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Original Paper

Testing Complementary and Alternative Therapies within a Research Protocol

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In patients with cancer, the demand for complementary and alternative medicine (CAM) is considerable. Unfortunately, however, for many of these interventions there is a lack of evidence for efficacy, effectiveness and safety in patients with cancer. This review focuses on the prospective, randomised, controlled trial (RCT) as a tool for evaluating CAM. Although a number of difficulties and limitations are acknowledged, the RCT will continue to be the gold standard for evaluating the efficacy, effectiveness and safety of CAM. Developments in clinical trial methodology and in psychosocial oncology have made it more appropriate and feasible to evaluate CAM using RCT methodology. Two different kinds of RCTs are now accepted as valid, namely explanatory and pragmatic trials. The latter does not necessarily require that the patient or the therapist is 'blind' to the treatment being given. Furthermore, pragmatic trials can be designed to take patient preferences into account. A number of practical issues are discussed, including the choice of comparator or control interventions, ways of assessing the effects of individual differences, minimising therapist variability, the problem of finding acceptable inclusion–exclusion criteria and the assessment of treatment outcome. A number of randomised, controlled trials have demonstrated the efficacy, effectiveness and safety of various complementary and alternative interventions (the Cochrane Data Base has now established a CAM field). The publication of positive results from randomised trials of complementary interventions that have not yet been studied using this methodology would do a great deal to alleviate the scepticism of conventional practitioners towards these types of CAM and would facilitate further the integration of complementary and conventional interventions. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

UNDOUBTEDLY, IN recent years, there has been a substantial burgeoning in the popularity of complementary and alternative medicine (CAM). In the U.K., it has been estimated recently that: 75% of the public support access to CAM via the National Health Service; 40% of General Practice partnerships in England actually provide access for National Health Service patients; each year 4–5 million people consult a CAM practitioner, and, at some time, 14–20% of all patients with a chronic disease consult a CAM practitioner [1]. The popularity of, and demand for, CAM is not restricted to Europe. In the U.S.A., $15 billion per annum is spent on CAM [2] and, in Australia, approximately 50% of the population spend cumulatively over Australian $1 billion per annum on these treatments [3].

More specifically, in patients with cancer, the demand for CAM is considerable [4]. Estimates in the U.K. have ranged from 32% in patients undergoing radiotherapy [5] to 16% in unselected oncology patients [6]. In the latter study, the most popular modalities were healing, relaxation, visualisation, diets, homeopathy, vitamins, herbalism and the Bristol approach. In an early, pioneering study in the U.S.A., as many as 13% of patients receiving treatment in a conventional cancer centre had used, or were currently using, complementary medicine [7].

The definition of CAM has been the subject of considerable discussion and debate [8–10]. There is agreement that CAM includes a very broad spectrum of therapies, ranging

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from the manipulative skills of osteopathy and chiropractice to various forms of self-care [1]. For the purposes of this paper, the definition adopted by the Cochrane collaboration will be used: ''complementary medicine is diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy, or by diversifying the conceptual frameworks of medicine'' [11]. In practical terms, this means that CAM includes techniques such as acupuncture, aromatherapy, reflexology, relaxation therapy, hypnotherapy, naturopathy, special diets and homeopathy.

As health services become increasingly driven by evidence-based medicine, there is an urgent need to evaluate the efficacy (specific effects), effectiveness (benefits in practice) and safety (morbidity and mortality) of the various complementary interventions. It cannot be assumed that complementary and alternative interventions (CAIs) are all harmless, effective, and cost-effective. For example, adverse effects have been reported for acupuncture [12] and for various psychotherapeutic interventions [13, 14]. The need for research was highlighted when, in 1992, the Congress of the U.S.A. legislated that the National Institute of Health create an Office of Alternative Medicine (OAM) to co-ordinate and conduct research in complementary and alternative medicine.

