

Defining an adequate dose of acupuncture using a neurophysiological approach – a narrative review of the literature

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Abstract

Many different styles of acupuncture practice exist, and lack of agreement on the optimal acupuncture treatment for any particular condition may mean that some patients do not receive the best treatment. This uncertainty also makes the negative results of sham controlled trials difficult to interpret. Unless we can be sure that both adequate acupuncture and an inactive sham were used in a particular trial, then that trial should not be interpreted as dismissing acupuncture for that condition.

Acupuncture practice clearly involves much more than needling procedures, but there is a strong argument for elucidating the role of those needling procedures first. The components of acupuncture needling procedures have been described in the STRICTA document, but it is also clear that the patient's perception of needling is relevant for the outcome of treatment.

We therefore recommend the concept of 'dose' of acupuncture needling, which should include both the stimulus given to the patient, and certain aspects of the patient's perceptions and response that are known to be linked to the subsequent therapeutic response. We propose the following definition of dose: the physical procedures applied in each session, using one or more needles, taking account of the patient's resulting perception (sensory, affective and cognitive) and other responses (including motor). The dose may be affected by the state of the patient (eg nervous, immune and endocrine systems); different doses may be required for different conditions.

The constituents of an adequate dose can be established initially by clinical opinion and subsequently by empirical evidence from experimental studies, which may be either clinical or basic research studies.

Systematic reviews which do not consider the adequacy of the acupuncture treatment may have unreliable conclusions. Out of 47 recent systematic reviews, only six have applied some criteria for adequacy. Five used a rating system or conducted a subgroup analysis, and one excluded studies from the analysis altogether if they did not meet criteria for adequacy.

Research into what constitutes an adequate dose of acupuncture has long been neglected and is now urgent. Clinical studies that compare the effects of different treatment protocols are probably the most reliable source of evidence, and may also demonstrate a dose-response relationship.

Keywords

Adequacy of acupuncture; treatment protocol; optimal acupuncture; study quality; intervention; dose finding study; systematic review.

Introduction

Acupuncture's development over two thousand years has taken place in different centres in China, Japan, Korea and other parts of the world, and

understandably many different styles of practice now exist. Currently, there is considerable disagreement among acupuncturists, particularly those trained in different schools, about what constitutes the best

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treatment for different conditions and for different patients. A treatment protocol (ie a precise description of the procedures and the schedule for a course of treatment) that is one practitioner's favourite may be dismissed by another.

Different opinions on what is the most effective form of acupuncture may seriously affect research: not only is there disagreement on adequate treatment, but there is also considerable uncertainty over what constitutes an ineffective, or sham, control treatment.

As a consequence, the negative results of sham controlled trials are difficult to interpret. Unless we can be sure that the acupuncture was adequate, and the sham was inactive, in that particular trial, it should not be interpreted as dismissing acupuncture for that condition. Some of the trials of the GERAC^{1,2} and ART³ series may be examples of one or other aspects of this problem, and treatment with electro-acupuncture, or sham treatment with blunt needles, may have yielded different results.

This is only one possible interpretation of the results, of course, and this line of reasoning should not be used by acupuncture proponents to explain away all negative results unless it can be supported by evidence. Nevertheless, clinical trials require huge investments of time and effort. They may not be the best way to answer the question of the specific efficacy of acupuncture (the effect beyond placebo) until we are more certain about the physiological effects of the needles.

The heterogeneity of acupuncture approaches has been described as 'the most formidable issue confronting systematic research'.⁴ Different clinical trials use significantly different treatment regimens, giving the impression that details of treatment are irrelevant, and inviting dismissal of the therapy as no more than a placebo. These trials may be scored as 'high quality' by conventional criteria, yet actually be of poor quality if they use an acupuncture protocol that most would view as inadequate.

It is inconceivable that any pharmaceutical company would spend resources on clinical trials of a new drug until they knew the characteristics of the dosage and the patients who were likely to respond. Yet, because acupuncture research has, for the most part, skipped some of the necessary earlier phases of research in which the dose-response relationship is carefully examined,⁵ there is a dearth of data upon which to base decisions about optimal acupuncture protocols.

In this paper, we extend an earlier discussion paper on this subject, to which many authors contributed,⁶ and build on the scant previous literature and attempt to map a way forward.⁷⁻¹⁰

An approach to adequacy of acupuncture

First, we must consider the questions of the rationale behind different approaches to acupuncture, and the individualisation of treatment. We recognise that the effects of acupuncture therapy are complex and due to many components – more than simply the result of needling specific locations. Every treatment involves a therapeutic relationship, and traditional acupuncturists regard the formulation of a diagnosis, provision of lifestyle advice, and sometimes other interventions, as part of 'acupuncture therapy'. These are important effects which are being addressed by some groups.^{11,12} This paper addresses the physical component of treatment: the physiological effects of the acupuncture needles.

