Acquisition, Distribution and Perspectives of Healthcare Information in Complementary and Alternative Medicines (CAM)

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PhD by publication

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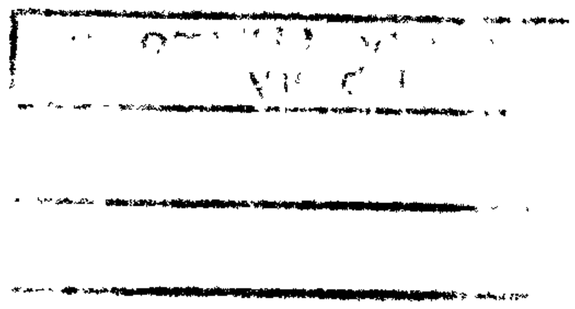
United Kingdom

May 2006

List of contents



Declaration

From April 2001 until September 2005 I worked as a Pilkington research fellow at the Department of Complementary Medicine, University of Exeter, which in 2002 was integrated as a unit of the Peninsula Medical School. All the publications presented here have been carried out during my time of employment in this post at the Complementary Medicine Unit of the Peninsula Medical School in Exeter, United Kingdom.

During the first few months of my research post in 2001 I recognized the importance of the Internet as a tool to obtain healthcare information. Under the supervision of Professor Edzard Ernst, director of CAM, I carried out five **Internet surveys**, of which I collected and summarized the data and drafted the first version of the manuscripts, which were then finalized by Professor Ernst's comments:

* Health risks over the Internet: advice offered by 'medical herbalists' to a pregnant woman.
* Reflexologists' responses to a patient with abdominal pain - a survey on Internet advice.
* Internet advice by acupuncturists - a risk factor for cardiovascular patients?
* Are asthma sufferers at risk when consulting chiropractors over the Internet?
* Aspects of MMR / MMR vaccination advice over the Internet.

In the years 2002 - 2005 I co-authored **systematic reviews**, which aimed at assessing the efficacy and safety of various CAM for specific health conditions. This co-authorship involved acting as a second, independent data extractor and working on finalizing the manuscript:

* Mistletoe for cancer? A systematic review of randomized clinical trials.

* Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: a systematic review.

* A systematic review of guided imagery as an adjuvant cancer therapy.

* Acupuncture for the relief of cancer-related pain - a systematic review.

* Ukrain - a new cancer cure? A systematic review of randomized clinical trials.

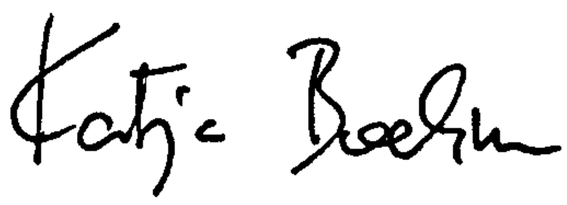
One systematic review I carried out as a first author, which meant I was first data extractor, summarized the data and drafted the first version of the manuscript. This project was carried out in 2002 and publication followed in 2004. Professor Ernst was the second author and thus second, independent data extractor. He also helped finalize the manuscript by commenting on it:

* Music therapies for patients with cardiovascular diseases - a systematic review.

Finally, I was lead researcher in an **international, multischool survey** assessing medical students' attitudes toward the concept of 'holism'. I conceptualized the project in that I identified a group of international collaborators, corresponded with the original

author of the instrument (which we then modified and validated), collected and entered data for one of the participating schools and drafted the first manuscript. Planning of this project began in 2001 and its finalization lasted 4 years; ending with its publication in 2005:

* Multischool, international survey of medical students' attitudes toward holism.



Abstract

Katja Boehm

Acquisition, Distribution and Perspectives of Healthcare Information in Complementary and Alternative Medicines (CAM)

There is an underlying need to gather information for a better understanding of the mechanisms of action, safety, efficacy and cost-effectiveness of CAM. Once this information has been collected, the research needs to be distributed amongst healthcare professionals, the public and governing bodies.

In my work, I looked at the range of German and UK general practitioners' attitudes toward CAM and medical students' CAM attitudes in the UK, USA, Canada, New Zealand and Hong Kong. GPs' CAM attitudes did not differ across countries but a lack of information regarding safety and efficacy, as well as CAM training opportunities were criticized. CAM education was found to vary across countries due to different curricula and personal CAM use was a better predictor of CAM attitudes than was CAM exposure in the medical schools' curricula.

I furthermore collected information on how CAM practitioners respond to specific patient and researcher health queries via e-mail. Medical herbalists, chiropractors, reflexologists, acupuncturists and homeopaths were contacted. It was found that response rates to a fictitious patient were significantly higher than those given to a

researcher. Some of the advice given online was interpreted as misleading or dangerous. Regulations for CAM practitioners dealing with potential clients' postal or online health queries should be put in place.

I co-authored various systematic reviews, which summarize data from clinical trials and thus assessed the efficacy of mistletoe, co-enzyme Q10, guided imagery acupuncture and Ukrain for cancer care and music therapy for cardiovascular conditions. To summarize these reviews I conclude that some CAM modalities play an important role as an adjunct to conventional medicine in palliative cancer care and are based on a non-specific effect. Specific effects of CAM for certain health conditions are rather small. There is a need to regulate how CAM information is distributed. More rigorous clinical trials need to be financed and carried out independently to assess CAM efficacy and safety in those CAM modalities where a specific effect is suspected and in others with non-specific effects possibly CAM therapist evaluations should be carried out. Further international regulations should be put in place regarding CAM education in medical schools and CAM training for healthcare professionals.

Critical appraisal

Nature of my work

During last two decades, there has been a combination of growing interest in complementary and alternative medicine (CAM) by the public and also by researchers worldwide.[e.g.1,2] There has been a slow albeit noticeable fusion between public interest and clinical medicine. The general public of the 'modern' world has become increasingly health-oriented and thus is seeking alternative ways of taking care of their bodies and minds. CAM, in particular, can be of interest due to so called "push and pull factors". Pull factors are, for instance, congruence with the philosophy, which a specific health system is based on (i.e. Ayurveda) or the wish to take personal control over one's health and medical treatment. Push factors can be dissatisfaction with (some aspects of) the orthodox healthcare system, rejection of science and technology or sheer desperation.

Conventional medicine on the other hand also strives to become more holistic and communicative. The press often likes to act as some sort of mediator between the two – at times to the disadvantage of both sides. Education about CAM in terms of teaching and learning of CAM is slowly being introduced in academic institutions due to a personal interest of academics, the increase noted in public CAM use and the employment of governing bodies (e.g. ministries, departments of education). Scientific evidence-based CAM research has so far explored the efficacy and safety of a variety of modalities when applied in specific health conditions by publication of systematic

reviews and meta-analyses. However, there have been suggestions that therapist evaluations as opposed to therapy efficacy and therapist training might be a better method of CAM assessment. [3]

CAM can be either of a diagnostic or a therapeutic nature and sometimes can act as both. As far as we can understand and rationally explain it, their mechanism of action is either on a physical, pharmacological or 'undefined energies' level. For some CAM (mainly herbal medicines) a specific effect has been investigated and pinpointed. Other CAMs are still labeled 'nonspecific effect therapy', simply because no other effect than the placebo or meaning-specific effect has so far been identified. It is still not understood what the 'placebo effect' or the 'meaning response' fully entails but it has been shown that its effects are physiological and psychological. The 'meaning response' is described as the meaning in the treatment of an illness during which process the patient experiences knowledge, symbol and meaning and follows from the interaction with the context in which healing occurs, whilst the patient's attitude and understanding of medicine play a fundamental role in the healing process.[4]

Thus, there is a need to a) gather information as to the mechanism of action, safety, efficacy and cost-effectiveness of CAM, b) distribute that information to all healthcare professionals and governing bodies and c) inform the public. Currently, a mix of confusion, misinformation and lack of evidence still exists in the general public as well as in healthcare professionals.