Although qualitative methods, single case studies, observational studies and case–control studies can be of value in defining research questions, providing some information on efficacy, and in identifying relevant outcome parameters, these methods have important inherent and/or practical limitations in establishing a causal relationship between a treatment and its effects [14–16]. Moreover, the results of such research are likely to have a limited influence on conventional 'evidence-based' therapeutic practice. Although it has been severely criticised [17–21], the randomised controlled trial (RCT) remains the gold standard for evaluating new treatments in medicine. Despite its limitations and problems, if CAIs are to be accepted by conventional practitioners, they will need to be evaluated using the RCT and the results published in peer-reviewed journals held in esteem by scientists and conventional practitioners. A number of prospective randomised studies demonstrating the effectiveness and efficacy of various complementary interventions have already been published, for example, psychosocial interventions for patients with cancer [22], and these trials appear to have had a significant influence on attitudes towards the management of patients with cancer [23].

The purpose of this paper, therefore, is to review the prospective, randomised, controlled trial as a way of evaluating efficacy, effectiveness and safety with particular reference to CAIs. For more general reviews of clinical trial methodology, the reader is referred to Spilker [24], Pocock [25] and Altmann [26].

EXPLANATORY VERSUS PRAGMATIC TRIALS

Essentially there are two types of clinical trial [27]. Explanatory clinical trials resemble controlled, laboratory experiments where the goal is to understand the cause of a phenomenon. For example, it was recently shown in a large prospective, randomised trial of women with breast cancer that relaxation therapy and guided imagery (visualisation of host defences destroying the tumour) resulted in a number of significant alterations in host defences, including enhanced lymphokine activated killer cell activity, an increase in the number and percentage of activated T cells ($CD25^+$ cells) and a reduction in circulating tumour necrosis factor-alpha [28]. Care had been taken to ensure that the amount and quality of the information and support given to the patients receiving the experimental intervention and the control patients was the same. The differences between the groups, therefore, is likely to reflect a genuine, specific effect of the intervention rather than 'non-specific' or 'placebo' effects.

Another example concerns the effect of belief on the perception of odour pleasantness. Knasko and Gilbert [29] told subjects that the water sprayed before them was pleasantly scented, unpleasantly scented or unscented. The results suggested that hedonic perception of odour is highly suggestible. As Martin [30] pointed out, this finding poses a problem for aromatherapy. What produces the change in aromatherapy? Is it the psychopharmacological effects of the odour, the individual's cognitions about the odour, or a combination of these? Explanatory trials can elucidate ambiguities such as this.

In contrast, a pragmatic trial involves carrying out a comparison under everyday conditions with a view to aiding clinical decision making in future. In this situation, provided that the criteria are clearly and reliably specified in the protocol (or in a separate treatment manual), it is possible to tailor the treatment to the individual patient. For some types of CAM that emphasise the 'holistic' approach, this is a very important consideration.

TYPES OF RANDOMISATION AND PATIENT PREFERENCE

Classically, patients are randomised to treatments. They have no choice whatsoever as to the treatment they receive. Apart from having a possible adverse effect on trial recruitment, where patients would normally be given a choice of treatment, classical randomisation may preclude evaluating certain treatments under everyday conditions. Many CAM practitioners emphasise the need for a genuinely collaborative approach to clinical decision making.

Zelen [31] put forward a possible solution to this difficulty. Each patient is randomised to one of two groups: a 'do not seek consent group' who receive standard treatment (which they would have received if they were not part of the study) or a 'seek consent group' who are asked if they would be willing to receive the experimental treatment. (Alternatively, this latter group may be asked which treatment they would prefer.) Some of the patients in the 'seek consent group' may decline the new treatment in which case they will receive the standard treatment. The assumption (with which all Ethics Committees may not agree) is that the consent of patients need only be sought if they are randomised to the 'seek consent group' as the other patients will receive the treatment they would have received if they were not part of the trial. By comparing the results of the 'do not seek consent group' with the 'seek consent group' (regardless of the treatment they received), the policy of offering patients a choice of the new treatment is compared with the policy of giving everyone the standard treatment.