Some acupuncturists hold that individualisation of acupuncture treatment enhances its effectiveness. Most would agree that treatment needs to be tailored to each patient's particular symptoms and responsiveness, but many use the term 'individualisation' to include establishing a traditional Chinese medicine (TCM) diagnosis as the basis for choosing acupuncture points. We are not considering traditional diagnosis here, as so far it has little evidence in support.¹³⁻¹⁵

In this paper, we adopt a neurophysiological approach because: it has good support from laboratory evidence,¹⁶ and from reviews;¹⁷ because the principal image of acupuncture therapy is of needle insertion and stimulation (manipulation or electrical stimulation) of needles, and the principal question is about the effectiveness of needles; because needling is the one component of acupuncture that is common to all varieties; and because acupuncture means 'needle puncture'. For all these reasons, exploring the parameters of needling, and the patient's response to it, is a pragmatic choice in establishing the effectiveness of acupuncture, though remaining aware that other components of the therapy may be synergistic.

We therefore suggest a definition of the 'dose' of acupuncture needling (see Box). Paradoxically, the concept of acupuncture dose has to involve both the stimulation given by the needles and the patient's

response. The clinical effect of acupuncture is not determined simply by the amount of needling stimulus, but also by the individual patient's perception, for example of the *de qi* sensation,^{18,19} by cognitive factors such as expectation,²⁰ and (for muscle trigger points) by twitch responses.²¹ These factors have to be taken into account to decide whether or not an individual patient has received an appropriate treatment. A description of the dose that any patient receives is not complete without including these factors.

The dose of acupuncture needling

The physical procedures applied in each session, using one or more needles, taking account of the patient's resulting perception (sensory, affective and cognitive) and other responses (including motor). The dose may be affected by the state of the patient (eg nervous, immune and endocrine systems); different doses may be required for different conditions.

The dose required to treat different health conditions will vary depending on the intended mechanism of the effect, eg whether local, segmental, extrasegmental or central. Some conditions, eg migraine or fibromyalgia, probably require several mechanisms to be activated if treatment is to be effective;²² and some conditions, again including fibromyalgia, may require a different dose according to the degree to which the nervous system is sensitised in a particular patient.²³ The effect of needling will vary at different sites in the body, and,

for simplicity, we shall not consider the site of stimulation in this paper.²⁴

Due to the properties of the nervous system, there are likely to be 'threshold' effects so that the relationship between dose and response is not linear. Also, clinical experience strongly suggests that responders and non-responders exist. This has long been recognised in animals, and may have a genetic basis.¹⁶ We do not suggest that it is easy to untangle these problems: but we do suggest it is urgent and vital to improve the productivity of the whole field of acupuncture research.

Evaluation of the effects of different doses of acupuncture should include diagnosis (eg using International Classification of Diseases ICD), and outcome evaluation should include symptoms and functional changes as well as expectation.

The kinds of components of the needling stimulus that are most likely to be significant are: the depth of insertion (tissue level); the intensity of manual stimulation (ranging from insertion only to intensive manipulation), and the nature of the *de qi* response; the intensity of electrical stimulation; the duration of needling; and treatment repeat intervals. The STRICTA reporting recommendations provide a starting point for treatment protocols for different fundamental approaches or styles of acupuncture.²⁵ A few examples of studies that provide empirical evidence on some of the STRICTA items are listed in Table 1.

More work needs to be done to know which perceptions should be recorded but meanwhile *de qi* sensation and the patient's expectation should certainly be recorded.^{18,20}

Table 1 Criteria for reporting an acupuncture treatment protocol based on STRICTA recommendations

Section	Criterion	Examples of studies
<i>Treatment rationale</i>	Style	Macklin et al ¹⁵ Allen et al ¹⁴ , Itoh et al ¹⁵⁸
<i>Needling details</i>	Points selected	Lundeberg et al ⁵⁹
	Number of points needed	None identified
	Depth of insertion	Ceccherelli et al, ⁶⁰ Pintov et al ⁶¹
	Responses elicited	Lundeberg et al, ⁵⁹ Hui et al ⁶²
	Needle stimulation – method and strength	Ceccherelli et al, ⁶³ Marcus, ⁴⁴ Harris et al, ³⁹ Deluze et al, ⁶⁴ Barlas et al ⁶⁵
	Needle retention time	Lundeberg et al, ⁵⁹ Hansen, ⁶⁶ Leung et al 2008 ⁶⁷
	Needle type	Marcus ⁴⁴
<i>Treatment schedule</i>	Number of treatment sessions	None identified
	Frequency of treatment	Ceccherelli et al, ⁶³ Harris et al ³⁹

References are to some studies using different criteria.

Methods for determining adequate acupuncture needling stimulus

In trying to determine an optimal or adequate dose of acupuncture for any particular condition, we should consider both *clinical opinion* and *empirical evidence*. The opinions of experts, particularly teachers or writers, are widely held in respect, though evidence suggests that it may be difficult for clinicians to separate out the specific from non-specific effects. The usual sequence for discovering an adequate treatment is likely to be clinical observation followed by confirmation of the clinical effect in trials, then further comparative trials to establish the best treatment protocol, which can be fed back into training and practice.

