controlled trials on homeopathic treatment of influenza. First, a short summary on the prevalence, quality, and most commonly cited shortcomings of homeopathic controlled trials in general is presented to support the more specific points within influenza trials alone. To this end, three areas of the homeopathic literature are examined; large meta-analyses looking at study quality and results across research areas, reviews on research within specific diagnostic categories, and the available reviews and primary studies on influenza treatment trials. The specific methodological designs of homeopathic influenza treatment trials are then compared, on a point by point basis, to pharmaceutical trials on influenza antiviral drugs. The goal of the evaluation is to highlight frequently cited problems in homeopathic trial design, suggest possible improvement for future studies, and make specific recommendations for homeopathic influenza trials based on a comparison to standardized antiviral trials.

Keywords: Influenza, Homeopathic Controlled Trials, Randomized Controlled Trials, Homeopathy, Study Quality, Design Methodology

Introduction

This review represents a continuation and follow-up to the previous review, by the authors, on randomized controlled trial (RCT) design in influenza studies[1]. In that paper, a subset of modern conventional antiviral studies on influenza treatment were analyzed for consistent study design elements, which were then presented as a model for improvement in future CAM trials examining influenza treatment. This review continues the discussion, moving into the subset of CAM influenza trials on homeopathic treatment, targeted specifically for three reasons. First, there are a number of available controlled trials in the homeopathic treatment of influenza, and though small, there are few more frequently studied specific areas of disease (See below). Second, there exists a consistent and well-accepted design standard within parallel trials of treatment by conventional antiviral medications, providing a good basis for offering improvements in homeopathic study design. Finally, the evidence from placebo-controlled homeopathic treatment of influenza available thus far points to a statistically significant, but small-sized positive effect compared to placebo[2], suggesting the need for further, well-designed studies.

Scope of the Review

The latest systematic review on homeopathic controlled trials by Shang[3] included 108 RCTs, of which 21 (19%) pertained roughly to upper respiratory tract infections (URTIs). This represents the greatest proportion of studies in a specific area of disease. Similarly, a 2003 review by Mathie[4] identified URTIs as the most represented disease area of homeopathic study, although no specific diagnosis within the general area (such as influenza, otitis media, common cold, etc.) had more than two or three RCTs. A search of PubMed through March 2008, for all English-language RCT and clinical trial articles and with the text word "homeopath*" revealed 198 results. After manually searching these, 9 were found to be RCTs targeting URTI treatment in general, of which 2 were on influenza, 4 on general URTIs, 1 on sinusitis, and 2 on acute otitis media[5-13]. Although there are more English-language studies on general URTI, influenza was targeted because of the greater consistency, more well-defined disease scope, and increased justification for further study based on repeated, positive findings. URTI study design is deserving of further attention, but has been reviewed in part by other authors[3, 4, 14, 15]. Another aspect of homeopathic trials outside the scope of this review is discussion of RCT findings in efficacy (See meta-analyses by Kleijenen[16], Linde[17], and Shang[3]), and how trial design and methodological quality relates to that issue (See review by Ludtke[18]).

Methods

In order to identify reviews and meta-analyses on homeopathic controlled trials, a literature search was completed on PubMed, limited to English-language reviews and meta-analyses, for all dates through January, 2009, using the search term "homeopath*" in all text fields. The search returned 404 results which were manually searched to identify reviews targeting design quality and results of homeopathic controlled trials in general[3, 4, 16-27]. Reviews that targeted controlled trials within disease-specific areas, and reviews that were not specifically targeting *controlled* trials, were not included. This summary review is not intended to be a systematic review of the literature, but rather to identify methodological design issues commonly cited in reviews on homeopathic trial quality and methods.