An alternative design, the partially randomised patient centred trial, has been suggested by Brewin and Bradley [32] as a way of evaluating interventions that require the active participation of the patient or where patients have strong treatment preferences. Patients are first of all asked if they have a treatment preference and, if so, they are given this

treatment. The remainder are then randomised. The main limitations with this design are that patients who agree to be randomised may not be typical and, in the case of CAIs in cancer, the vast majority may express a preference leading to a difficulty recruiting enough patients willing to be randomised. However, it is clear that there are potential ways of incorporating patient preference into the trial design.

BLINDING

Classically, in medicine, RCTs are conducted 'double-blind' by which it is meant that neither the doctor nor the patient knows which treatment a given individual is receiving (or 'triple-blind' where, in addition, an independent assessor does not know treatment allocation). This is primarily to ensure that data collected by the physician or assessor are unbiased and that the attitude of patients to the treatment being assessed or to the comparator treatment (e.g. placebo or 'standard treatment') will not influence their response to treatment.

In drug trials, it is usually possible to produce matching placebos or comparator preparations, thereby preserving the blind. Unfortunately, in the case of CAIs, it is often impossible to maintain the double-blind. For example, a reflexologist or aromatherapist knows what treatment he/she is administering. Usually, however, a CAI can be given 'single-blind', that is the therapist, but not the patient, knows if the CAI is, for example, 'genuine' reflexology or a sham (control) procedure.

Where double-blinding is impossible, the best that can be achieved is to ensure that the therapist does not assess the outcome of treatment. This should be done by a third party who, like the patient, is blind to the actual intervention received. Care has to be taken to ensure that the patient does not give the assessor details of the treatment that might unblind the assessor. Often the problem is no worse than in 'double-blind' trials where the patient's reporting of side-effects potentially jeopardises the blind. The inclusion of appropriate self-report inventories to assess outcome is one approach to solving this problem (ideally, the person who administers and scores the tests should also be blind to the treatment received).

CHOICE OF CONTROL OR COMPARATOR INTERVENTION

The choice of an appropriate control or comparator intervention can be problematic in CAM trials. If the trial is intended to provide evidence of a specific effect of the CAI (for example, the effects on lymphocyte response to polyclonal mitogens of visualising host defences attacking cancer cells), it is important that the comparator is as similar as possible to the CAI. Factors that should be standardised as far as possible include duration, frequency and number of sessions, credibility of the treatment to the patient (and, if possible to the therapist), amount and content of conversation, and the physical situation in which the treatments are administered. In the case of reflexology, for example, the control procedure might be the use of theoretically inappropriate pressure points on the foot or, alternatively, scalp massage. As an illustration, Oleson and Flocco [33] randomly assigned 35 women with premenstrual syndrome to genuine reflexology or to placebo reflexology (stimulation of zones considered irrelevant to the symptoms). Patients received eight weekly sessions lasting 30 min. Women receiving true reflexology reported significantly fewer physical and psychological symptoms during treatment and at follow-up.

However, if the aim of the trial is to compare a CAI with an alternative, established treatment (such as medication), the treatment will not be blind to the therapist or the patient. Comparison of the outcome measures at the end of the study will yield information about the relative effectiveness and safety of the two procedures, although the reason for any differences may not be apparent as the treatments will have differed in a number of ways that might have affected the outcome. It should be noted, however, that this limitation is not confined to evaluations of CAM: the same situation, in principle, would arise if a surgical and medical procedure were being compared.

Baseline assessments that might shed light on between-treatment differences in outcome can be used. For example, if the extent to which patients believed each of the treatments to be effective was considered important, patients could be given detailed information about the treatments prior to randomisation and their expectations of effectiveness of each treatment assessed, for example, by means of visual analogue or other scales.