Prior to my PhD-related work I carried out a survey using postal questionnaires and conducted additional interviews assessing what the range of German and UK general practitioners' (GPs) attitudes towards complementary and alternative medicines (CAM) are (Schmidt, Jacobs and Barton 2002).[5] It was of particular interest to identify cross-cultural differences and to assess for which health conditions GPs may apply or recommend CAM to their patients. The results showed that CAM attitudes varied, many of which were positive. The difference between UK and German GPs' CAM attitudes was not statistically significant although German GPs were slightly more positive. Favorite CAM modalities which GPs referred their patients to included acupuncture, chiropractic treatment, osteopathy and herbal medicine. The majority of practitioners noted a lack of clear information as to the safety and efficacy of CAM and a number of them requested more training and education about CAM. This piece of work was the first of its kind in assessing cross-culturally GPs' CAM attitudes. Personally, it lays for me the first stone for further CAM investigations. However, one aspect I did not assess with this study due to the chosen population that I studied was to inquire about the attitudes of medical students during the course of their curricula. Additionally, I had not used a validated and reliable instrument with which to measure CAM attitudes.

This was achieved by a further international, multischool survey (Schmidt, Rees, Greenfield et al 2005).[6] The survey was carried out at locations in the UK, USA, New Zealand, Canada and Hong Kong and revealed that CAM education varied greatly according to different medical schools' curricula. Within the UK, differences were noted between 'traditional' medical schools that still teach according to 'content learning' as

opposed to the more currently adopted style of 'problem-based learning'. There was also the notion that prior CAM exposure and current personal consumption of CAM acted as a better predictor of the concept of 'holism', which is the core of what the CAM idea envelopes, than CAM exposure in the medical school's curriculum.

After having shed some light on the extent of CAM healthcare information available to the medical profession and the range of attitudes toward holism the question remained as to what type of information about CAM the general population is being provided with. Specifically, I wanted to know how CAM practitioners respond to patients and researchers when being approached with a precise health-related problem. I therefore carried out 5 Internet-based surveys of various natures. Apart from the first conducted survey the population was randomly divided into 2 groups, one of which was contacted via e-mail by a researcher and one of which was contacted by a (fictitious) patient. We involved medical herbalist, chiropractors, reflexologists, acupuncturists and homeopaths. The first study assessed the advice given to a pregnant woman when contacting medical herbalists regarding the problem of morning sickness.[7] Specifically, the woman asked about three herbs: ginger, raspberry and juniper. It was found that advice was readily available and its action ranged from misleading to dangerous. Respondents were, however, additionally giving general lifestyle advice.

Similar results were found in another survey assessing UK reflexologists' responses to a patient with abdominal pain, weight loss and fatigue - presenting a potential case of liver cirrhosis or liver cancer.[8] Here, the sample (all members of the

UK Association of Reflexologists who provided an email address) was randomly divided into 2 groups. The response rate was twice as high when the reflexologist was approached by a patient compared to a researcher and the respondents replied in a much more careful fashion regarding claims and diagnosis when approached by a researcher as opposed to a 'potential' client. The majority of reflexologists, however, responded in a responsible manner in that they advised the patient to seek help from a physician or other healthcare professional.

A third Internet survey included all acupuncturists internationally whose email address was listed on a public directory. [9] The population was randomly divided into three groups: group A (fictitious patient), group B (fictitious patient 'living in therapist's area', i.e. potential client), and group C (researcher). All participants were asked to comment on the application of electroacupuncture for smoking cessation in a patient with a pacemaker. Concerns with administering electroacupuncture were issued by a third of all respondents but, again, acupuncturists in group C were more cautious in giving and the nature of their advice.

Chiropractors approached over the Internet in a similar fashion showed a readiness to provide advice regarding asthma treatment, which is often not evidence-based. [10] The majority encouraged a patient with asthma, who had been treated with corticosteroids and thus may suffer from osteoporosis (as there is a link between higher doses of corticosteroids and osteoporosis)[11] to seek chiropractic treatment for their asthma relief.

Finally, having joined a timely debate regarding vaccinations against measles, mumps and rubella (MMR) for a 1 year old by approaching homeopaths, chiropractors and GPs,

it was found that a) GPs refused to give any advice whatsoever, b) very few homeopaths and chiropractors openly advised against the MMR vaccination and c) indirect advice to seek alternatives to the MMR was given. [12,13]

Systematic reviews (SRs) can be carried out when there are more than two clinical trials assessing one therapy for a treatment of a certain health condition. The randomized clinical trial (RCT) is seen as the 'gold standard' to draw any meaningful evidence-based conclusion. The SR of mistletoe (*Viscum album*) for cancer included 10 randomized clinical trials (RCTs) that met the predefined inclusion criteria. [14] This review concluded that although the studies of weaker trial design suggested benefits of mistletoe extracts in terms of quality of life, the stronger studies exhibited no efficacy in survival, quality of life and other outcome measures.

In another systematic review assessing the therapy coenzyme Q10, six randomized clinical trials and three non-randomized trials were included. [15] The review suggests that CoQ10 may provide some protection against cardiotoxicity or liver toxicity during the cancer treatment.

Guided imagery (GI) is also employed as a mind-therapy to adjuvant cancer patients' conventional treatments. In a systematic review including six randomized clinical trials poor analysis and heterogeneous endpoints made a firm conclusion impossible. [16] However, it was suggested that GI may be psycho-supportive and increase comfort in patients undergoing therapy.

Acupuncture is applied to relieve cancer-related pain. In a systematic review including one randomized clinical trial, two non-blinded clinical trials and 4 uncontrolled clinical trials inadequate trial design, poor reporting and small sample size were prevalent. [17] No evidence of efficacy of this treatment for cancer-related pain was found.

Ukrain is a plant extract of the plant greater celandine (*Chelidonium majus* L.) and is being used as an anticancer drug. In vitro studies, animal experiments, case reports and case series exist. In a systematic review 7 RCTs were included. [18] All studies suggest that Ukrain has curative effects on a variety of different cancer types. However, all studies come from the same research team and are published in the same journal. Additionally, the methodological design is weak, their sample size small and data are poorly reported.

Music therapy is often employed as a distraction stimulus for stressful procedures in hospitals. [19, 20] In a systematic review of music therapy specifically applied to patients who underwent coronary conditions (bypass, artery grafting, myocardial infarction recovery) 12 randomized clinical trials were included. [21] The review found that 8 of the trials found a significantly positive effect compared to the control group in a number of endpoints such as blood pressure, respiratory rate, heart rate, skin temperature but also in psychological outcome measures such as the State Trait Anxiety Inventory (STAI).

The systematic reviews I chose to present here show that specific effects of a CAM therapy are small and tend to play a major role in palliative cancer care and in patient supportive care. Thus, CAM is of use to modern medicine for certain health conditions, albeit its application should be seen as in addition to rather than a replacement of

conventional medicine.

It was my intention to present an assimilation of my work, ranging from postal and Internet surveys to systematic reviews. With the help of my colleagues I have gathered information as to the safety and efficacy of various CAM modalities in cancer care. I have shed light on how that information is distributed to healthcare professionals with a multinational survey, which showed that education on CAM varies and is dependant on the medical school's curriculum. With my Internet surveys I have shown that when contacting CAM practitioners via e-mail the public can expect a range of replies including responses that are of responsible manner and responses that may be inconsistent with the practitioner's training. Some CAM practitioners also have been shown to give advice which is contrary to conventional medical advice, such as the use of vaccination.

Significance of my work

Safety of CAM

The safety of CAM should always be considered before its efficacy to avoid harm to the public. In my Internet surveys I have shown that most CAM practitioners act responsibly in correspondence with the public but some give advice that might be considered harmful.

Examples for direct risks of CAM therapies are, for instance, toxic oral remedies (e.g. adulteration, contamination), infected needles, trauma (e.g. spinal manipulation

therapies). Indirect risks could contain a general hindering of access to effective therapy, usage of harmful diagnostic practices and unnecessarily high costs.

Herbal medicines hold their own possible risks. The quality of the product needs to be considered. The toxicity of plants and therefore correct dosages need to be established. Interactions with other medication and herbal therapies might occur. Precautions may have to be taken especially in pregnancy and during the lactation period.

The safety of acupuncture has been established and the therapy is considered safe if applied by a qualified practitioner.