Clinical opinion

The anecdotes that make up clinical opinion can be brought up to the level of reliable evidence in several ways: firstly, by repeated observations of practice of different practitioners. For example, an observational study of acupuncturists in out-patient clinics in Beijing and Wanjing found they used markedly different points for essentially similar patients, which was confirmed in detail in choice of points used for recovery from stroke.²⁶ Secondly, by establishing some kind of *clinical consensus* using methods such as the Delphi method,²⁷ consensus surveys or conference type processes,²⁸⁻³² or a step-wise procedure to develop protocols in a 'treatment manualisation' process, based on a model from psychotherapy.³³ Thirdly, by examining the traditional acupuncture texts,⁸ though the value of this approach may be limited by difficulties of translation.

One research group planning a clinical trial of acupuncture for back pain conducted a survey of 56 practitioners' treatment records;³⁴ they asked seven practitioners to examine a single case of back pain and to detail how they would treat the patient.^{35,36} In fact, they found poor agreement, and in the trial itself practitioners were able to do largely what they wanted.³⁷ It is worth commenting that this disagreement between clinicians on the diagnosis and treatment of back pain is probably universal in all kinds of medicine, complementary and orthodox.³⁸

Empirical evidence

The most reliable method of determining an adequate acupuncture protocol would be by directly comparing

different protocols in patients in a tightly controlled, explanatory trial, ideally in conditions in which one form of acupuncture has already been shown to be effective. The protocols would need to be established using various combinations of clinical consensus and basic research, and so the choice of protocol would vary between different 'schools'.

One group of researchers used this approach for fibromyalgia, and found that relief of symptoms depended neither on the point location nor the manner of stimulation of the needles – though it did depend on how frequently the treatment was given.³⁹ Studies in other conditions may have very different results.

The major problem with direct comparisons is that the differences between protocols may produce only small differences in outcomes, and so need large sample sizes to demonstrate such effects.

Another experimental approach is basic research, which seems to be of two general types. Some studies investigate the mechanisms of acupuncture, eg the intensity of needle stimulation needed to recruit different afferent nerve fibres, usually in animal models.^{16;40-42} This information can be used as a basis for designing protocols. Other studies test a surrogate for a clinical symptom in healthy human volunteers – such as pain threshold changes as a surrogate for treatment of chronic pain.⁴³⁻⁴⁵ Results suggest that stimulation intensity is the single most important determinant of analgesia, and that there is inter-individual variation as to how people respond to this type of stimulation. However, it is not always possible to apply the findings of experiments in healthy volunteers to patients with clinical conditions since our knowledge of the mechanisms of symptoms such as chronic pain, joint stiffness, depression, hot flushes and so on, is incomplete.

An indirect method of using empirical evidence is within a systematic review of the trials on effectiveness, which offers the opportunity to compare the effects of different treatment regimens. In one well known example, Ezzo and colleagues demonstrated that trials using six or more sessions of acupuncture for osteoarthritis of the knee were more likely to be positive than those using fewer than six.⁴⁶

However, conventional statistical analysis of clinical trials considers the average effects over the whole group and so obscures the heterogeneity of treatment effects in individual patients. These could

Table 2 Summary of some approaches to establishing adequate acupuncture

Clinical opinion methods	Applications
Observation of practice	Surveys Reliability assessments
Published protocols	Textbook review Trial protocol review
Consensus methods	Delphi Consensus conference
Combination of above	Manualisation
Empirical evidence methods	
Basic research	Studies of mechanism Clinical surrogates in healthy volunteers
Clinical trials	Direct comparison of protocols
Systematic reviews	Subgroup analysis of different forms of acupuncture Individual patient data meta-analysis

be revealed by the use of individual patient data to allow a much more detailed linking of outcome with the patient's characteristics. The Acupuncture Trialists' Collaboration is an ambitious attempt to determine aspects of acupuncture treatment associated with improved outcomes by conducting individual patient data meta-analysis. At the time of writing, the collaboration has 25 members, and plans to analyse raw data from 24 randomised trials of acupuncture for chronic pain, a total sample of 17,801 patients. The data will be combined into a single database and analysed to determine whether characteristics of acupuncture such as the number of treatment sessions, treatment style or practitioner qualifications affect outcome.

Comparing results of different trials may have limited value, because differences in outcome can arise from a whole range of other factors that may not be known or measurable. For example, treatment variables could not explain the responses in different trials included in a systematic review of acupuncture for knee pain.⁴⁷ Another factor that limits these comparisons is possible 'ceiling' effects of an adequate treatment, or of co-interventions.⁴⁸ Furthermore, there is a question over the validity of drawing conclusions from data compared in ways that were not originally intended.