Results

Summary Review on Homeopathic Controlled Trials

The most recent systematic review of placebo controlled trials of homeopathy identified 110 reports that met the reviewers' quality criteria, eliminating 60 trials where there was insufficient information, ineligible study design,

repetition of publication, or no match in conventional medical trials on the condition addressed[3]. In another recent systematic review of homeopathic randomized controlled trials (RCTs) by Mathie[4], 93 original articles on either placebo-controlled (79 trials) or controlled comparative (14 trials) trials are reported and examined. These investigations cover 35 different specific medical conditions, some covered by only one study. All the available reviews on homeopathic controlled trials conclude that much improvement is needed in the quality of these studies, despite the fact that the several in which homeopathic controlled trials were compared to conventional drug trials showed a trend towards higher quality rating in the homeopathic trials[3, 17]. In the review by Shang[3], only 19% of included homeopathic trials were rated as being "higher quality" studies (vs. 8% of reviewed conventional trials). Overall, the availability of randomized controlled trials in homeopathy that are of satisfactory quality has increased slowly over the years. In four large reviews from the last 11 years, the pool of included trials making cut-off based on internal or pre-existing quality criteria has shown a slow but increasing size, from 59-89 in reviews looking at studies up to 1995-7, to 110 in a review looking at studies through 2005[3, 17, 25]. The general picture is one of a low volume of studies which also lack replication over time and among a diversity of sites[24]. This may be due in part to insufficient infrastructure and budget to run these studies, as Linde[17] suggests, but failure to meet standards of methodological design is a ubiquitous issue, and an aspect most easily addressed in future studies.

One of the most frequently cited problems is poor, insufficient, or incomprehensible reporting of study design methodology. Multiple reviews note areas where over 80% of trial reports failed to clearly or sufficiently describe either the randomization process chosen, the funding sources, or the selection process for participant samples[16, 25]. Potential bias in the studies was also a concern noted in many of the meta-analyses, due in large part to the poor reporting of methods. These biases will continue to be assumed unless more transparent reporting of design and results of studies is made a primary goal.

The most frequently cited problem within the study design itself is very clearly the lack of well-defined, appropriate, and objective outcome measures[3, 4, 16, 17, 19, 20, 22, 25, 27]. Among the reviews, the range of studies reported to have either poorly described, insensible, crude, descriptive only, poorly chosen, subjective or otherwise unsuitable outcome measures was anywhere from 27-50%. As noted in Merrell[20], the majority of the studies reviewed having a positive findings utilized outcome measures that were subjective and difficult to quantify. A related problem was poor definition of the clinical condition being studied, affecting appropriate inclusion of patients into the study and analysis of results[17]. Objective, well-defined, and acceptable measures for clinical definition, inclusion, analysis, and outcome measures is an important area needing improvement in homeopathy RCTs.

Other noted issues mentioned often among reviews are the small sample sizes used in homeopathic trials and inadequate concealment of allocation found in over half of reviewed trials[3, 16]. Overall, the methodological and reporting problems in homeopathic controlled trials are well recognized, agreed upon, and for the most part easily addressable in future studies. Issues on methodological design are followed up on in the next sections of this paper, which look specifically at the design of homeopathic influenza treatment trials, and comparison to consistent design elements in conventional influenza antiviral trials.

Quality and design of controlled trials in homeopathic influenza treatment

One clinical area of study that has been frequently assessed in review articles covering homeopathy is the prevention and treatment of influenza[2, 4, 14, 17, 28]. Influenza is a particularly relevant topic of discussion in the current research on complementary and alternative medicine (CAM), as can be seen in recent reviews[14]. As concluded by Vickers [2] the current evidence points to a positive effect of the remedy *Oscillococcinum* in influenza treatment, though the results only point to a 0.28 day reduction in length of illness, a number which, if accurate, will require much larger studies to confirm. However, there are methodological issues even with the positive studies that, if improved upon, might clarify the data regarding homeopathy and influenza.