Efficacy of CAM

In healthcare there are various outcomes that healthcare providers need to consider. These are of physical, psychological and social nature. Many CAM therapists and CAM supporters claim that some of the CAM therapies encounter many of the symptoms at once. CAM for cancer palliation, for instance, claims to enhance the quality of life of cancer patients, to promote relaxation and reduce stress and pain, to reduce some of the side effects caused by chemo- or radiotherapy and to improve the quality of sleep. The widespread and well-documented use of CAM by patients has lead to an intensive research focus on the efficacy and safety of some of the CAM modalities. Some of these therapies are promoted as prevention, some are suggested as so-called 'cures' and some are used for supportive healthcare. Evidence-based data for supportive healthcare suggest that some forms of CAM have gained an important role as some of the data have shown to favor the CAM therapy, especially if it was applied in addition to

a conventional therapy. However, the present evidence for most therapies is controversial. [22] Furthermore, interpretation of studies differs depending on what methodological quality is being determined as adequate. Additionally, some medical interventions, such as CAM, can be seen as more complex than the more or less 'straight-forward' methods used to evaluate pharmacological studies. Some elements of the therapeutic approach may work synergistically and simultaneously. Therefore, the possibility of a different approach of assessment may have to be considered. The circular model of evaluation suggests a consideration of whether a clinical study used a method well-suited to answer the research question and also whether it implements this method with the necessary scientific rigor. [23]

This area clearly deserves more research; in particular, it needs to be established whether treatments are in any way superior to conventional methods of healthcare. However, until more data are available, CAM can be cautiously recommended if the risk for harm is minimized through adequate supervision. All patients should inform their general practitioner and health specialist if they are using or thinking about using any forms of CAM.

Regulation of and education about CAM

There is a need to regulate how CAM information is distributed. As I have shown in my Internet surveys, CAM practitioners' responses vary greatly. Many systematic reviews that I have co-authored have shown that more rigorous clinical trials need to be financed and carried out independently to assess CAM efficacy and safety in those

CAM modalities where a specific effect is suspected and in others with non-specific effects possibly CAM therapist evaluations should be carried out. Further international options and regulations should be put in place regarding CAM education in medical schools and CAM training for healthcare professionals, as my surveys have underlined a need for these was expressed by general practitioners and medical students.

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Published work (Appendices)

Cross-cultural differences in GPs' attitudes towards complementary and alternative medicine: a survey comparing regions of the UK and Germany

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SUMMARY. **Objective: To investigate whether there is a difference in general practitioners' attitudes towards CAM in the UK and Germany. Study design: A descriptive questionnaire was developed and sent to 97 GPs in the UK and 99 GPs in Germany. Results: The overall response rate was 68%. German GPs showed a (non-significant) overall more positive attitude towards CAM than did British GPs. British GPs made more referrals to complementary practitioners. The most popular CAM therapies that UK GPs referred their patients to were chiropractic treatment, acupuncture and osteopathy. German GPs referred their patients mainly to acupuncture treatment, chiropractic treatment and herbal medicine. A significantly higher number of German GPs reported having practised as a CAM practitioner before and having personally used CAM themselves. Seventy percent of British GPs and 76% of German GPs thought it is safe to prescribe complementary medicine and therapies to patients. Conclusion: There are small national differences in referring patients to various CAM modalities. Both nations have an overall positive attitude toward and a high interest in CAM. Lack of scientific evidence and information on training opportunities were important points that were continuously raised by GPs in both countries.**

INTRODUCTION

Complementary and alternative medicine (CAM) is being used as an umbrella term in this study, despite the valuable argument that each CAM modality needs individual attention. The use of and interest in CAM has been growing rapidly over the last decades. One-third to one-half of the general population is using one or more forms of alternative therapies.[1] The demand for CAM also has an impact on the general practitioner. In a comprehensive literature review of surveys examining the practices and beliefs of GPs between 1982 and 1995 it was found that large numbers of physicians are either referring to or themselves practising some of the more prominent

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doi: 10.1016/S0965-2299(02)00056-0, available online at http://www.idealibrary.com on IDEAL®

forms of CAM.[2] The review also found that a number of GPs believe that some forms of CAM are useful or efficacious. In the UK about 40% of GPs now provide some complementary services for their patients.[3] Sixty-seven percent of Health Authorities are purchasing at least one CAM treatment.[4] Sixty-five percent of British hospital doctors believe that CAM therapies have a place in mainstream medicine.[5]

The market for herbal medicine is also expanding, especially in Germany, and it has been claimed that the number of the German "Heilpraktiker" has risen to around 10,000 in 1997[6] and by 1995, 8.4% of all drugs prescribed were herbal medicinal drugs and homeopathics.[7] In Britain non-medically trained practitioners are the main providers[8] of CAM. Medical doctors in Germany and the UK also refer patients to CAM practitioners.[9] The increase in CAM over recent years has been accompanied by an increasing scepticism with regard to both the underlying principles associated with the practice of CAM, and the efficacy and safety of CAM.[10] Patients' use of CAM without their GPs' knowledge may also cause problems. Some herbal remedies can be dangerous to patients with epilepsy or diabetes and to those taking, for instance, warfarin. Ideally, GPs should routinely ask patients about CAM use in order to reduce the incidence of "complementogenic" disease.

There are national and cultural differences regarding referral to, use of and attitudes towards CAM. The organised, non-medically trained profession of the "Heilpraktiker" (literally translated meaning 'health practitioner') in Germany has no UK equivalent. In the UK, however, there are homeopathic hospitals, which are part of the NHS. There is a very high prescription of herbal medicine in Germany whereas in the UK herbal medicine is not often prescribed. There are different traditions of practice within various CAM professions. Ethnic minorities also play an important role when establishing differences of CAM use and interest. However, little is known about these differences. In this study, we investigated differences in the perception of, and attitude towards CAM in two European countries, the UK and Germany. To our knowledge cross-cultural differences in attitudes to and perceptions of CAM have not been investigated in this way before.

METHODS

A questionnaire was developed to study the attitudes, perceptions, experiences of, types of referral made, perceived efficacy, and concerns about CAM, and to elicit views about the future direction of CAM use within a national health provision (Appendix A). The questionnaire was developed using a two-stage approach. In stage one a review of the current literature was carried out on Medline and the literature from the last three decades was searched for potential studies. Search terms used were 'use' and 'complementary medicine', 'use' and 'alternative medicine' to identify the main issues surrounding CAM use. Bibliographies of identified articles were checked for further potential trials. No restrictions regarding language of publication were applied. After reviewing the literature we decided to ask GPs about their overall attitude toward CAM, the number of referrals they made to CAM or CAM practitioners, specific illnesses to be treated with CAM, personal CAM practice and use, perceived safety of CAM, implementation and popularity of CAM. Demographic data were additionally sought and participants were asked to give a definition of CAM. For the overall attitude scale respondents had to rate their attitude on a scale ranging from 1 to 10 with '1' meaning 'no interest' and '10' meaning 'active interest' towards CAM.

In stage two the questionnaire was presented to three GPs for refining questions, clarifying issues and considering ease of use by participants.

The local health authority provided a list of addresses for GPs by electoral ward in the Plymouth area. This list did not constitute a random sample but was ordered according to geographical area. German GPs were selected by randomly choosing addresses from the Yellow Pages for Mecklenburg–Vorpommern, a north-eastern region in Germany (formerly German Democratic Republic).

In the period March–July 2000, 196 questionnaires were posted to participants, along with a letter detailing the study aims and a freepost envelope for responses. Ninety-seven questionnaires were sent to GPs in the south-west of England and ninety-nine to GPs in the north-east of Germany. The covering letter explaining the purpose of the study addressed each GP by name. It was suggested to tear off this letter when returning the questionnaire and thus a numbering system was applied to record response rates for participant anonymity. A 1-month follow-up reminder letter and questionnaire were sent out to all initial non-responders. Data were entered into SPSS datasheets for analysis. Chi-square analysis was used to test for significant differences between groups. The significance level was set at $P < 0.05$.

RESULTS

One hundred and thirty-three replies were received (response rate: 68%), of which 66 were from British GPs and 67 from German GPs. The majority of UK (94%) and German (63%) respondents were of male gender (Table 1). Age was distributed similarly and most participants were between 40 and 69 years of age (Table 1). The British sample showed less variation in years of practice when compared to the German respondents. In the British sample there were only two GPs who had practised less than 10 years, in the German sample there were 16 GPs who had practised less than 10 years.