Evaluating acupuncture in systematic reviews

Lack of knowledge about the minimum criteria for adequate acupuncture could limit the value of systematic reviews, as trials that apply an inadequate treatment will underestimate the possible effects of acupuncture and could lead to false negative results of the review. These studies will also increase heterogeneity making results less reliable. This negative influence would be quite independent of the conventional 'quality' of the study; interestingly, most conventional issues of poor study quality, such as poor randomisation or inadequate concealment, lead to false positive findings.

The influence of inadequate treatment on the results of a review has been elegantly exemplified for TENS.⁴⁹ In the studies which used stimulation that was defined as 'adequate', analgesic consumption was reduced by 36%; in those that did not, the reduction was only 4%.

The first time that the adequacy of acupuncture treatment was considered in a systematic review in acupuncture, as far as we are aware, was in an early series of systematic reviews of acupuncture by a team of Dutch epidemiologists.⁵⁰⁻⁵² As part of the quality assessment, they awarded points for 'good quality of acupuncturist mentioned', presumably looking for items such as length of practical experience and hours of training.

A different approach was used by Linde and colleagues.⁵³ Four experienced acupuncturists were asked to rate the included studies with an overall assessment for 16 characteristics of the acupuncture treatment such as: choice of points; duration, number and frequency of sessions; education and experience of the therapist (Linde, personal communication). Agreement was poor, and some raters refused to score some studies on the grounds that the treatment was only used for an experimental context and was clinically meaningless. Subsequently, an experienced acupuncturist was asked to evaluate the adequacy of the sham acupuncture.⁵⁴ This led to the conclusion that points that were supposed to be 'inactive' according to one study were used in the treatment arms of other studies. In another example, in a review of acupuncture for back pain, experienced acupuncturists, independent of the research team, were asked to provide an overall rating for the adequacy of acupuncture in each study.⁵⁵ More recently, an experienced acupuncturist was asked to

