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The Context and Meaning of Placebos for Complementary Medicine

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Key Words
Alternative medicine · Placebo · Randomized controlled trial

Summary
Calls for placebo-controlled randomised trials in complementary and alternative medicine (CAM) are entirely reasonable. However, they present major methodological problems, particularly when we understand so little about the underlying biological mechanisms involved for many of these therapies. Designing a placebo in CAM is frequently dependent on unsubstantiated assumptions about the specificity of a particular CAM intervention. In this paper we address the development and application of placebos to clinical trials of homeopathy, acupuncture, kinesiology, Chinese herbal medicine and healing. Each therapy-based vignette is authored by a researcher from the Complementary and Integrated Medicine Research Unit at the University of Southampton who has specific expertise in the field. The essential research question within this review is; can we legitimately claim to have placebos for these particular CAM interventions? In some areas of CAM the debate has become very involved and sophisticated, for instance in acupuncture but for other areas, such as healing, our understanding of placebos is currently limited and very naïve. For instance, if acupuncture is not point specific, then many so-called 'placebo-controlled' acupuncture trials are both misconceived and misleading. We have addressed this debate in what we hope is a thoughtful and rigorous manner with a view to developing realistic, reliable and credible placebos for randomised controlled studies when and where possible. However, our conclusions suggest that we are some way from developing valid, credible and reliable placebos for most CAM therapies.

Schlüsselwörter
Alternativmedizin · Placebo · Randomisierte kontrollierte Studie

Zusammenfassung
Der Ruf nach placebokontrollierten randomisierten Studien in der Komplementärmedizin (CAM) ist vollkommen vernünftig. Dabei stellen sich jedoch große methodische Probleme, insbesondere weil wir so wenig wissen über die zugrunde liegenden biologischen Mechanismen, die bei vielen dieser Therapien eine Rolle spielen. Die Entwicklung eines Placebos für CAM hängt häufig von unsicheren Annahmen über die Spezifika einer bestimmten CAM-Intervention ab. In der vorliegenden Arbeit behandeln wir die Entwicklung und Anwendung von Placebos für klinische Studien in der Homöopathie, Akupunktur, Kinesiologie, chinesischen Phytotherapie und im Bereich Geistheilung. Jede therapiebezogene Vignette stammt von einem Forscher der Abteilung für Complementary and Integrated Medicine Research der Universität Southampton, der auf dem jeweiligen Gebiet besonders kundig ist. Die grundlegende Forschungsfrage dieser Arbeit lautet: Können wir berechtigterweise behaupten, dass es Placebos für die verschiedenen CAM-Intervention gibt? In einigen CAM-Gebieten gibt es zu dieser Frage sehr engagierte und differenzierte Diskussionen, beispielsweise in der Akupunktur; in anderen Gebieten wie der Geistheilung ist unser Wissen über Placebos jedoch noch sehr begrenzt und naiv. Wenn zum Beispiel die Akupunktur gar nicht punktspezifisch wirkt, dann sind viele sogenannte placebokontrollierte Akupunkturstudien sowohl falsch angelegt als auch irreführend. Wir sind diese Erörterungen, wie wir hoffen, besonnen und präzise angegangen, mit dem Ziel, möglichst realistische, verlässliche und glaubwürdige Placebos für randomisierte kontrollierte Studien zu entwickeln. Unsere Schlussfolgerungen legen jedoch nahe, dass wir noch ein gutes Stück Weg vor uns haben, bevor wir für die meisten CAM-Therapien valide, glaubwürdige und reliable Placebos entwickelt haben werden.

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Introduction

The placebo has been conventionally conceptualised as an inert agent or procedure that leads to a therapeutic effect through the induction of a variety of psychological mechanisms, including expectation of clinical improvement and Pavlovian conditioning that both trigger self-healing [1]. In the late 1970s, the demonstration of a measurable opioid response [2] first confirmed that the effect of placebo is a 'real' physiological process, rather than 'all in the mind'. Since then, the specificity and complexity of these responses has become increasingly clear. Sophisticated technologies have demonstrated effects within the brain that mimic and overlap with the effects of verum treatments for conditions such as chronic pain [3], Parkinson's disease and depression [1]. One of the problems for complementary and alternative medicine (CAM) as well as other complex psychosocial interventions is in distinguishing verum from placebo interventions, particularly when we are unclear about the exact mechanisms involved in treatment.