Table 1 Demographic data of GPs

	Gender		Age group					
	Male	Female	<29	30–39	40–49	50–59	60–69	70+
British ($n = 66$)	62 (94%)	4 (6%)	0	5 (8%)	22 (33%)	29 (44%)	10 (15%)	0
German ($n = 67$)	42 (63%)	25 (37%)	0	10 (15%)	19 (28%)	25 (37%)	13 (20%)	0

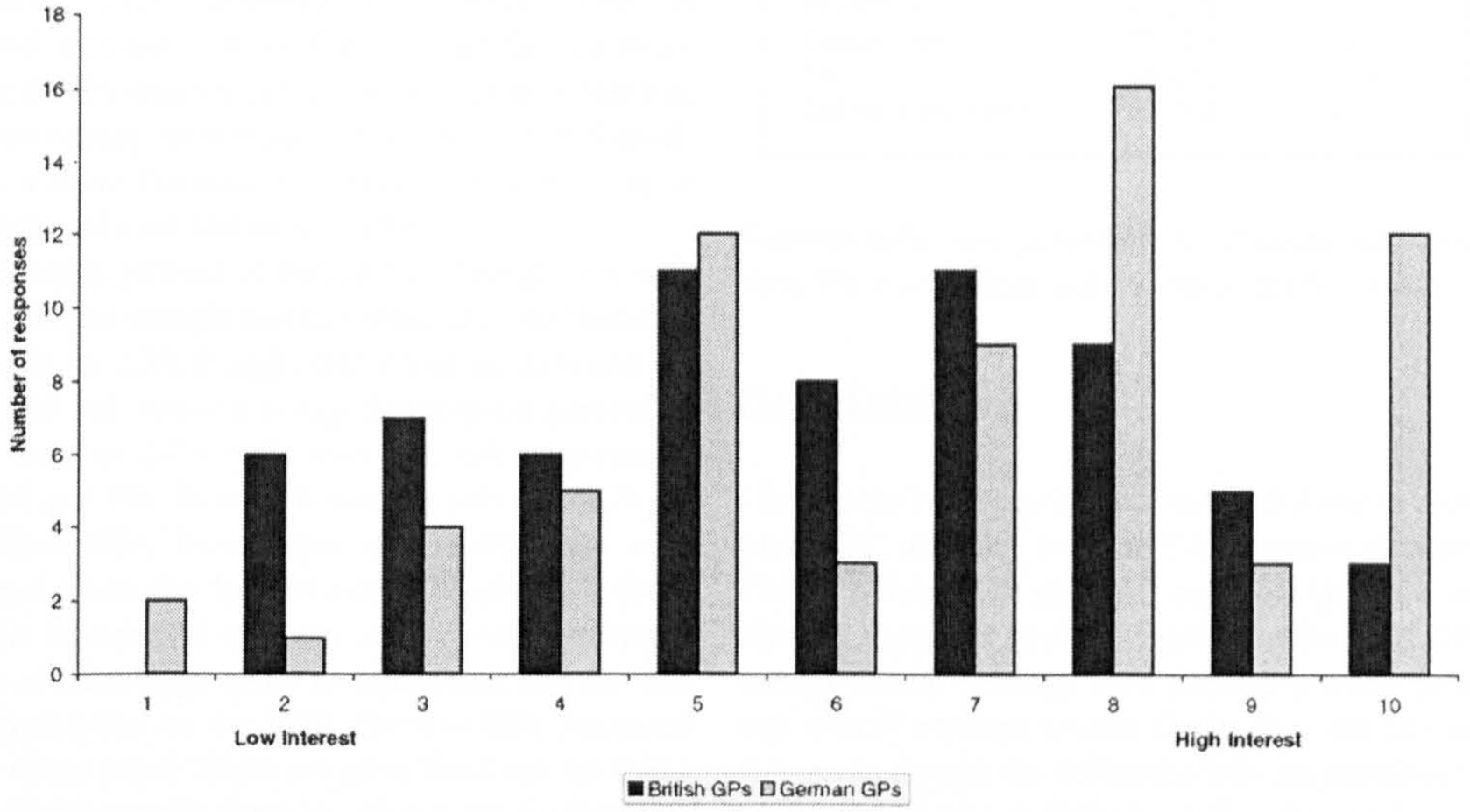

Fig. 1 Attitudes to CAM.

The overall GPs attitude toward CAM was more positive in the sample of German GPs (mean = 6.75) compared to the attitude expressed by British GPs (mean = 5.81). However, the difference between German and British GPs' attitudes toward CAM is not statistically significant (Fig. 1).

British GPs reported higher levels of referrals to alternative therapists than German GPs. The most popular CAM therapies that UK GPs referred their patients to were chiropractic treatment (79%), acupuncture (67%) and osteopathy (66%). German GPs referred their patients mainly to acupuncture

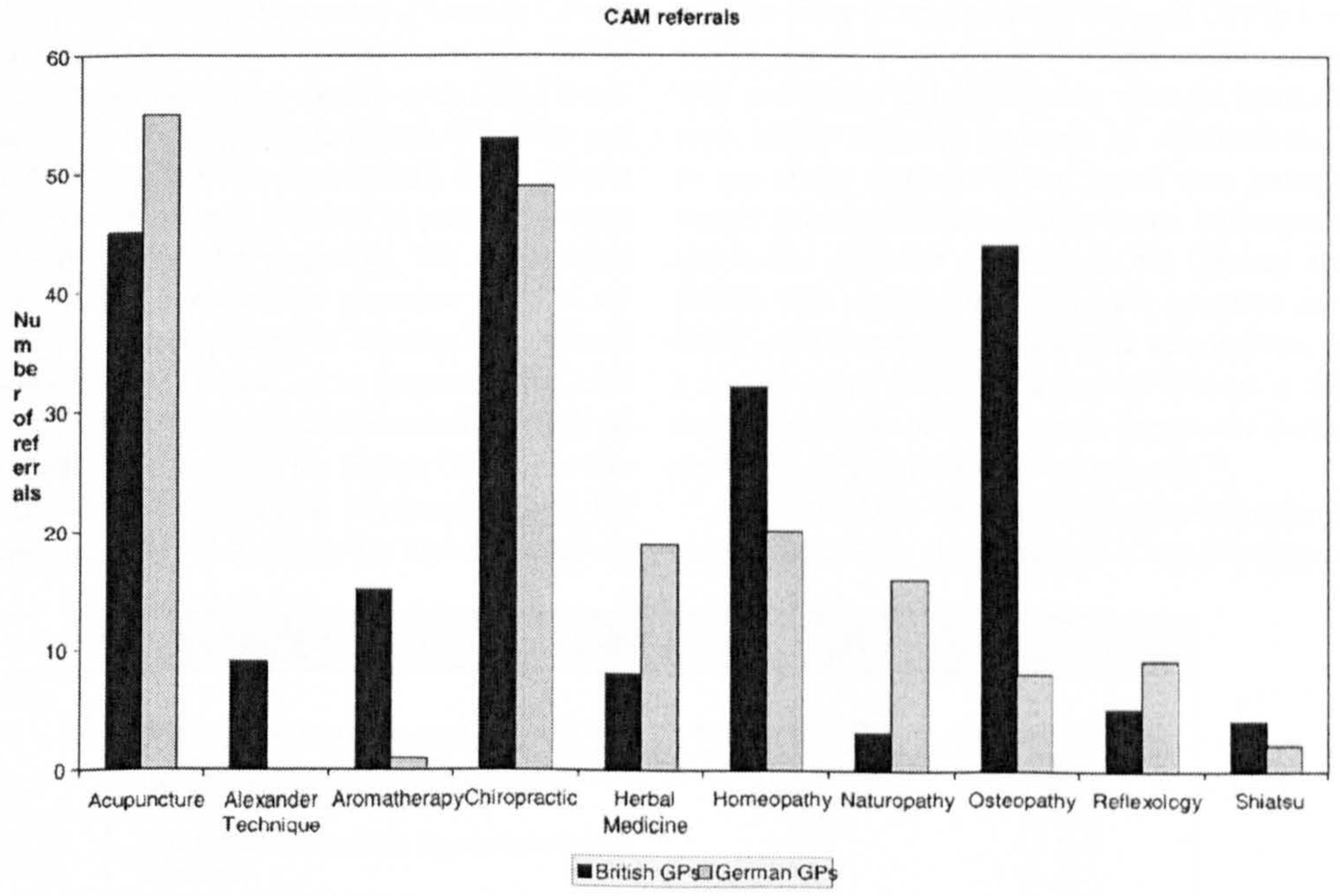

Fig. 2 Referrals to CAM.