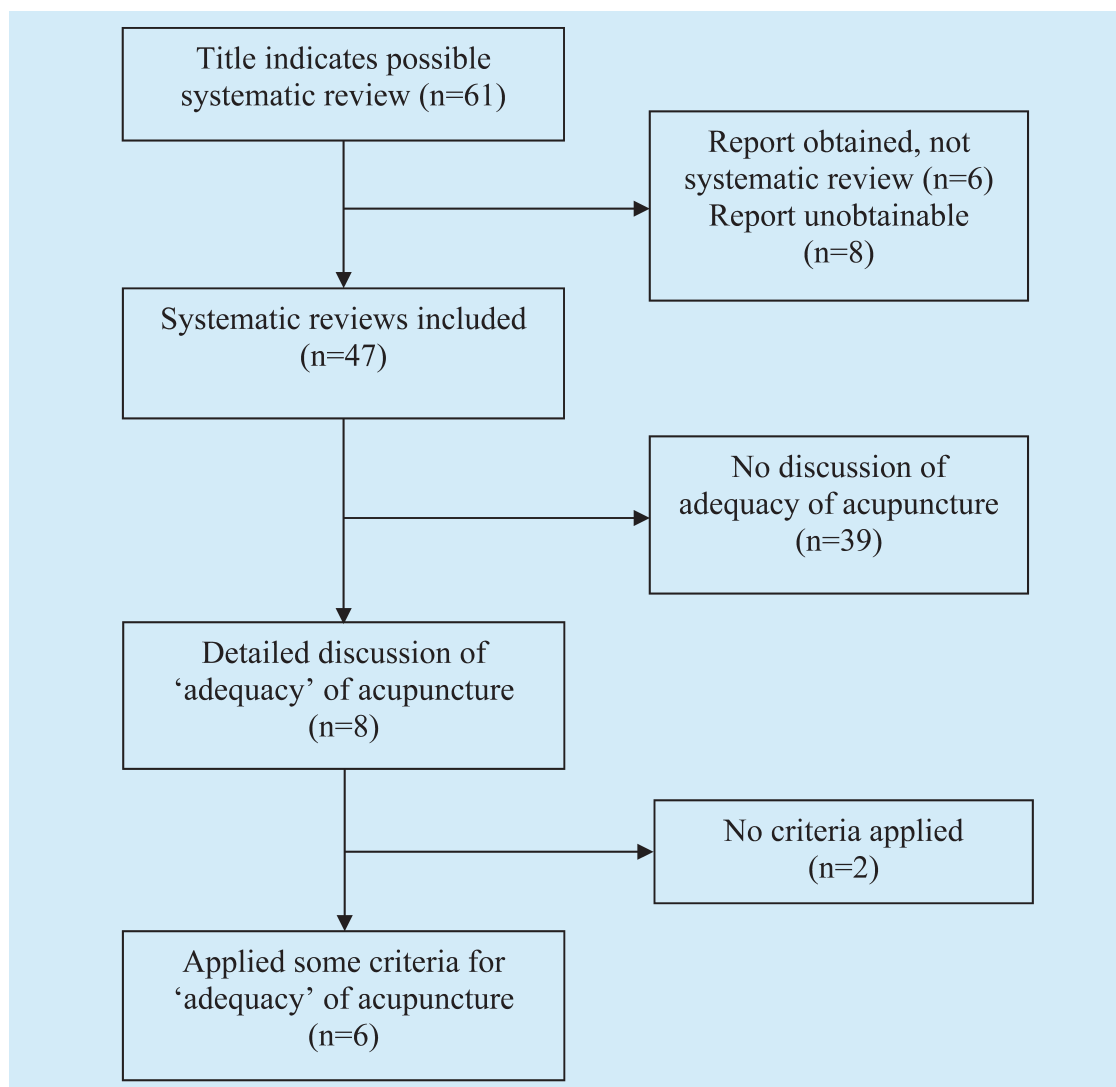


Figure 1 This flow chart shows that only six out of 47 systematic reviews of acupuncture (2000-2007) applied some method to take account of the adequacy of acupuncture treatment in the studies.

rate to what extent he would treat the patients in the way described, and how confident he was that the acupuncture would be successful in treating the particular patients in each of the studies.⁵⁶

Current systematic reviews

In order to find out how recent reviews have addressed the problem of the adequacy of acupuncture, we searched titles and abstracts in PubMed (2000 to August 2007 regarding these as reflecting the current state of the evidence) for systematic reviews of acupuncture in English, excluding studies on safety or cost-effectiveness only.

Out of 47 systematic reviews included, we found only six that considered the question of adequacy of

acupuncture and applied criteria (Table 3). Three approaches were used: an overall statement about the quality of the acupuncturist; a rating or judgement of the acupuncture, sometimes based on stated criteria; and a set of specific objective criteria that could be applied to each study. In the last case, the review excluded from the analyses any studies that did not meet the five criteria, which had derived from an understanding of acupuncture mechanisms and literature, and clinical experience.⁵⁷

“...we defined acupuncture as ‘adequate’ if it consisted of at least six treatments, at least one per week, with at least four points needed for each painful knee for at least 20 minutes, and either needle sensation (*de qi*) achieved in manual acupuncture, or

Table 3 Systematic reviews from PubMed 2000-7 that have stated and applied criteria for the adequacy of acupuncture

Author(s)	Condition	Criteria on adequacy of acupuncture applied
D'Alborto A 2004 ⁶⁸	Cocaine/crack abuse	'Good quality of acupuncturist mentioned'. Application: quality scale points awarded (5/100)
Manheimer E et al 2005 ⁶⁹	Low back pain	≥6 sessions vs <6; individualised vs formulaic treatment, number of needles, obtaining <i>de qi</i> , number of treatments, length of each session, number of sessions per week, and manual vs electrical stimulation. Application: subgroup analyses
Furlan AD et al 2005 ⁷⁰	Low back pain	Consensus opinion of 3 author panel based on: 1) Choice of acupoints, 2) Number of sessions, 3) Needling technique and 4) Acupuncturist experience. Application: all trials rated 'adequate' and included