The updated meta-analysis by Vickers[2] reviews four RCTs[11, 29-31] examining efficacy of the homeopathic remedy Oscillococcinum in treating influenza. The other reviews that cover influenza treatment either refer to this study, or analyze some subset of the same four RCTs included. A search of PubMed and the Cochrane Central Register of Controlled Trials through February 2009 reveals no further published trials on homeopathic influenza controlled trials in English (search: homeopath* AND influenza). The reviews are in agreement as to the quality of the studies, and the possible issues and biases inherent to them. In general, the two studies by Cassanova et al.[30, 31] are similar and can be looked at as a group, as can the studies by Ferley et al.[11] and Papp et al.[29], in which the second is specifically designed to mirror and reconfirm the first. For the various criteria examined by Vickers et al.[2], which were graded A, B, or C indicating a low, medium, and high risk of bias, the two studies by Cassanova et al. received all B ratings, while the studies by Ferley et al. and Papp et al. received all A ratings. Table 1 presents the individual categories and scores for the rating of quality assessment of these four RCTs as presented in three reviews[2, 14, 17]. The following sections present more specific comments on both the positive and negative attributes of these RCTs.

TABLE 1: **Quality Assessment Scores in Homeopathic Influenza RCTs**

	Specific Criteria	*Cassanova 1984*	*Cassanova 1992*	*Ferley 1989*	*Papp 1998*
Jadad score (Guo[14], Linde[17])*		2	2	3	5
Internal-validity score (Linde[17])**		Not rated	57	79	Not rated
8 Criteria* (Guo[14])**	Randomization performed using adequate method?	D	D	D	Y
	Treatment allocation concealed?	D	D	Y	Y
	Groups similar at baseline regarding important prognostic indicators?	Y	Y	Y	Y
	Patient blinded?	Y	D	Y	Y
	Care provider blinded?	Y	D	Y	Y
	Withdrawal/dropout rate unlikely to cause bias?	D	D	D	Y
	Outcome assessor blinded?	D	D	Y	Y
	Predefined primary outcome measure and result reported?	N	N	Y	Y
5 Criteria** (Vickers[2])**	Treatment allocation rating	B	B	A	A
	Performance bias rating	B	B	A	A
	Observer blinding rating	B	B	A	A
	Exclusions/withdrawals rating	B	B	A	A
	Allocation concealment rating	B	B	A	A

*A score based on methodological quality criteria developed by Jadad[33]. Scores is out of 5.
**An internal validity score developed by the authors based on 7 quality criteria. Score is out of 100.
***Y = Yes, N = No, D = Do not know
****A = Low risk of bias, B = Possible bias or partially met, C = High risk of bias

Cassanova et al. 1984[31] and Cassanova et al. 1992[30]

The two trials by Cassanova et al. generally received more criticism and have more omissions of important information as compared to the studies by Ferley et al. and Papp et al. The 1992 study by Cassanova et al. is unpublished, and the other Cassanova et al. study was only reported in a general medical periodical rather than a peer-reviewed scientific journal. As a result, there is scanty information available on both. One criticism made in both Guo[14] and Vickers[2] is that, though the two trials had basically the same design, it appears that the 1992 trial eliminated 2 of the 5 symptoms that had been examined as outcome measures in the 1984 study[31], raising

questions of selective reporting biasing more positive outcome measures. The 1984 study reported data for patient assessment of temperature, chills, aches, rhinitis, night cough, and day-time cough; the 1992 study only reported temperature, chills, and aches. Furthermore, the length of the follow up varied between the two studies, with the first reporting data for day 8 and the second for day 4, which may have been a more favorable comparison. Also, there are no details about which participants were excluded, or on numbers of or reasons for withdrawals in either of the trials. Vickers et al.[2] conclude that outcome measures based on individual symptoms are more likely to be biased, and that a more appropriate outcome measure to ensure unbiased study results would be based on the presence or absence of clinically identifiable influenza, or possibly the use of concomitant medications.