A recent review [4, 5] has challenged the notion that placebo is inert or that it should be considered distinguishable from its context, method of delivery, or the process of care-giving. Instead, it has been proposed that placebo be redefined as 'the simulation of an active therapy within a psychosocial context' [4, p 567]. This reflects the capacity of the human body to produce therapeutic and side-effects identical to those of active treatment in response to a range of environmental factors that influence the patient's expectations, desires, and emotions. In clinical trials that involve the treatment of chronic benign illnesses, it appears that the major therapeutic effects of any intervention are non-specific and contextual rather than specific [6, 7]. This is not only true for CAM but equally applicable to other medical interventions such as the use of antidepressant medication [8], chronic pain [3], and Parkinson's disease [1]. The constituents of 'active treatment' within CAM vary considerably according to the locations and contexts in which they are administered, the expertise and authority with which they are delivered, the processes of investigation, diagnosis and treatment, and the rituals that accompany these, as well as the nature of the intervention and its method of delivery, all of which have been shown to influence outcomes [9, 10] and have the potential to exert strong influences on the clinical outcome of CAM interventions. A review of the evidence from clinical trials [4] identified a maximum effect size for placebo as 0.59 (≥0.5 is classified as large) [11]. This would appear to demonstrate that significant therapeutic benefit is potentially available from placebo alone.

While the placebo-controlled randomised controlled trial (RCT) is firmly established as the gold standard for testing the clinical effects of medical interventions, it is not always possible to employ effective placebos in situations that do not involve pharmaceutical agents. Michael Rawlins in his recent Harveian oration draws this to our attention and suggests that we need to consider a broad range of evidence when evaluating data related to specific therapeutic effects [12]. Walach et al. address similar issues in their view of appropriate evidence synthesis [13], and Gabbay and Le May clearly demonstrate that clinical decisions are frequently not dependent on the classical pyramidal evidence-based hierarchy [14]. We may not be completely dependent on the placebo-controlled trial for evidence of clinical effects but nevertheless, it will continue to be an important part of evidence-based medicine and the evaluation of specific clinical effects for a variety of interventions, particularly those involving conventional medications. The RCT was originally designed to evaluate the effectiveness of drugs for which identical placebo substances can be delivered using 'double-blind' procedures where neither patient, nor practitioner, nor researcher knows which treatment is 'real'. In this paper, we consider the problems arising from this approach, based on our practical experience as a sophisticated group of CAM researchers who have been involved in evaluating a number of different complementary therapies. We will consider the implications of these observations within the context and meaning of placebos for CAM and its rigorous scientific investigation within the complex debate that currently surrounds evidence-based medicine. We do not think that placebo-controlled trials are the only basis for clinical decision making but they are an important element of clinical evidence

Each of the following sections is written by an individual who has both clinical and research experience in that specific field. The main research question we address is whether it is currently possible to design reliable, effective, and realistic placebos in these therapies. Do we understand enough about the interventions to know when we are using a placebo?

Providing a Placebo for Acupuncture Research

Researching an intervention which is clearly invasive can be very challenging. The central issue for acupuncture research is whether we can investigate a non-pharmacological invasive intervention in the same way that we can investigate a drug? Acupuncture is best described as the insertion of very fine needles into the body at varying depths according to the underlying structures. These needles are routinely manipulated to produce a sensation defined as 'Deqi' or needling sensation, before they are deemed to have their full effect [15]. There is evidence suggesting that the neurological networks responding to acupuncture are stimulated both centrally and peripherally carrying the impulses from this peripheral sensory input into the spinal column and up to the higher centres [16]. This raises a number of problems with 'placebo' acupuncture if we adhere to the criteria for a rigorous randomised, controlled clinical trial methodology.

In order for acupuncture to have the full effect, the patient must actually feel it, meaning that a directly comparable

Table 1. Components of a complex intervention*

Total effect
Spontaneous change
Associated/context effects
Meaning
Co-interventions
Practitioner effect
Diagnosis and how this is understood by the patient
Direct effects of consultation process
Attributable therapy effect

After Linde K: The specific placebo effect. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2006;49:729–35.

placebo must also be 'felt'. Lundeberg et al. [17] have suggested that the general parameters for treatment for painful conditions with western acupuncture are well-established; the needles should be inserted to a specific depth, retained for a defined period of time, and used on a reasonable number of occasions [17] in the treatment of any clinical condition. If these parameters vary substantially, the patient will be aware. While some may disagree with Lundeberg, the majority of RCTs using western acupuncture for pain do follow these very general guidelines.