Table 2 GPs' response to safety[a]

CAM is generally safe to be prescribed	British GPs (%)	German GPs (%)
'Yes'	47 (71)	51 (76)
'No'	15 (23)	13 (19)

[a] Not all GPs have responded to this question

treatment (82%), chiropractic treatment (73%) and herbal medicine (28%) (Fig. 2). Significantly more British GPs referred patients to Alexander technique, aromatherapy, homeopathy and osteopathy. Significantly more German GPs referred their patients to herbal medicine and naturopathy.

Seventy percent of British GPs thought it is safe to prescribe complementary medicine and therapies to patients, 22% thought that it was not safe and the rest did not mention safety. Seventy-six percent of the German GP sample said it is safe to prescribe CAM and 19% thought it was not safe (Table 2).

Most GPs, irrespective of country, were concerned about the lack of scientific evidence about CAM. British GPs were also highly concerned about lack of knowledge about its indications and the lack of availability on the NHS. German GPs expressed that many practitioners are prejudiced against CAM and that generally there is less patient feedback on alternative methods (Table 3).

GPs reported various illnesses for which they thought some CAM would be useful, the top three include stress, headache and depression (Table 4). However, considerably less British GPs would prescribe CAM for headaches and more British GPs would prescribe CAM for stroke, HIV/AIDS and ME (post-viral fatigue syndrome) compared to German GPs.

A significantly higher number of German GPs reported having practised as a CAM practitioner before ($n = 30$) and having personally used CAM themselves ($n = 31$) compared to British GPs. This was specifically the case for acupuncture. Eight percent of British respondents claimed to practise or have practised chiropractic treatment, 5% acupuncture treatment, 5% homeopathic treatment and 3% osteopathy. Nineteen percent of German GPs claimed to work or have worked as an acupuncturist, 11% as a chiropractor, 6% as a homeopath and 3% as an osteopath. Six percent of the British GP sample has personally used chiropractic treatment before, 2% acupuncture and 2% homeopathy. Eleven percent of German GPs have personally used acupuncture before, 7% chiropractic and 5% homeopathy (Table 5).

Table 4 Illnesses for which CAM might be useful

Illness	British GPs (%)	German GPs (%)
Common colds	21 (32)	27 (40)
Depression	45 (68)	38 (57)
Asthma	14 (21)	24 (36)
Headache	39 (59)	58 (87)
Stress	54 (82)	46 (69)
Stroke	11 (17)	0 (0)
HIV/AIDS	11 (17)	0 (0)
Cancer care	21 (32)	22 (33)
ME	36 (55)	18 (27)
Digestive disorders	33 (50)	27 (40)

DISCUSSION

This survey is unique in that it is the first one to compare GPs' attitudes towards CAM cross-culturally. The relatively high response rate (68%) might indicate a reasonably positive general attitude of GPs toward CAM. German GPs showed a more positive overall attitude toward CAM than did British GPs, even though the difference was not statistically significant. However, looking at the amount of referrals made to complementary therapies, German GPs were not as active as were the British GPs. There are national differences in particular when referring patients to aromatherapy, herbal treatments, naturopathy and osteopathy. The variation in responders' age could either be due to chance or to a greater number of younger GPs in Germany in general. However, we have not assessed whether age is related to the degree of attitude toward CAM. Our findings confirm those of another study amongst GPs in Liverpool where it was found that acupuncture along with osteopathy and chiropractic were the therapies most highly regarded in terms of effectiveness.[11] In our study, German GPs referred their patients mainly to acupuncturists, chiropractors, homeopaths and herbal medicine and some of the German and British GPs reported that they have practised as a CAM practitioner, mainly applying acupuncture. In a similar small survey in Germany 95% ($n = 38$) used some form of CAM, most commonly herbal medicine, neural therapy or homeopathy.[12]

Safety of CAM was perceived almost equally in both groups. Both groups related a low intention of

Table 3 GPs' reasons for low intention to CAM use

Reasons for low intention of CAM use	British GPs (%)	German GPs (%)
Little knowledge about indications of CAM	34 (52)	12 (18)
Prejudice	24 (36)	36 (54)
Less patient feedback on alternative methods	9 (14)	18 (27)
Availability	39 (59)	21 (31)
Lack of scientific evidence	55 (83)	52 (78)

Table 5 Self-practice and personal use of CAM

CAM	British GPs (%)		German GPs (%)	
	Self practice	Self use	Self practice	Self use
Acupuncture	5 (8)	2 (3)	19 (28)	11 (16)
Chiropractic	8 (12)	6 (9)	11 (16)	7 (10)
Homeopathy	5 (8)	2 (3)	6 (9)	5 (7)
Reflexology	0	2 (3)	3 (4)	0
Phytotherapy	0	1 (2)	2 (3)	4 (6)
Naturopathy	0	0	2 (3)	0
Aromatherapy	1 (2)	2 (3)	1 (1)	1 (1)

CAM use mainly to the lack of scientific evidence. British GPs further believed that lack of availability of CAM in the NHS is another reason for its rare application in the NHS compared to orthodox medicine. German GPs felt that prejudices against CAM deter patients from using it and GPs from prescribing it. Many British GPs believed that especially a lack of knowledge about the indications of CAM and its availability are reasons for a low intention for its use. British and German GPs both agreed that due to the media the population has increased expectations of the medical profession, which is the main information supplier. Additionally, some GPs mentioned that possibly dissatisfaction with the conventional medical system such as, for instance, waiting lists and lack of medical explanations to every problem causes many patients to turn to CAM therapists. Many GPs asked for more information on training opportunities for certain CAM modalities and CAM education for doctors.

Perkin et al.[13] carried out one of the first studies in the UK comparing the attitudes of GPs, hospital doctors and medical students towards alternative medicine. They asked GPs and hospital doctors to rate their attitude towards and knowledge of five alternative therapies, including acupuncture, chiropractic, homeopathy, osteopathy and naturopathy. Seventy percent of hospital doctors and 93% of GPs had, on at least one occasion, suggested a referral for alternative treatment. In another study, 72% of the GPs participating in the study had made referrals to CAM.[14] Twelve percent of hospital doctors and 20% of GPs were practising alternative medicine. The majority of the respondents felt that alternative medicine should be available on the NHS and that medical students should receive some tuition about alternative therapies. Other studies also support the outcomes of this study by having shown an increased interest in complementary medicine and therapies among GPs in the UK and in Germany e.g. [13,15–17]. Reilly's study, for instance, confirmed that there is a contrast to the picture frequently painted by the media and the public of narrow-minded, drug orientated doctors.

Most GPs in the UK and in Germany would like to be able to consider different CAM treatments on their respective merits if more scientific evidence was available from high quality research. Others believe that it does not matter if a cure has not been fully understood as long as it might help some patients to get better or to improve their quality of life. Some GPs may fear for their financial existence and more competition and therefore, reject any alternative treatments.

One of the main differences to take into account when interpreting the data of this study is the diversity of medical health systems and training provided in the UK and Germany. The health system in Great Britain is mainly provided by the state and there are additional independent insurance plans. In Germany there is no direct ownership by the state but instead the health system consists of nationally guided insurance agencies and the state offers controlled private and public insurance plans. In 1994, the UK was the only EU country to have CAM hospitals in the public sector.[8] As far as the training of a complementary practitioner is concerned the situation is similar in the UK and Germany. Apart from osteopaths and chiropractors complementary practitioners can legally practise without any training. However, most practitioners complete further education in CAM disciplines, despite the fact that there is a great variation in quality among the many training institutions since main registering bodies of the relevant disciplines accredit only few courses. In the German medical curriculum familiarisation with non-conventional medicine is compulsory.

As with most investigations there are various weaknesses of this study. The sample size in this survey is relatively small due to limited financial resources and time constraints. Additionally, the participants' selection was not randomised and only involved a small area. We also have no information about the GPs who failed to respond to our survey. There is evidence from population surveys that the use of CAM in the south-west of England is high—16% instead of the national average of 10%.[3] Therefore, the samples involved in this study cannot be seen as representative for all GPs. Additionally, we must concede that respondents are likely to be among those GPs more interested in CAM.

This study was an attempt to show any differences in GPs' attitudes toward CAM in two different countries. Further research needs to expand the area of receiving responses from GPs by, for instance, sending out questionnaires to surgeries all over the

country, including cities, towns, and rural areas. For further research more semi-structured interviews should be carried out, involving British and German GPs with different levels of attitudes toward CAM.