Ferley et al. 1989[11] and Papp et al. 1998[29]

Unlike the two Cassanova et al. studies, these RCTs did report outcomes that depended on the presence or absence of clinically determined influenza-like syndrome, although neither of these studies identified the true influenza population through laboratory testing. The pre-specified main outcome measure that both studies used was comparing the number of participants with 'recovery after 48 hours' (no fever, no key influenza symptoms) in homeopathic treatment versus placebo. These studies also reported patient assessment of treatment success, and the use of concomitant medications. Participants were required to meet a pre-defined standard for influenza-like syndrome based on temperature and the presence of certain key symptoms, and there were clear exclusion criteria outlined, including presenting after 24 hours since influenza onset, immune deficiency, influenza vaccination, and certain medication uses. These studies were generally rated as being well reported, with sufficient data presented, as compared to the two Cassanova et al. studies which were poorly reported[2].

In general, these four influenza treatment trials as a group are rated as moderate in methodological bias, but meeting basic criteria of good studies such as being multi-centered and using blinded medication[2]. Vickers[2] also concludes that there was insufficient data to determine the effect of *Oscillococcinum* on concomitant medication use, or on vulnerable sub-groups such as the elderly. They conclude that confirmatory trials of *Oscillococcinum* as treatment are warranted, but will require a very large sample size. Based on the quarter day difference found between control and treatment in the better studies by Papp et al.[29] and Ferley et al.[11], and with the power set at 90%, the required sample size quoted is 2000 participants. A similar or larger sample size would be needed to confirm other outcomes as well, such as days to return to work[2]. Other than conducting larger studies, they also suggest planning further sub-group analyses to look at specific populations within the study.

Discussion

Comparison of Homeopathic Influenza Trials to Conventional Antiviral Trials

Another way to examine potential areas for improvement in homeopathy studies of influenza treatment is to compare the trials that have been performed to the established standards in the study of conventional treatments of influenza, specifically the antiviral treatments such as neuraminidase inhibitors. Standard design elements for these trials have been explored and summarized in a previous paper by the authors[1]. An item by item comparison of relatively standardized design elements most commonly seen in conventional influenza antiviral studies versus the study design of the four homeopathy RCTs reviewed in this section is presented in Tables 2 and 3. Comparison is made to the design aspects of conventional antiviral trials that are most consistent in terms of quality and acceptability as cited by reviewers. However, design elements that are poorly rated in a majority of cases, such as allocation concealment or reporting, are not looked at in this study[1].

TABLE 2: **Homeopathic versus Conventional RCT Design in Influenza (Cassanova 1984, 1992)**

	Design Criteria	*Cassanova 1984*	*Cassanova 1992*	*Conventional Antiviral Standards**
Demo-graphics	Study size	100	300	350 - 650
	Study length	NR	NR	21 OR 28
	Study design	RCT	RCT	RCT
Inclusion Criteria	Age (years)	NR	NR	12+ OR 16-65
	Flu onset (h)	< 48	NR	36 OR 48
	Fever (ºC)	NR	NR	>37.8º OR Feverishness
	Subjective symptoms	Influenza-like syndrome	NR	2 or more of headache, myalgia, cough, sore throat OR 1 respiratory symptom (cough, sore throat, nasal symptom) and 1 constitutional symptom (headache, malaise, myalgia, sweats/chills, fatigue)
Exclusion Criteria	Chronic Illness	NR	NR	Immunocompromised OR unstable chronic disease
	Drug Use	NR	NR	Antiviral drug use (recent/current) OR immunosuppressant medications OR drug/alcohol abuse history
	Pregnancy	NR	NR	Pregnant or risk of pregnancy
	Vaccination	NR	NR	Vaccinated this year
	Bacterial infection	NR	NR	Suspected concurrent bacterial infection
Primary Outcome Measures	Time to alleviation of influenza	NR	NR	Temperature < 37.8º C, score of 0 on feverishness, score of 0-1 on other influenza inclusion symptoms maintained for 24 hours
Secondary Outcome Measures	Individual symptom scores	Chills, aches, rhinitis, night cough, day cough, fever (day 8 only)	Temp (daily), chills, aches (day 4 only)	Temp, headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness, loss of appetite (all recorded daily)
	Quality of life scores	Patient global assessment of health	NR	Sleep disturbance OR time to return to normal activities OR overall symptom severity rating
	Viral load	NR	NR	Viral shedding/viral load
	Relief medication use	NR	NR	Use of relief medications for influenza symptoms
	Complications	NR	NR	Secondary complications of influenza OR use of antibiotics
	Adverse events	NR	NR	Effects of study drug (safety measures)
Lab Testing	Lab confirmation of influenza status	No	No	Yes