A single application of acupuncture is rarely enough to produce the cumulative neurochemical and clinical changes which are thought to underpin the effect of this intervention. If Deqi is thought by some [18] to be an essential neurological component of acupuncture, but if it can be elicited with a placebo, then, while this makes the placebo valid in the eyes of the patient and the researcher, it potentially confounds the outcome of any trial.

Placebo needles, resembling stage daggers collapsing into their handles, have been used with some success [19, 20]. These do not actually penetrate the skin, although the sensation felt by the patient, who cannot see the tip, is usually convincing. Use of these needles is not straightforward and involves considerable skill on the part of the researcher [21]. While this has the potential of being able to blind the patient as to the type of acupuncture received, the operator cannot be blinded as the two needling techniques are quite different [21]. A newer version of these needles is now available [22], where it is claimed that it is possible to blind the acupuncturist by having the needle, already within the plastic insertion tube, either inserted into some soft material at the skin or directly into the skin. There has been no substantial research completed using these new needles.

The main problem with all of these sham needles is that the occurrence of Deqi and the subsequent activation of peripheral C fibres from skin contact with the blunt needle may alleviate pain. The intervention cannot therefore be a truly inert placebo if we believe that Deqi is part of active acupuncture treatment. It may therefore be preferable to abandon the idea of a sham needle and design and consider an inert non needle-based intervention of a completely different kind such as a sham acupuncture laser or TENS stimulation. This would provide a control intervention for real acupuncture that would not be a direct placebo and its validity would depend on the patient rating the two inventions equally.

Many conditions which present for treatment with acupuncture are self-resolving making it even more difficult to be sure that the specific effects of the therapy are responsible for all or any of the recorded changes. With a complex intervention, the attributable effect becomes smaller the more rigorous the study design.

It is not really possible to indicate how much of the total effect may be represented by each of the components suggested in table 1 but it is probable that spontaneous changes vary from condition to condition, while the associated or context effects may vary depending on the type of consultation taking place. It is also probable that the practitioner is the most important variable [9]. Clearly, where there is both an element of ritual and an extensive clinical interview, the placebo effect of the intervention will be reinforced substantially [23] and may be both practitioner and dose-dependent [10].

Some very valuable work has been done within acupuncture to indicate that there is more than a placebo effect [3]. Using positron emission tomography (PET) scans the effect of a sham needle involving superficial sensory stimulus only has been eliminated, together with the additional effect of the patient's belief and expectation, leaving a visible effect in another part of the brain entirely.

This raises an important ethical question. Some acupuncture trials in Germany with substantial patient numbers and careful methodologies have failed to demonstrate a significant difference between the placebo and verum acupuncture interventions [24–27]. Where the specific effect is so small, the importance of this is either vital or really irrelevant. The question is which?

It is understandable that we require a clear answer as to what the exact physiological effects of acupuncture may be and how they can be best reproduced. It is equally clear that the clinicians might prefer to use the research process to refine the context in which a therapeutic intervention is delivered and thus improve its effect. In view of the fact that acupuncture appears to be more effective than conventional care for many conditions, even if it is 'placebo' [28], the next question is whether it would be unethical to withhold acupuncture in clinic. (VH)

Is Homeopathy a Placebo?

One of the challenges that affects research into homeopathy is the uncertainty surrounding the plausibility of the homeopathic remedy. This has lead to research that has consistently attempted to find specific effects of homeopathy from the remedy alone, treating the remedy as if it was a biomedical

drug with specific physiological effects. Such focus has lead to conflicting evidence about efficacy [29–35] suggesting that the clinical effects of homeopathy are placebo effects which are a result of the therapeutic encounter that is experienced as part of the consultation [30, 36–39].