Appendix A. CAM attitude Questionnaire

(please circle where appropriate)

Gender: Female / Male
Age: <29 30-39 40-49 50-59 60-69 70+
How many years have you worked in general practice?.....
Are you member of the Royal College of GPs? Yes / No
I am member of other professional organisations (please specify).....

1. Please rate your overall attitude to alternative / complementary therapies
1= no interest.....10= active interest
1 2 3 4 5 6 7 8 9 10

2. How would you define alternative / complementary medicine?
.....

3. Have you ever made a referral to one of the following therapies? (please indicate)
- ☐ Acupuncture
- ☐ Alexander Technique
- ☐ Aromatherapy
- ☐ Chiropractic
- ☐ Herbal Medicine
- ☐ Homeopathy
- ☐ Naturopathy and Nutrition
- ☐ Osteopathy
- ☐ Reflexology
- ☐ Shiatsu
- ☐ Others (please specify).....

4. Can you personally relate to the following statements:
4a. I do not use complementary therapies. Agree / Disagree
4b. I do not believe in complementary therapies. Agree / Disagree
If you 'agreed' in both questions can you please turn to question No. 8

5. For which specific illness was your last referral to alternative / complementary therapy?.....

6. Have you ever practised as an alternative therapist? Yes / No
If 'Yes' please specify:

7. Have you ever used alternative / complementary medicine or therapy for your own health? Yes / No
If 'Yes' please specify:

8a. Do you think it is generally safe to prescribe alternative medicine and therapies?
Yes / No
8b. If 'No' why not?.....

9. Do you believe a low intention to use alternative / complementary medicine stems from: (please indicate)
- ☐ Lack of knowledge about indications of alternative therapies
- ☐ Prejudice
- ☐ Less patient feedback on alternative treatments
- ☐ Availability on the NHS (British GPs only)
- ☐ Lack of scientific evidence of efficacy and safety

10. Do you believe alternative therapies have a place in (please indicate):
- ☐ common colds
- ☐ depression
- ☐ asthma
- ☐ headache
- ☐ stress
- ☐ stroke
- ☐ HIV / AIDS
- ☐ cancer care
- ☐ ME (post-viral fatigue syndrome)
- ☐ digestive disorders (e.g. IBS)
- ☐ not at all applicable

11. Which complementary therapies and medicine do you feel should be available in the NHS?
.....
12. In the last decade the popularity of alternative / complementary medicine and therapies has grown across Europe and in the UK. Why do you think this might be?
.....
13. Do you have any other comments?

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Multischool, International Survey of Medical Students' Attitudes toward "Holism"

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Abstract

Purpose
Core and optional courses of study in complementary and alternative medicine (CAM) are being incorporated into medical curricula. The authors carried out this study to validate a tool to examine students' attitudes toward holism and CAM and explore the relationships between their attitudes and other demographic and education-related characteristics in a large, multischool, international sample of medical students.

Method
In 2003 the authors used a modified version of the Integrated Medicine Attitude Questionnaire (IMAQ) to survey students at a total of six medical schools in the United Kingdom, New Zealand, Canada, the United States, and Hong Kong, China. A three-factor model was tested using confirmatory factor analysis, and the internal consistency of the factors were identified using Cronbach's alpha coefficients. A multiple-indicator multiple-cause (MIMIC) analysis was carried out to determine the relationship between IMAQ factors and student characteristics.

Results
The authors validated a three-factor model for the IMAQ: (1) attitudes toward holism, (2) attitudes toward the effectiveness of CAM, and (3) attitudes toward introspection and the doctor–patient relationship. Cronbach's α coefficients ranged from .41 to .71. The MIMIC model indicated that various background variables were associated with IMAQ factors (gender, race/ethnicity, and school), depending on whether students had previously visited a CAM practitioner and whether students were willing to undertake a special study module in CAM.

Conclusions
Further development work on the IMAQ is required and qualitative research to verify and examine the reasons behind the relationships found in this study between students' attitudes to holism and their demographic and education-related characteristics.

Acad Med. 2005; 80:955–963.

The reported prevalence of complementary and alternative medicine (CAM) use by the general public has gradually increased over the last two decades.[1,2] The United Kingdom's House of Lords Sixth Report on Science and Technology[3] assigned particular priority to CAM research. Over a similar period there has been evidence of some cooperation between CAM and orthodox medicine as well as the slow introduction of CAM teaching and learning into health professions education in the United Kingdom, Canada, and the United States.[4–6] Regarding the latter change, the drive has arisen from a combination of interested academics, the change noted in the public's use of CAM, and the input of responsible bodies, such as the ministries and the departments of education. We carried out the study described in the present report to validate a tool that explores students' attitudes toward CAM and holism and to examine the relationship between students' attitudes toward CAM and other student characteristics.

Background

Globally, accreditation bodies for undergraduate medical education have begun to provide recommendations regarding the incorporation of learning about the history, efficacy, and safety of CAM into medical school curricula. The United Kingdom General Medical Council states that graduates should have an awareness of the range of CAM therapies available to patients and their effectiveness.[7] In Canada, there has been a multiphased education initiative, funded by Health Canada in 2001, aimed at increasing the CAM knowledge of medical students. Over the past five years, several Canadian medical schools have taken steps to introduce CAM into the existing medical school curricula.[8] In 2000, the Australian Medical Council reported on a working party charged with the responsibility of developing standards for CAM education within curricula in Australia and New Zealand.[9] Medical schools in the United States are responding with a small but growing number of courses addressing CAM.[10] In Hong Kong, China, both of the city's medical schools have recognized the relevance of CAM in current and future clinical practice and have introduced some core and optional courses.[11] This curriculum change has recently been positively acknowledged by the Hong Kong Medical Council during their review visit.[11] However, although many medical educators agree that CAM can no longer be absent from their curricula, there is still an ongoing debate about how to include CAM.

Previous studies about students' attitudes toward CAM

Using electronic databases such as PubMed, EMBASE, Cinahl, and AMED, and using hand searches and personal files, we identified 13 studies that have assessed medical students' attitudes with sample sizes greater than 100.[12–24] The surveys were carried out during the past

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decade: four in the United Kingdom,[12–15] three in Germany,[16–18] two in the United States,[19,20] two in Israel,[21,22] and one each in Australia[23] and Hong Kong, China.[24] Of these, nine were single-site studies, and all surveys employed their own instrument, which was constructed by each research group. These instruments were not validated, nor was their reliability tested.

The key results from the United Kingdom surveys show that medical students' attitudes were generally positive, that there were no significant differences in their attitudes toward any individual CAM therapies in particular, that 37.3% had used CAM before,[12] and that students displayed a greater level of knowledge of acupuncture and hypnosis compared than of other CAM modalities.[13] Surveys showed that CAM experience was most common for aromatherapy, homeopathy, and chiropractic therapy.[14] In Germany, medical students expressed a high interest in learning about acupuncture, homeopathy, massage, reflexology, and autogenic training.[16,17] The U.S. surveys revealed that estimated CAM use among medical students was between 40% and 74%,[19] and the most popular modalities were massage and relaxation techniques.[20] In Israel, there were high levels of interest amongst students in hypnosis, relaxation, meditation, acupuncture, and biofeedback.[21] Fifty-four percent of Israeli students surveyed in another study had prior theoretical knowledge of CAM through personal reading or had practical experience through treatments or courses.[22]

Most surveys showed a positive correlation between previous CAM use and a more positive attitude toward CAM. Younger medical students in the United Kingdom displayed a more positive attitude toward CAM and CAM teaching than did older students,[12] and several studies demonstrated that women had more positive attitudes toward CAM.[12,20,22] Another survey also found that students from two medical schools in the United Kingdom displayed different levels of specific attitudes toward CAM when surveyed concurrently.[15]

Shortcomings of previous studies

Although all of the studies discussed above have provided some understanding of medical students' attitudes toward CAM, they are not without their methodological problems. Nine of the studies report attitudes in single populations and schools, at different times, and with tools that had not been used before. There are no data to support the item reliability and validity of those tools. None of the studies have comprehensively examined the relationships between students' attitudes toward CAM and other correlates such as age, gender, and race/ethnicity, whereas general-population surveys in the United Kingdom and North America have found significant relationships between attitudes toward CAM and these characteristics, plus social status and health status.[1,15,25,26,27] These North American and United Kingdom surveys have shown that CAM users are more likely to be younger, female, better educated, wealthier, and of poorer health status.