*Standard design criteria from conventional influenza antiviral treatment trials, as reported by Herscu[1]
**NR = Not reported in the literature

TABLE 3: Homeopathic versus Conventional RCT Design in Influenza (Ferley 1989, Papp 1998)

	Design Criteria	*Ferley 1989*	*Papp 1998*	*Conventional Antiviral Standards**
Demo-graphics	Study size	487	372	350 - 650
	Study length	7	7-10	21 OR 28
	Study design	RCT	RCT	RCT
Inclusion Criteria	Age (years)	> 12	12 - 60	12+ OR 16-65
	Flu onset (h)	<24	< 24	36 OR 48
	Fever (ºC)	> 38 (rectal)	> 38 (rectal)	>37.8º OR Feverishness

	Subjective symptoms	At least two of: headache, stiffness, lumbar and joint pain, shivers	Muscle pain or headache, plus one of: shivering, cough, spinal pain, nasal irritation, malaise, thoracic pain, joint pain	2 or more of headache, myalgia, cough, sore throat OR 1 respiratory symptom (cough, sore throat, nasal symptom) and 1 constitutional symptom (headache, malaise, myalgia, sweats/chills, fatigue)
Exclusion Criteria	Chronic Illness	Immune deficiency, depression	Immune deficiency	Immunocompromised OR unstable chronic disease
	Drug Use	Immunomodulating medication use	Immunomodulating treatment OR use of antibiotics, analgesics, or anti-influenza agents in first 48 hours post-randomization	Antiviral drug use (recent/current) OR immunomodulating medications OR drug/alcohol abuse history
	Pregnancy	NR	NR	Pregnant or risk of pregnancy
	Vaccination	Immunization against influenza	Immunization against influenza	Vaccinated this year
	Bacterial infection	Local infection	NR	Suspected concurrent bacterial infection
Primary Outcome Measures	Time to alleviation of influenza	*Illness status at 48 hours* post-treatment (temp < 37.5, absence of five flu inclusion symptoms)	*Illness status at 48 hours* post-treatment (rectal temp < 37.5 and no headache or muscle pain)	Temperature < 37.8º C, score of 0 on feverishness, score of 0-1 on other influenza inclusion symptoms *maintained for 24 hours*
Secondary Outcome Measures	Individual symptom scores	Temp, flu inclusion symptoms (morning and night), also recorded cough, coryza, fatigue, side effects	Temp, presence of aches, headache, shivers, back or side pain, joint pain, spinal pain, cough, rhinitis, sore throat (2x/day)	Headache, myalgia, cough, sore throat, nasal symptoms, fatigue, feverishness, loss of appetite
	Quality of life scores	Patient assessment of success, time until return to work	Patient assessment of success, time until return to work	Sleep disturbance OR time to return to normal activities OR overall symptom severity
	Viral load	NR	NR	Viral shedding/viral load
	Relief medication use	Y	Y	Use of relief medications for influenza symptoms
	Complications	NR	NR	Secondary complications OR use of antibiotics
	Adverse events	NR	Y	Effects of study drug (safety measures)
Lab Testing	Lab confirmed influenza status	No	No	Yes