The challenge of researching homeopathy is compounded by the poor quality of many homeopathic trials compared to clinical trials in conventional medicine [40]. Additionally, the RCT has frequently not investigated homeopathy as it is practiced in a 'real world' situation, for instance the blinding of homeopaths participating in a trial interferes with their normal practice routine of an individualised patient response to a far greater extent than with a conventional medical prescription [41]. Furthermore, the use of isopathy is not a routine part of classical homeopathy [42, 43]. The value of examining the specific effects of a therapy (the remedy) as separate to the non-specific effects (the effects from the practitioner-patient relationship etc.) of a therapy has been questioned. For example, it has been proposed in homeopathy that the specific and non-specific effects may interact rather than just being an additive effect of the homeopathic intervention [41]. This view is reiterated in Paterson and Dieppe's [44] observations on acupuncture research. These and other challenges can be addressed by thoughtful design in the application of RCT method investigating CAM, for example, the use of pragmatic approaches [45], and by combining RCTs with qualitative methods [46].

In order to fully understand a CAM intervention such as homeopathy, research must address its separate components, whilst allowing the system to remain intact because of synergy between the different components [46]. The process and context are fundamental to effective treatment and positive outcomes for any therapy, not just homeopathy [46]. The process and context of a therapy refer to components such as the relationship between the patient and the practitioner, expectations, and how an intervention is delivered. The therapists' contribution to these components can only be understood by exploring the consultation in depth from the practitioners' perspectives.

My research into the nature of homeopathy has focused on understanding homeopaths and how they consult so that we may better understand the nature and models employed by them during a homeopath consultation. This has enabled me to recognise the power of the therapeutic interaction in the homeopathic consultation which includes the use of a remedy. I have explored homeopathic practitioners' experiences and perspectives of the consultation and have developed a theoretical model of the process of the homeopathic consultation from their perspective which demonstrates that the practitioner-patient relationship is crucial to all the processes in the homeopathic consultation. The process of identifying, choosing, and giving the homeopathic remedy appears to be specific to homeopathy as it has a central role in the homeopathic consultation and may therefore play an active part in promoting therapeutic benefit. My findings corroborate a previous theoretical explanation by Weatherley-Jones [41], in that the homeopathic remedy cannot be treated independently to the effect of the consultation, and hence it is meaningless to separate out the remedy from the consultation. This is consistent with the theoretical model of entanglement in homeopathy between the patient, the practitioner, and the remedy [47, 48]. But the implications and relative effect sizes of the consultation and the homeopathic remedy require further investigation within the context of rigorous controlled trials.

The terms 'placebo' and 'non-specific effects' are therefore inadequate in explaining the nature of the catalyst for the specific mechanism that is activated within homeopathy as a whole system. The term 'context effects' is an alternative explanation that has been proposed to refer to healing that results from the clinical encounter and the practitioner-patient relationship [49]. This is almost consistent with the proposed theoretical model; however, it assumes that the healing is distinct from a specific efficacy of treatment interventions which is inconsistent with my research. It appears the homeopathic remedy is an indivisible and specific part of the homeopathic consultation.

Therefore, an alternative explanation is needed. A framework that sits comfortably within the findings of my research is Moerman and Jonas' [50] concept of the 'meaning response' which relates to the response that people experience as a result of the meanings that they attach to their interventions or treatments. Similarly, motivational concordance posits that if a particular treatment is in accord with the patient's own preferences and motivations, then the patient will be more likely to engage in that treatment, and it is the degree of engagement in the treatment that may lead to symptom reduction [51]. An important part of the homeopathic consultation is the narrative aspect which elucidates connections and meanings [52], and these may be symbolically represented by the homeopathic remedy [53, 54]. This framework takes into account the different meanings of the terms 'placebo effects', 'non-specific effects' and 'context effects' and delivers an understanding of these terms within a cultural context that allows for the complexity of meanings, rituals, and symbols that are attached to the objects and activities that contribute to the homeopathic consultation. (CE)

Kinesiology

In my role as a practitioner-researcher, I was interested to develop a sham kinesiology intervention to attempt to discover whether there was indeed a specific treatment effect over and above the non-specific effects, but as the mechanisms of kinesiology are as yet unclear, providing an inert treatment as a control was challenging. Noll et al. [55] suggest that a plausible but ineffective placebo treatment is required to control for the potentially therapeutic effects of