Ezzo JM et al 2006 ⁷¹	Chemotherapy-induced nausea or vomiting	Descriptions of acupuncture-point stimulation rated by 2 authors (adequate, not adequate, or not enough information). Application: narrative
Manheimer E et al 2007 ⁷²	Osteoarthritis of the knee	Rating of adequacy by 2 acupuncturists: choice of points, number of sessions, needling technique, and experience of practitioner. Application: subgroup analysis
White A et al 2007 ⁵⁷	Chronic knee pain	≥6 treatments, at least one/wk, ≥4 points, ≥20 minutes each session, either <i>de qi</i> or ≥ minimal sensation (EA). Application: inclusion criterion for analysis

electrical stimulation of sufficient intensity to produce more than minimal sensation."

From these approaches, the 'core' components of an adequate protocol seem to be attention to: the number of needles used; the needling technique; specific elicitation of a needling sensation; the number of treatment sessions; and the experience of the acupuncturist.

Conclusions

The lack of agreement on what is 'adequate' acupuncture is an obstacle to good patient care, and to research into acupuncture. While the effect of acupuncture therapy clearly involves much more than needle insertion and manipulation or electrical stimulation, nevertheless there is a strong argument for elucidating the role of the needling procedures and the patient's immediate response to them, because this is the central feature of the therapy common to all approaches. If the specific needle stimulation is not the critical factor in treatment, then future research should explore other aspects of acupuncture.

There is an urgent need for studies to guide decisions about what is an 'adequate' dose of acupuncture for different conditions. One approach is direct comparison of treatment protocols in highly controlled circumstances and homogeneous groups of patients. It is also readily acceptable ethically, since all patients receive a treatment that could be considered active. The design could effectively be

a 'dose finding study' to explore whether there is evidence of a dose-response relationship. A second approach, used in parallel, could be to combine individual patient data from high quality trials to provide sufficiently large datasets to examine the effects of different components of the acupuncture protocol.