*Standard design criteria from conventional influenza antiviral treatment trials, as reported by Herscu[1]
**NR = Not reported in the literature

As can be seen, the two studies by Cassanova et al. either provide no information on, or do not meet many of the design criteria found in most antiviral studies. The two RCTs by Ferley et al. and Papp et al., in contrast, do mirror many of the design criteria, albeit with some important differences. General inclusion criteria are similar to conventional studies, as both are looking for clinical confirmation of influenza through fever plus some specific respiratory and body symptoms. However, the specific symptoms are variable among Papp et al. and Ferley et al., and both of these differ from the more standard set of inclusion symptoms in conventional trials. Most of the exclusion criteria are the same, yet there is one central distinction. In Papp et al., patients are

excluded from the study if, within 48 hours of beginning the study medication, they receive any anti-influenza treatment, including antiviral, vaccination, analgesics, antibiotics, or immune stimulatory or suppressive therapies. It is unstated in the original literature report why this exclusion is made, though it is possible that it is due to concern with anti-influenza drugs disrupting the action of the homeopathic study medication. A more beneficial way to handle this situation may be to include those patients, recording any drug use, and later analyze them as a sub-population if need be.

Both the Ferley et al. and Papp et al. studies, as well as the majority of antiviral studies, use as a primary outcome measure the alleviation of influenza-like illness. These two RCTs however define the primary comparison as absence of influenza at 48 hours, rather than just looking at time to alleviation of influenza versus placebo. Also, in Papp et al., not all the inclusion symptoms have to be eliminated for the patient to count as recovered, only fever, headache, and muscle pain. In Ferley et al., all five of the inclusion criteria for influenza-like illness, as well as the fever, must be gone to count as recovery. In most conventional studies, the requirement to meet the 'recovered' status is the loss of fever, and a rating of mild or none on the influenza inclusion symptoms, and this must be maintained for 24 hours. These are significant differences in design methodology that must be considered.

In terms of secondary measurements of outcome, the homeopathy RCTs and the conventional antiviral studies cover some range of individual symptoms, patient assessments of health and normal activity, adverse affects, concomitant drug use, and other measures.

Perhaps the largest difference between conventional antiviral studies and the homeopathy RCTs on influenza treatment that have been published to date concerns laboratory confirmation of influenza infection. Laboratory testing and confirmation of influenza virus and subtype is a standard component of influenza antiviral studies [1], and allows for the retrospective analysis of the specific subgroup of the study population who actually has influenza infection versus other upper respiratory tract infections that may present like influenza. A review of antiviral studies [1] shows demographics of the proportion of influenza study populations that have laboratory confirmed influenza ranging from 57-78%. This indicates that in some studies, over 40% of patients may be presenting with an influenza like illness not caused by influenza virus; thus the study is not specifically giving feedback just on the treatment of influenza. None of the homeopathic influenza treatment studies have looked at this subset, thus conclusions drawn from these studies are only applicable to influenza-like illness which comprises a number of different specific conditions.

The general criticism of homeopathy studies in influenza appears to be mostly aimed at the possible introduction of biases into the study, either through poorly chosen outcome measures, selective reporting of symptoms, simple omission of important methodological standards, or other biases in study reporting. However, what is also clear from comparison to conventional trials is that many of the specific design elements, even if generally similar, lack consistency between homeopathy trials and standard antiviral trials. As Mathie[4] suggests, the study of acute conditions with homeopathy does lend itself to placebo-controlled randomized trials, and the initial body of evidence from homeopathy studies such as those reviewed in Vickers [2] evidences statistically significant positive effects. However, based on the small effect sizes observed and the need for reconfirmation through much larger trials, it may be useful to explore whether it is not changes in basic methodological design and study quality, rather than larger study groups, that will yield the most significant and telling results. In addition, these specific suggestions pertain most specifically to further trials of *Oscillococcinum*, but trials with different remedies using different inclusion and exclusion criteria, outcome measures, and other design elements would have different requirements not predictable from these trial results. As suggested by Walach[19], pre-trial pilot studies are an important way of gaining valuable predictions of necessary study size and length, and should be considered in future trials in order to optimize methodological design. In regards to specific, acceptable design criteria for elements like inclusion criteria, clinical definition, and outcome measures, attempting to mirror the current standards in conventional antiviral trials is one possible approach.