In an effort to address the problems surrounding the measurement tools, Schneider et al.[28] developed and validated their 29-item Integrated Medicine Attitude Questionnaire (IMAQ) to explore holistic attitudes in U.S. health care providers and medical students. The tool's items were established from focus groups with 196 faculty, fellows, visiting residents, and medical students at the University of Arizona Program in Integrative Medicine.

Using exploratory factor analysis (EFA, principal components analysis with varimax rotation), Schneider et al.[28] reported a two-factor structure for the IMAQ: *openness to new ideas and paradigms* (21 items) and *value of both introspection and relationship to patient* (eight items). They reported a Cronbach's α of .89 ($n = 196$) for the entire tool rather than for the two factors alone. Furthermore, Lie and Boker[20] examined the reliability of the 29-item IMAQ with 272 U.S. medical students and also found it to have satisfactory internal consistency (Cronbach α =. 83). However, there are two key problems with the original validation study: first, they assumed, by using orthogonal rotation, that the factors were not correlated to each other (which we think is erroneous), and, second, the two factors explained only 38% of the variance in the responses, which we think is unacceptably low.

Method

Using a large, cross-sectional sample of medical students across institutions and countries, we carried out the current study in 2003 to address some of the methodological and size weaknesses of previous studies. Our research aims were to

- validate a three-factor structure of the IMAQ,
- determine the internal consistency of the IMAQ factors, and
- examine the relationship between students' attitudes toward holism and CAM, as measured by the IMAQ, and other demographic characteristics of the students, such as age, gender, race/ethnicity, school, and willingness to study CAM.

Sampling and recruitment

A total of 1,154 first-year medical students at six medical schools in five countries were asked to participate in a multischool anonymous survey: 131 from the medical program of the Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; 360 from Birmingham Medical School, United Kingdom; 130 from Peninsula Medical School, United Kingdom; 150 from Hong Kong Medical School, Hong Kong, China; 199 from University of Toronto Medical School, Canada; and 184 from Georgetown University School of Medicine, United States. The questionnaire was designed to measure their attitudes toward the concept of "holism" in medicine, using a modified IMAQ. These schools were chosen for both theoretical and pragmatic reasons. Not only did the schools represent geographical and cultural diversity, but good relationships existed among the researchers, thus aiding the successful conduction of such a large and international study. All first-year students (second-year students in New Zealand *) at these medical schools were invited to participate by face-to-face invitation. In each case a researcher described the purpose and procedures of the study before or after a scheduled teaching session, and students were able to read the information sheet, sign the consent forms, and fill in their questionnaires in

*Auckland has an "overlapping" year 1, where all health sciences programs are taught a common foundation. Year 2 is the start of the separate medical program; we thought that year 2 equated better to year 1 at the other study institutions.

their spare time. The study instrument was anonymous and was kept separate from the consent forms.

Instrument

As the original questionnaire was developed for a U.S. setting, the 29-item IMAQ developed by Schneider et al.[28] was piloted with a small sample of medical students from Auckland ($n = 7$) and Birmingham ($n = 25$). During the pilot we determined how comprehensive the tool was, considering that different terminology for certain concepts is sometimes used around the world. During the pilot study, it became apparent that some of the questions were ambiguous, double-barrelled, or repetitive. Therefore, a number of small changes to wording were made, and item 26 ("Osteopathic manipulative therapy is a valuable method for resolving a wide variety of musculoskeletal problems") was deleted because it was perceived to be virtually the same as item 16 ("Chiropractic is a valuable method for resolving a wide variety of musculoskeletal problems"). Thus, our modified IMAQ version included 28 instead of 29 items. Each item was accompanied by a seven-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). A "don't know" option was also provided. Thirteen of the items were rewritten as negatively worded questions (items 1, 2, 4, 6, 7, 8, 10, 11, 13, 17, 18, 25, and 27) to control for response bias. Additionally, demographic data were collected on age, gender, race/ethnicity, school, previous CAM exposure, and willingness to study CAM. We also included a glossary of terms at the end of the tool to make sure students understood the meaning of each term.

Data analysis

Validity and reliability of the Integrated Medical Attitude Questionnaire. Confirmatory factor analysis (CFA) was used to investigate the construct validity of the IMAQ and to determine whether the two factors reported by Schneider et al.[28]—*openness to new ideas and paradigms* (factor 1) and *value of both introspection and relationship to patient* (factor 2)—provided a sufficient account of the data in the North American medical student population ($n = 265$). We also used CFA to develop and test an alternative model, which included three factors: attitudes toward holism (factor 1), attitudes toward the effectiveness of CAM treatments (factor 2), and attitudes toward introspection and the doctor–patient relationship (factor 3). This model was initially tested and refined using data from the sample of North American medical students mentioned above. Data from the sample of United Kingdom medical students ($n = 236$) were then used to cross-validate the revised model. The use of CFA was appropriate in this context because Schneider et al.[28] had previously reported the factor structure of the IMAQ. In the two-factor structure for the IMAQ reported by Schneider et al., items 1–13, 16–19, and 25–27 loaded on factor 1, and items 14, 15, 20–24, and 28 loaded on factor 2. This two-factor CFA model was encoded into MPlus software Version 2.14 by defining the items that contributed to each factor and instructing the program to allow correlations between the factors.[29] The fit of the model to the data was explored using the chi-squared test of model fit, the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardised root mean square residual (SRMR). Models with nonsignificant chi-square values, with CFIs of more than 0.95, RMSEA values of less than 0.06, and SRMR values of less than 0.08 are generally considered to have good fit. However, the chi-square test is highly sensitive, and the value is often significant even when the fit is considered to be unacceptable by other fit indices. All the analyses were carried out using maximum likelihood estimation with the Satorra-Bentler correction to allow for departures from multivariate normality. This methodology has been used successfully in this way in previous medical education research.[30]

We hypothesized our own three-factor model because we had two major concerns about the two-factor structure, as mentioned previously. Schneider et al.[28] found that while 21 items loaded on their first factor, only eight items loaded on their second factor. We thought that some of the items loading on the first factor were conceptually different from one another and could be thematically separated into two related but different aspects of *openness to new ideas and paradigms*: the first is *attitudes toward holism* (our factor 1, which encompasses items 1, 2, 5, 6, 7, 9, 11, 17 and 19); the second is *attitudes toward the effectiveness of integrated medicine treatments* (our factor 2, which encompasses items 3, 4, 8, 10, 12, 13, 16, 18, 25, 26 and 27). We maintained that all of the items loading on their factor 2 (*value of both introspection and relationship to patient*), with the exception of items 15 and 24, did hang together well conceptually. Therefore, with the exception of items 15 ("In research, measuring the quality of life is equally important as measuring disease-specific outcomes") and 24 ("Counselling on nutrition should be a major role of the doctor toward the prevention of chronic disease"), we kept those eight items in our model but renamed Schneider et al.'s factor 2 as our factor 3, which encompassed items 14, 20, 21, 22, 23, and 28. We thought that items 15 and 24 should load on our factor 1 (i.e., *attitudes toward holism*) so we added these to that factor (see Table 1).

This three-factor CFA model was encoded into MPlus software by defining the items that contributed to each factor and instructing the program to allow correlations between the factors. Using the North American data first ($n = 265$), a number of changes were made to the model, in response to the factor loadings, the standardised path coefficient data, and the model modification indices until a solution with reasonable fit to the data was achieved. The fit of the model to the North American data was explored again using the chi-squared test of model fit, the CFI, RMSEA, and the SRMR. Once the fit had been established with the North American data, the fit of our model was then cross-validated using the United Kingdom data ($n = 236$).

The internal consistency of the factors identified through the above process was determined for the North American and United Kingdom samples separately using Cronbach's α coefficients on SPSS version 11 (SPSS Inc., Chicago, Illinois).