We recommend that future systematic reviews of the effectiveness of acupuncture should, at the very least, provide a subgroup analysis including only the studies that meet criteria for 'adequate' acupuncture, or consider limiting the included studies only to those which have used a protocol that meets the adequacy criteria.

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Reference List

1. Scharf HP, Mansmann U, Streitberger K, Witte S, Kramer J, Maier C *et al.* Acupuncture and knee osteoarthritis - a three-armed randomized trial. *Ann Intern Med* 2006;145(1):12-20.
2. Haake M, Muller HH, Schade-Brittinger C, Basler HD, Schafer H, Maier C *et al.* German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med* 2007;167(17):1892-8.
3. Brinkhaus B, Witt CM, Jena S, Linde K, Streng A, Wagenpfeil S *et al.* Acupuncture in patients with chronic low back pain: a randomized controlled trial. *Arch Intern Med* 2006;166(4):450-7.
4. Leo RJ, Ligot JS, Jr. A systematic review of randomized controlled trials of acupuncture in the treatment of depression. *J Affect Disord* 2007;97(1-3):13-22.
5. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D *et al.* Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000;321(7262):694-6.
6. White AR, Filshie J, Cummings M. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complement Ther Med* 2001;9(4):237-45.
7. Vincent CA, Richardson PH, Black JJ, Pither CE. The significance of needle placement site in acupuncture. *J Psychosom Res* 1989;33(4):489-96.
8. Birch S. Issues to consider in determining an adequate treatment in a clinical trial of acupuncture. *Complement Ther Med* 1997;5:8-12.
9. White AR. Acupuncture research methodology. In: Lewith G, Jonas WB, Walach H, editors. *Clinical Research in Complementary Therapies: Principles, Problems and Solutions*. Edinburgh: Churchill Livingstone; 2001. p. 307-23.
10. Sherman KJ, Cherkin DC. Developing methods for acupuncture research: rationale for and design of a pilot study evaluating the efficacy of acupuncture for chronic low back pain. *Altern Ther Health Med* 2003;9(5):54-60.
11. Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ* 2005;330(7501):1202-5.
12. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE *et al.* Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 2008;336(7651):999-1003.
13. Ghia JN, Mao W, Toomey TC, Gregg JM. Acupuncture and chronic pain mechanisms. *Pain* 1976;2(3):285-99.
14. Allen JJ, Schnyer RN, Chambers AS, Hitt SK, Moreno FA, Manber R. Acupuncture for depression: a randomized controlled trial. *J Clin Psychiatry* 2006;67(11):1665-73.
15. Macklin EA, Wayne PM, Kalish LA, Valaskatgis P, Thompson J, Pian-Smith MC *et al.* Stop Hypertension with the Acupuncture Research Program (SHARP): results of a randomized, controlled clinical trial. *Hypertension* 2006;48(5):838-45.
16. Han JS, Terenius L. Neurochemical basis of acupuncture analgesia. *Annu Rev Pharmacol Toxicol* 1982;22:193-220.
17. Moffet HH. How might acupuncture work? A systematic review of physiologic rationales from clinical trials. *BMC Complement Altern Med* 2006;6:25.
18. Kong J, Gollub R, Huang T, Polich G, Napadow V, Hui K *et al.* Acupuncture de qi, from qualitative history to quantitative measurement. *J Altern Complement Med* 2007;13(10):1059-70.
19. Hui KK, Nixon EE, Vangel MG, Liu J, Marina O, Napadow V *et al.* Characterization of the "deqi" response in acupuncture. *BMC Complement Altern Med* 2007;7:33.
20. Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B *et al.* The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* 2007;128(3):264-71.
21. Hong CZ. Lidocaine injection versus dry needling to myofascial trigger point. The importance of the local twitch response. *Am J Phys Med Rehabil* 1994;73(4):256-63.
22. Filshie J, White AR. *Medical Acupuncture: a Western scientific approach*. Edinburgh: Churchill Livingstone; 1998.
23. Lundeberg T, Lund I. Did 'The Princess on the Pea' suffer from fibromyalgia syndrome? The influence on sleep and the effects of acupuncture. *Acupunct Med* 2007;25(4):184-97.
24. Han JS. Physiology of acupuncture: review of thirty years of research. *J Altern Complement Med* 1997;3, Supp 1:S101-S108.
25. MacPherson H, White A, Cummings M, Jobst K, Rose K, Niemtow R. Standards for reporting interventions in controlled trials of acupuncture: The STRICTA recommendations. S'Tandards for Reporting Interventions in Controlled Trails of Acupuncture. *Acupunct Med* 2002;20(1):22-5 (also at <http://www.medical-acupuncture.co.uk/journal/trials.shtml>).
26. Napadow V, Liu J, Kaptchuk TJ. A systematic study of acupuncture practice: acupoint usage in an outpatient setting in Beijing, China. *Complement Ther Med* 2004;12(4):209-16.
27. Webster-Harrison P, White A, Rae J. Acupuncture for tennis elbow: an E-mail consensus study to define a standardised treatment in a GPs' surgery. *Acupunct Med* 2002;20(4):181-5.
28. MacPherson H, Schroer S. Acupuncture as a complex intervention for depression: A consensus method to develop a standardised treatment protocol for a randomised controlled trial. *Complement Ther Med* 2007;15(2):92-100.
29. Foster N, Barlas P, Daniels J, Dziedzic K, Gray R. Use of acupuncture by physiotherapists in the treatment of osteoarthritis of the knee: current trends inform a clinical trial. Birmingham, UK: Proceedings of the Chartered Society of Physiotherapists Congress, Oct; 1999. p. 27.
30. Witt C, Brinkhaus B, Jena S, Linde K, Streng A, Wagenpfeil S *et al.* Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005;366(9480):136-43.
31. Molsberger AF, Boewing G, Diener HC, Endres HG, Kraehmer N, Kronfeld K *et al.* Designing an acupuncture study: the nationwide, randomized, controlled, German acupuncture trials on migraine and tension-type headache. *J Altern Complement Med* 2006;12(3):237-45.
32. Molsberger AF, Streitberger K, Kraemer J, Brittinger CS, Witte S, Boewing G *et al.* Designing an acupuncture study: II. The nationwide, randomized, controlled German acupuncture trials on low-back pain and gonarthrosis. *J Altern Complement Med* 2006;12(8):733-42.
33. Schnyer RN, Allen JJ. Bridging the gap in complementary and alternative medicine research: manualization as a means of promoting standardization and flexibility of treatment in clinical trials of acupuncture. *J Altern Complement Med* 2002;8(5):623-34.
34. Sherman KJ, Cherkin DC, Hogeboom CJ. The diagnosis and treatment of patients with chronic low-back pain by traditional Chinese medical acupuncturists. *J Altern Complement Med* 2001;7(6):641-50.