MINIMISING THERAPIST VARIABILITY

In the literature on psychotherapy, a number of studies have shown that the experience of the therapist is related to the outcome of treatment [34]. It is essential that therapists have had appropriate training in the particular CAI under investigation. There is increasing interest in defining and monitoring standards of training and practice [1].

In addition, it is crucial that the treatment is delivered according to the agreed protocol. Usually, a treatment manual detailing the precise procedures to be followed should be available. Moreover, it may be appropriate to record sessions on audio-tape, or video-tape. These recordings can then be sampled by an independent researcher to check adherence to the treatment protocols and to assess the extent to which other factors, for example the amount and content of discussion between the therapist and patient, are similar across the treatment arms.

If possible, it may be helpful to employ more than one therapist. Each should treat similar numbers of patients in the treatment arms to control for therapist variability: some people are more helpful than others. If numbers permit, the results of the two therapists can be compared. If only one therapist is employed, the extent to which the results can be generalised will be limited.

ASSESSING THE EFFECTS OF INDIVIDUAL DIFFERENCES

The effects of an intervention may be moderated by psychological, as well as clinical, variables. For example, the frequency with which women with locally advanced breast cancer practice progressive muscular relaxation, cue controlled relaxation and guided imagery is negatively correlated with their scores on the neuroticism and psychoticism scales of the Eysenck Personality Questionnaire [35, 36]. Moreover, it appears that response to chemotherapy may be predicted by quality of life and other psychosocial parameters [37–39]. There may be merit, therefore, in carrying out a baseline assessment of various psychological characteristics, such as mood [40], personality [35], coping style [41] and health

locus of control (the extent to which individuals believe they are responsible for their own health) [42].

In addition to their subsequent use as prognostic factors, these measurements can be used to check that randomisation, as intended, has produced comparable groups: otherwise statistical adjustment can be carried out (e.g. analysis of covariance).

INCLUSION–EXCLUSION CRITERIA

As they are based on different approaches to understanding health and disease, in some cases different diagnostic criteria are used in CAM and conventional medicine. Where two or more CAIs are being compared, it may be possible to define rigorous inclusion and exclusion criteria appropriate to the interventions, thereby achieving optimally homogeneous patient samples and maximum statistical power. The key requirement is that the criteria can be assessed reliably. Moreover, as Ernst and colleagues [43] point out, when CAIs and conventional treatments are being compared, it may be possible to combine orthodox and unorthodox inclusion and exclusion criteria.

EVALUATING THE OUTCOME

A related issue arises in the assessment of outcome. In some forms of CAM, traditional outcome criteria such as symptom relief, cure or survival may not be appropriate. Rather, they would wish to evaluate outcome in terms of alterations in energy balance, healing, ability to cope with the problem, and so on. However, the development of psychosocial oncology has resulted in the development and validation of a range of measures applicable to conventional medicine and CAM, including measures of quality of life, mood, symptoms, pain, patient preference and patient satisfaction [44, 45].

CONCLUSIONS

Although a number of difficulties and limitations are acknowledged, we conclude that the RCT will continue to be the gold standard for evaluating the efficacy, effectiveness and safety of CAM. A number of developments in clinical trial methodology and in psychosocial oncology have made it more appropriate and feasible to evaluate CAM using RCT methodology. Two different kinds of RCTs are now accepted as valid, namely explanatory and pragmatic trials. The latter does not necessarily require the patient or the therapist to be 'blind' to the treatment being given. Furthermore, pragmatic trials can be designed to take patient preference into account.

A number of randomised, controlled trials have demonstrated the efficacy, effectiveness and safety of various complementary and alternative interventions in cancer management [46–51] and the Cochrane Data Base has now established a CAM field. The publication of positive results from randomised trials of complementary interventions that have not yet been studied using this methodology would do a great deal to alleviate the scepticism of conventional practitioners towards these types of CAM and would facilitate further the integration of complementary and conventional interventions.

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