touch in manual therapies. Therefore, the sham treatment needed to look as much like the real treatment as possible, be credible to patients, but be devoid of anything considered therapeutic in kinesiology theory. Kinesiology appears to be a complex whole-system intervention utilising touch, talking, techniques, and lifestyle change and it is not certain what the active ingredients are or how they relate to each other. Furthermore, these factors are not necessarily additive but may be synergistic. It was clearly not possible to perform any treatment without touch but it was possible to limit the conversations of the placebo group to theoretically benign subjects thus controlling for the effect of touch in both groups. Despite these challenges, I have recently developed an apparently credible sham treatment designed to be minimally effective for use in a single-blind RCT [56]. This has been a complex procedure but it has resulted in the development of the standardised sham (placebo) Kinesiology process that will begin to allow us to separate the specific and non-specific therapeutic elements of this intervention. At this point, it is impossible to know if Kinesiology has any specific active components or what constitutes as specific or non-specific intervention within a Kinesiology context. A true placebo for Kinesiology still seems a long way away! (SH)

Healing

Spiritual healing, whilst probably one of the oldest medical treatments, is a comparatively neglected area for research, yet there is a growing recognition of the importance of spiritual well-being in patient care [57, 58]. Anecdotal evidence for spiritual healing suggests that it is a multi-dimensional therapy that operates in several domains simultaneously [59]. Healees (those receiving healing) can experience profound relaxation which can alleviate stress, anxiety, and the perceptions of pain while experiencing feelings of well-being and empowerment [60–63]. While some consumers appear content with anecdotal evidence about the clinical effects of healing, there is a pressing need for solid evidence of effectiveness and safety, if healing is to be widely used in support of orthodox medical interventions.

Discussions around spirituality and health care can combine a myriad of concepts including 'miracle' cures, ritual, prayer, meditation, and healing, while spiritual healing itself has being linked erroneously to the occult and religious practice rather than an energy-based CAM therapy. Spiritual healing is a generic term which includes Reiki and Johrei and does not diagnose, prescribe, seek, or claim a specific therapeutic outcome; it does not seek to cure in a medical sense but claims to address the symptomatic needs of a patient and involves a holistic approach to mind, body, and spirit. There are two distinct forms of spiritual healing, contact healing given in the presence of the patient and distant healing where the patient is absent. Distant healing can be distinguished from prayer which seeks the intervention of a higher being to facilitate a specified result. In studies of both distant and contact healing, it is possible that patients who enrol into a clinical study may have expectations linked to their enrolment which may not replicate real-world therapeutic interaction and thus, the context in which the therapy is given (or not given) may be crucial to the outcome [13].

The two forms of spiritual healing present different challenges for the researcher. Walach et al. [64] have demonstrated that the expectation of actually receiving healing may play a vital part in the outcome of distant healing. In contact healing there are likely to be additional non-specific effects due to the various healer-healee interactions within the therapy session. It is also unclear if healer and/or researcher intentionality impacts on the healing outcome [65] and whilst theoretical models such as entanglement and week quantum theory seek to explain healing [66], the exact mechanisms are unclear. Therefore, sham or placebo healing could be working through exactly the same mechanisms as real healing and may therefore not be true placebos. Furthermore, systematic and critical reviews of healing studies have found the methodology of many of the published RCTs inadequate [67–71]; these criticisms include issues of blinding, inadequate power, and the poor reliability of the outcome measures employed.

Healing organisations claim everyone has the potential to heal, thus actors [67, 72–74] and trainee healers [75–77] may be delivering healing unbeknownst to themselves or the researchers. In the light of such confusion it would be inappropriate to use placebo healers in RCTs of either contact or distant healing. Thus, studies of spiritual healing are challenged to generate knowledge about this holistic therapy when research methods such as RCTs are designed to isolate and examine specific elements of any intervention. It would seem that a mixed-method approach designed to address whole complex interventions is necessary allowing initially qualitative methodologies to inform further research [78, 79]. It may also be valuable to consider approaches that involve waiting list controls [59, 80, 81] or pragmatic studies that address the overall effectiveness of healing [82].

As a consequence, I have chosen, in my role as a practitioner-researcher, to employ qualitative methodology to understand breast cancer patients' experience of contact spiritual healing delivered by a group of healers. Using unitary appreciative inquiry [83, 84] allowed the patients on the study to be involved in the conceptualisation of the results at each stage of the study, avoiding researcher bias and informing further research. This will allow me to model the process of healing from the patients' perspective and through this better understand the individual mechanisms involved. It is only with the level of rigour, that we will be able to have any real chance of developing a credible and viable placebo within this field. (FB)

Chinese Herbal Medicine

Over the past 40 years, at least 17,000 RCTs have been conducted in China investigating the effectiveness of Traditional Chinese Medicine (TCM) [85, 86] with the majority of these trials related to Chinese herbal medicine (CHM) [85]. However, whilst there is a vast and growing corpus of CHM research, its value as an evidence base has been compromised by a lack of methodological rigour and transparency [86]. Inadequate randomisation, small sample size, and lack of blinding in particular have left the interpretation of this research vulnerable to the distorting effects of selection, reporting, and assessor biases.