35. Kalaoukalani D, Sherman KJ, Cherkin DC. Acupuncture for chronic low back pain: diagnosis and treatment patterns among acupuncturists evaluating the same patient. *South Med J* 2001;94(5):486-92.
36. Hogeboom CJ, Sherman KJ, Cherkin DC. Variation in diagnosis and treatment of chronic low back pain by traditional Chinese medicine acupuncturists. *Complement Ther Med* 2001;9(3):154-66.
37. Cherkin DC, Eisenberg D, Sherman KJ, Barlow W, Kaptchuk TJ, Street J ^{et al.}. Randomized trial comparing traditional Chinese medical acupuncture, therapeutic massage, and self-care education for chronic low back pain. *Arch Intern Med* 2001;161(8):1081-8.
38. Foster NE, Pincus T, Underwood M, Vogel S, Breen A, Harding G. Treatment and the process of care in musculoskeletal conditions. A multidisciplinary perspective and integration. *Orthop Clin North Am* 2003;34(2):239-44.
39. Harris RE, Tian X, Williams DA, Tian TX, Cupps TR, Petzke F *et al.* Treatment of fibromyalgia with formula acupuncture: investigation of needle placement, needle stimulation, and treatment frequency. *J Altern Complement Med* 2005;11(4):663-71.
40. Backer M, Hammes MG, Valet M, Deppe M, Conrad B, Tolle TR *et al.* Different modes of manual acupuncture stimulation differentially modulate cerebral blood flow velocity, arterial blood pressure and heart rate in human subjects. *Neurosci Lett* 2002;333(3):203-6.
41. Kagitani F, Uchida S, Hotta H, Aikawa Y. Manual acupuncture needle stimulation of the rat hindlimb activates groups I, II, III and IV single afferent nerve fibers in the dorsal spinal roots. *Jpn J Physiol* 2005;55(3):149-55.
42. Sato A, Sato Y, Schmidt RF. *The Impact of Somatosensory Input on Autonomic Functions*. Heidelberg: Springer-Verlag; 1997.
43. Barlas P, Lowe AS, Walsh DM, Baxter GD, Allen JM. Effect of acupuncture upon experimentally induced ischemic pain: a sham-controlled single-blind study [In Process Citation]. *Clin J Pain* 2000;16(3):255-64.
44. Marcus P. Towards a dose of acupuncture. *Acupunct Med* 1994;12(2):78-82.
45. Zaslawski CJ, Cobbin D, Lidums E, Petocz P. The impact of site specificity and needle manipulation on changes to pain pressure threshold following manual acupuncture: a controlled study. *Complement Ther Med* 2003;11(1):11-21.
46. Ezzo J, Berman B, Hadhazy V, Jadad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? A systematic review. *Pain* 2000;86(3):217-25.
47. Vas J, White A. Evidence from RCTs on optimal acupuncture treatment for knee osteoarthritis—an exploratory review. *Acupunct Med* 2007;25(1-2):29-35.
48. Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E *et al.* Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. *BMJ* 2007;335(7617):436.
49. Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain* 2003;7(2):181-8.
50. Ter Riet G, Kleijnen J, Knipschild P. Acupuncture and chronic pain: a criteria-based meta-analysis. *J Clin Epidemiol* 1990;43(11):1191-9.
51. Ter Riet G, Kleijnen J, Knipschild P. A meta-analysis of studies into the effect of acupuncture on addiction. *Br J Gen Pract* 1990;40(338):379-82.
52. Kleijnen J, Ter Riet G, Knipschild P. Acupuncture and asthma: a review of controlled trials. *Thorax* 1991;46(11):799-802.
53. Linde K, Worku F, Stör W, Wiesner-Zechmeister M, Pothmann R, Weinschütz T *et al.* Randomised clinical trials of acupuncture for asthma: a systematic review. *Forschende Komplementärmedizin* 1996;3:148-55.
54. Linde K, Jobst K, Panton J. Acupuncture for chronic asthma (Cochrane Review). *The Cochrane Library, Issue 1*, 2000. Oxford: Update Software; 2000.
55. White AR, Ernst E. A trial method for assessing the adequacy of acupuncture treatments. *Alternative Therapies in Health and Medicine* 1998;4(6):66-71.
56. Melchart D, Linde K, Fischer P, Berman B, White A, Vickers A *et al.* Acupuncture for idiopathic headache. *Cochrane Database Syst Rev* 2001;(1):CD001218.
57. White A, Foster NE, Cummings M, Barlas P. Acupuncture treatment for chronic knee pain: a systematic review. *Rheumatology (Oxford)* 2007;46(3):384-90.
58. Itoh K, Hirota S, Katsumi Y, Ochi H, Kitakoji H. Trigger point acupuncture for treatment of knee osteoarthritis - a preliminary RCT for a pragmatic trial. *Acupunct Med* 2008;26(1):17-26.
59. Lundeberg T, Hurtig T, Lundeberg S, Thomas M. Long-term results of acupuncture in chronic head and neck pain. *The Pain Clinic* 1988;2:15-31.
60. Ceccherelli F, Bordin M, Gagliardi G, Caravello M. Comparison between superficial and deep acupuncture in the treatment of the shoulder's myofascial pain: a randomized and controlled study. *Acupunct Electrother Res* 2001;26(4):229-38.
61. Pintov S, Lahat E, Alstein M, Vogel Z, Barg J. Acupuncture and the opioid system: implications in management of migraine. *Paediatric Neurology* 1997;17(2):129-33.
62. Hui KKS, Liu J, Marina O, Napadow V, Haselgrove C, Kwong KK *et al.* The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. *Neuroimage* 2005;27(3):479-96.
63. Ceccherelli F, Gagliardi G, Rossato M, Giron G. Variables of stimulation and placebo in acupuncture reflexotherapy. *J Altern Complement Med* 2000;6(3):275-9.
64. Deluze C, Bosia L, Zirbs A, Chantraine A, Vischer TL. Electroacupuncture in fibromyalgia: results of a controlled trial. *BMJ* 1992;305(6864):1249-52.
65. Barlas P, Lowe AS, Walsh DM, Baxter GD, Allen JM. Effect of acupuncture upon experimentally induced ischemic pain: a sham-controlled single-blind study. *Clin J Pain* 2000;16(3):255-64.
66. Hansen JA. A comparative study of two methods of acupuncture treatment for neck and shoulder pain. *Acupunct Med* 1997;15(2):71-3.
67. Leung AY, Kim SJ, Schulteis G, Yaksh T. The effect of acupuncture duration on analgesia and peripheral sensory thresholds. *BMC Complement Altern Med* 2008;8:18.
68. D'Albarto A. Auricular acupuncture in the treatment of cocaine/crack abuse: a review of the efficacy, the use of the National Acupuncture Detoxification Association protocol, and the selection of sham points. *J Altern Complement Med* 2004;10(6):985-1000.

69. Manheimer E, White A, Berman B, Forys K, Ernst E. Meta-analysis: acupuncture for low back pain. *Ann Intern Med* 2005;142(8):651-63.
70. Furlan AD, van Tulder MW, Cherkin DC, Tsukayama H, Lao L, Koes BW *et al.* Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev* 2005; (1):CD001351.
71. Ezzo JM, Richardson MA, Vickers A, Allen C, Dibble SL, Issell BF *et al.* Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database Syst Rev* 2006;2:CD002285.
72. Manheimer E, Linde K, Lao L, Bouter LM, Berman BM. Meta-analysis: acupuncture for osteoarthritis of the knee. *Ann Intern Med* 2007;146(12):868-77.