One important issue not discussed in this article, but worthy of separate attention, is the process of choosing the homeopathic medicine for the influenza treatment study. This issue is discussed at length in another paper by the authors[32].

Conclusion

The availability of homeopathic controlled trials of good, or even satisfactory, quality has increased only slowly over the last 20 years. The most recent systematic study includes 110 trials, only 19% of which are rated as being "higher quality". Regardless of the fact that low study quality also afflicts conventional drug trials, possibly even to a greater degree, future homeopathic trials should be able to fix some essential problems. Primarily, with potential bias being a frequently cited concern, homeopathic trial reporting in the literature must improve. With reviews citing multiple areas in which over 80% of trials report unclearly, insufficiently, or not at all, bias will continue to be assumed. Description of randomization process, funding sources, and participant inclusion is frequently lacking. Equally important is improvement in the definition, applicability, and objectiveness of outcome measures. Reviews found generally poor outcome measures in up to 50% of controlled trials. A related problem cited is the lack of acceptable definitions for clinical conditions and thus trial inclusion. Because inclusion criteria, exclusion criteria, and outcome measures are design elements that may often have acceptable standards among existing trials, there should be more effort made to standardize them where possible in homeopathic trials. As noted in one review, many of the positive homeopathic controlled trials have used subjective and difficult to quantify outcome measures, casting doubt onto their results. Other recognized issues are small sample sizes, insufficient patient follow up or unacceptable drop-out rates, inadequate allocation concealment, and inappropriate study length.

Within the specific group of homeopathic influenza treatment trials, four trials of moderate to good quality exist. The two higher quality studies, while having similar basic design to conventional antiviral trials as RCTs, nevertheless differ in some important areas. Definitions for inclusion criteria, exclusion criteria, and outcome measures vary significantly between the homeopathic and conventional trials. Instead of following the length of illness as in conventional trials, the homeopathic trials look specifically at those who have recovered by a particular time. In addition, because the homeopathic trials fail to verify influenza through lab-testing, the analysis can only pertain to influenza-like illness whereas conventional trials can do a sub-group analysis of actual flu sufferers, and thus be able to report more specific efficacy of the drug against influenza in particular. Overall, the flu studies suggest a positive effect of relatively small size for one specific homeopathic remedy in a group of both flu sufferers and those with influenza-like illnesses, both necessitating much larger trials for confirmation and raising the question of what exactly is being tested. These same concerns and questions are not raised with conventional antiviral trials precisely because of the higher quality and general acceptability of their study design. Thus, considering the mirroring of conventional RCT design elements in future influenza trials with homeopathy seems justifiable.

Although this paper focuses on methodological concerns in RCTs, which is where the burden of proof will continue to lie for homeopathy clinical research, it is important to note the ongoing discussion on what basic types of research are most applicable to homeopathy. Walach[19], for example, notes that although there are fewer studies, it appears to be easier to prove the equivalence of homeopathic remedies to standard treatments as opposed to their efficacy compared to placebo. Other important areas of consideration not discussed in this paper are observational studies and other alternatives to the RCT, which are also deserving of further attention. Simultaneously to exploration of these questions, however, RCTs in homeopathy will continue, and there is good reason to improve their quality. As presented in this paper, one possible way to proceed is by mirroring conventional study design parameters, such as in influenza treatment trials.

Conflict of interest

There were no conflicts of interest.

Funding source

The cost of the study was supported by the authors.

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