The balance between rigour and relevance is particularly difficult to achieve in CHM. Rigour can and has been introduced by proper randomisation and enhanced by placebo controls that have been evaluated for their credibility in a number of studies [87, 88]. However, CHM as it is most commonly practiced involves a decoction (boiling up) of a complex formulation of herbs that changes according to individual presentation and again will be adjusted several times during the course of treatment. This is difficult to match with an equivalent and convincing placebo and so the tendency has been to either standardise the decoction or omit the decoction altogether and rely on encapsulated herbal powders or pills to deliver both verum and placebo treatments. Despite the pragmatic appeal of these designs, neither a standardised decoction nor encapsulation are generally considered as examples of optimum CHM practice. Relevance is diminished to suit the requirements of rigour.

However, as part of a feasibility study exploring the role of CHM in the treatment of endometriosis, we have designed a novel methodology that manages to combine relevance with rigour. Using simple extraction technology imported from Korea it has been possible to dispense individualised decoctions for each trial participant in the active arm of the trial that can be matched by a placebo decoction made from commonly used vegetables and culinary herbs available in the UK. The practitioner writes a prescription which is then emailed to a distant pharmacy where it is randomised to active or placebo, cooked, and then sent to the trial participant. Both verum and placebo are strong tasting and dispensed in identical sealed sachets. This allows for a double-blind, placebo-controlled RCT.

The trial has now completed and blinding was successful with neither recipient nor practitioner able to reliably predict group allocation. Patients in both groups showed significant improvement and we were able to identify a clear and powerful response to placebo CHM as well as real CHM treatment. An obvious problem to this approach is the possibility that the common foods that we used could have had a therapeutic effect. Even so, it seems reasonable to expect a focused herbal intervention to be able to demonstrate a better therapeutic effect than what is effectively a glorified vegetable soup. The next stage is to develop a placebo using food flavourings which have no active compounds and can be more readily regarded as inert. This is now entirely possible and should enable a more effective placebo-controlled comparison.

There is a danger that in comparing active and placebo herbs we will focus on the specific effects of CHM and exclude the contextual effects of CHM intervention. CHM is a whole-medical system [78] that has developed extremely effective ways of enhancing the contextual effects of treatment including a sophisticated enhancement of the therapeutic relationship via an in-depth diagnostic process that is highly attentive, intimate, and caring. Pulse diagnosis, for example, involves the practitioner maintaining a steady and relaxed contact with the patient for several minutes, which is both diagnostic and probably therapeutic. CHM diagnosis frequently uses naturalistic, metaphorical language such as 'hot', 'cold', 'flaring of Fire' that manages to be both slightly mysterious and exotic but is also prosaic and resonant to a patient's experience of their illness. In many ways, the contextual effects of CHM are uncharted territory, although there are obvious parallels with work done on the importance of the consultation in acupuncture [9]. However, it is extremely likely that these effects exist and that they constitute an important component of the therapeutic effect of the treatment. The danger is that if we are looking to test the active herbs against the placebo, we may be excluding other active effects of the whole-system of CHM intervention. Whilst intellectually interesting, this is not an accurate pragmatic assessment of the clinical effects of CHM.

One possible way around this obstacle would be to have a waiting-list control as a third arm. This would enable a comparison of active and placebo groups leading to an estimation of the specific and contextual effects, respectively, of treatment. However, waiting-list controls may have a high drop-out rate and being in the waiting-list group is not a neutral or 'inert' act. Resentment, anticipation, and other responses to being in this group could easily introduce their own confounding effect.

It seems that we have to accept that any research design has the capacity to introduce its own bias. All measures of specific, contextual, or combined effects of treatment are going to be compromised by the complexity of the human recipients who react in unpredictable and idiosyncratic ways to their health care. However, with these limitations in mind we should still proceed cautiously with placebo-controlled trials. They will allow an estimation of both the overall and the specific and contextual effects of treatment which will help to establish the areas in which CHM may be most able to contribute to health care in the West, to explore the healing effects of the consultation process, and at the same time to identify and refine our understanding of key components of treatment relating to, for example, dosage, herb selection, and method of administration. As long as we are mindful that 'placebo' is in-built into the whole-system of CHM and indeed all medical interven-

tions as a way of eliciting a healing response, then an exploration of the placebo response can generate new, interesting, and constructive insights into Chinese medicine. (AF)

Conclusion

We are aware that placebo-controlled randomised trials are a single and limited scientific tool. Rawlins clearly placed this in context when viewing the RCT as one of the many mechanisms of obtaining valuable clinical evidence [12]. In this paper, we are simply focusing on the design of appropriate placebos for particular CAM interventions and the scientific issues that this raises, rather than primarily addressing the whole contextual debate about best methods available for obtaining clinically relevant evidence for the treatment of many chronic conditions. Our research group has been working together for over 10 years now and we have consistently addressed the issues of credible true placebos in the context of the clinical trials we have designed for specific CAM therapies. Some of our mechanistic investigations have indicated that real placebos may be possible in such fields as diverse as acupuncture and kinesiology [3, 56] but we are only too aware that conceptually, placebos may simply be neither credible or indeed possible at the moment for some interventions such as spiritual healing. Each of the therapies considered in this article are at slightly different stages in their research development. Consequently, each CAM intervention requires a slightly different strategy in relation to addressing the nature of placebos and the specific and non-specific components of any particular intervention. We hope that our discussions around each intervention not only show our ability to develop and innovate, but also address the problems that investigating whole-medical systems such as TCM and Kinesiology must address within the context of placebo-controlled trials [78, 89, 90].

We do wish to create a rigorous but thoughtful scientific environment through which CAM can be effectively used and evaluated. We believe that first we need to pay particular attention to the underlying mechanisms that may be involved in each therapy and therefore, the identification of a 'true placebo,' if that is possible, and how this should be developed in the context of a clinical trial. This will be through a combination of qualitative modelling and the investigation of the basic biochemical, neurological and physiological pathways involved in each therapy. We will then need to carefully evaluate the effects of various experimental placebos within RCTs specifically designed to address the feasibility of delivering the placebo intervention as well as its credibility. Finally, we should begin to have placebos that will be credible, viable, and can be realistically delivered within the context of a randomised study.

We also understand the methodological debates and limits of the placebo-controlled RCT and would argue that those who wish to absolutely reject the placebo-controlled RCT are equally as foolish as those who see it as the only rigorous methodology that can reliably evaluate clinical effects. The placebo-controlled RCT has its part to play within the context of clinical evidence but it appears that its dominant role is being challenged effectively by health-service researchers and the use of sophisticated pragmatic trial methodology [91]. We are only too aware that whole-systems research [89, 90] may demand substantial changes in our strategic approach and furthermore, that we may need to look at evidence in a non-hierarchical manner [13]. As with acupuncture [9], it is very likely that our assumptions about the specificity of needling within the context of acupuncture as a whole-system are incorrect. It could be that there are therapy-specific effects which the clinical trial may deem non-specific by virtue of its design and focus on acupuncture point specificity. What is clear is that this is a complex area where both context and the often unsubstantiated therapeutic assumptions about specificity within different CAMs need to be examined with care and rigour.

If we are to realistically develop such placebos for the purposes of rigorous RCTs, then a coherent research strategy is required which takes into account the context of the intervention, its impact as a whole system, and its potential mechanisms. Acupuncture is a good example, and while it may have been very reasonable to think that acupuncture was 'simply about needling a particular point on the body' 30 years ago, our current understanding of the process of acupuncture treatment and its mechanisms makes this now appear both ludicrous and unscientific. This is clearly an area where both context and often unsubstantiated 'traditional' assumptions about therapeutic specificity within different CAMs need to be examined. It is apparent from our collective experience that simply 'inventing a placebo' for a particular trial might sound attractive, but methodologically must represent great intellectual poverty and fundamental misunderstandings in scientific thinking. This process requires careful and thoughtful development if we are to continue to use placebo-controlled trials to provide us with relevant, applicable and valuable clinical evidence for CAM interventions.

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