How students' characteristics influenced their ranking on the IMAQ factors. A multiple-indicator multiple-cause (MIMIC) model was developed from the CFA using the complete data set from all schools. Of the 639 completed questionnaires, 35 questionnaires showed missing data, therefore the analysis was carried out for 604 complete responses. The MIMIC model was incorporating the extent to which background variables about the students (i.e., age, gender, race/

Table 1

Factors and Associated Items for the Revised Integrated Medicine Attitude Questionnaire Used in This Study *

Factor		
1 (attitudes toward holism)	1	A patient is completely cured once the underlying pathological processes are controlled.
	2*	The doctor's role should be primarily to promote health rather than to treat disease.
	5	It is appropriate for doctors to use intuition (gut feelings) as a major factor in determining appropriate therapies for patients.
	6*	The spiritual beliefs of doctors play an important role in patient care.
	7	The spiritual beliefs of patients play an important role in their recovery.
	9	End-of-life care should be valued as an opportunity for doctors to help patients heal.
	11	Healing, in a sense of reaching a state of contentment, is not possible when the disease is incurable.
	15†	In research, measuring quality of life is equally as important as measuring disease-specific outcomes.
	17‡	The doctor's goal should be primarily to treat disease, not to address the personal change and growth of the patient.
	19	The innate self-healing capacity of patients often determines the outcome of illness regardless of treatment interventions.
	24†	Counselling on nutrition should be a major role of the doctor toward the prevention of chronic disease.
2 (attitudes toward the effectiveness of IM treatments)	3	Patients whose doctors know about complementary and alternative medicine, in addition to conventional medicine, benefit more than those whose doctors are only familiar with conventional medicine.
	4	Doctors should advise against the use of well-established traditional herbs (botanical medicine) until the herbs have undergone rigorous testing such as is required for any pharmaceutical drug.
	8	Acupuncture has been found to be effective for chemotherapy-related nausea and vomiting. The system relies on unknown mechanisms (meridians). It is irresponsible for doctors to recommend acupuncture for conditions such as chemotherapy-related nausea and vomiting.
	10*	It is not desirable for a doctor to take therapeutic advantage of the placebo effect.
	12	Doctors who know about complementary and alternative practices (e.g. Traditional Chinese Medicine) in addition to conventional medicine, generate improved patient satisfaction.
	13	Therapeutic touch is not credible as a form of treatment.
	16	Chiropractic or osteopathy is a valuable method for resolving a wide variety of musculoskeletal problems.
	18	Massage therapy may make patients "feel better" temporarily, but cannot lead to objective improvement in long-term outcomes for patients.
	25	Doctors should avoid recommending herbs (botanicals) based on observation of long-term use in other cultures and systems of healing, because such evidence is not based on large randomized controlled trials.
	26	Information obtained by research methods other than randomized controlled trials has little value to doctors.
	27	It is ethical for doctors to recommend therapies to patients that involve the use of subtle energy fields in and around the body for medical purposes.
3 (attitudes toward introspection and the doctor–patient relationship)	14	Doctors who lead a balance lifestyle (i.e., attending to their own health, social, family and spiritual needs, as well as interests beyond medicine) generate improved patient satisfaction
	20	A strong relationship between patients and their doctors is an extremely valuable therapeutic intervention that leads to improved outcomes.
	21	Doctors who strive to come to terms with themselves generate improved patient satisfaction.
	22	Instilling hope in patients whenever reasonable is a doctor's duty.
	23*	Doctors should be prepared to answer patients' questions regarding the safety, efficacy, and proper usage of commonly used herbs (botanicals).
	28	Doctors who strive to come to terms with themselves provide better care than those who do not.

* These items did not load significantly on the expected factors and were removed from the model.
† These items loaded significantly on factor 1 and 2, so they were removed from the model.
‡ This item was removed from factor 3 and added to factor 1 because it made more theoretical sense to do that.

ethnicity, and geographical location of school) predicted students' rankings on the IMAQ factors. The model was also extended to explore the way in which attitudes to integrated medicine affected whether or not students themselves had visited a CAM practitioner and students' willingness to undertake a special study module in CAM. This was done by treating these two binary variables as additional indicators, which were initially allowed to load on all the factors. MIMIC modelling allows the effect of each background and indicator variable to be explored, while controlling the other background variables. It also estimates the correlations between factors, with any effects of the background variables removed. Paths that did not display significant influences were deleted in order to achieve the most parsimonious model. Again, this methodology has been used previously in this way.[30]

Results

Participants' characteristics

From the 1,154 medical students who were invited to participate, 639 students completed the questionnaire, giving a response rate of 55.4%. Of those, 144 (23%) of the responses were received from the Georgetown University School of Medicine, 142 (22%) from Birmingham, 125 (19%) from Toronto, 110 (17%) from Auckland, 94 (14%) from the Peninsula Medical School in Exeter and Plymouth, and 33 (5%) from Hong Kong. (As stated earlier, 35 of the questionnaires had missing data, and therefore the analysis was carried out using only the remaining 604 satisfactory questionnaires.) From the responders who provided demographic data, 485 (80.4%) were born in Europe, North America, or Australasia; 98 (16.3%) in Asia; and 20 (3.3%) in Africa. A total of 345 (57.1%) of the students were white, 235 (38.9%) were Asian, and 24 (3.9%) were black. Students' ages ranged from 18 to 57 years (median = 22, interquartile

range = 19–23). Over half of the responders (343; 56.8%) were women, over a third (245; 40.6%) had previously used CAM, and 136 (22.5%) reported that they had previously visited a CAM practitioner. More than two-thirds of the responding students (463; 72%) expressed their willingness to participate in a special study module on CAM.

Construct validity and reliability of the IMAQ

The first iteration of our CFA model was based on the North American sample ($n = 265$), and tested the two-factor structure of Schneider et al.[28] The output indicated that the fit of this model to the data was unsatisfactory ($\chi^2 = 786.442$, df = 349, $p < .001$, CFI = 0.677, RMSEA = 0.069, SRMR = 0.081). These poor fit indices reinforced our a priori concerns about Schneider et al.'s original study.

The first series of analyses testing our three-factor model were also conducted on the sample from North America noted above. The first iteration of our model ($\chi^2 = 733.9$, df = 347, $p < .001$, CFI = 0.715, RMSEA = 0.065, SRMR = 0.075) demonstrated that most items loaded significantly on their expected factors, with the exceptions of items 2 and 6 (factor 1), item 10 (factor 2), and item 23 (factor 3). In addition, item 17 was found to load significantly on factor 1 and factor 2. Furthermore, the values of the fit indices showed that the fit of our model was not satisfactory. The model modification indices suggested that the fit of our model, without items 2, 6, 10, 17 and 23 ($\chi^2 = 478.02$, df = 227, $p < .001$, CFI = 0.790, RMSEA = 0.065, SRMR = 0.071), could be improved if the residuals of some pairs of items were allowed to correlate. The relevant pairs of items were items 3 and 12, 4 and 25, 7 and 9, 20 and 22, and 25 and 26. These correlated residuals are indicative of shared influences on the two items in question over and above any factor that loads on them both. Typically, these shared influences derive from the two items being conceptually similar. The correlated residuals were considered appropriate, given the content of the relevant items. The final version of our model, incorporating these changes, produced a moderate fit of the model to the North American data ($\chi^2 = 340.005$, df = 222, $p < .001$, CFI = 0.887, RMSEA = 0.045, SRMR = 0.063).

The RMSEA and SRMR values indicate a good fit, but the CFI is less satisfactory and the significant chi-square value indicates some disparity between the data and the model. The CFI measures fit relative to a null model, which assumes that all the manifest variables are independent. It thus tends to be lower when applied to scales where correlations between the items are less than typical. This is the case with the IMAQ.

We then cross-validated our model derived from the North American data using data from the United Kingdom sample ($n = 236$) and found the following fit indices for our model: $\chi^2 = 285.99$, df = 222, $p = .002$, CFI = 0.894, RMSEA = 0.035, SRMR = 0.065). Unusually, and reassuringly, there was no deterioration in fit on cross-validation. Although the model is not perfect, it was considered a satisfactory working approximation on which to base the remaining analyses.

The internal consistency of the factors for the North America data was .5584 (factor 1), .6597 (factor 2), and .7087 (factor 3). For the United Kingdom data, it was .4103 (factor 1), .6568 (factor 2), and .6683 (factor 3).

How students' characteristics influenced their ranking on the IMAQ factors

The MIMIC model was based on the complete data set ($n = 604$) and on the three-factor CFA model outlined previously. The influence of background variables (i.e., age, gender, race/ethnicity, and geographical location of school) and indicator variables (i.e., whether students had previously visited a CAM practitioner and students' willingness to undertake a special study module in CAM) on the IMAQ factors were considered. The final model ($\chi^2 = 960.892$, df = 422, $p < .001$, CFI = 0.810, RMSEA = 0.046, SRMR = 0.054) indicated that the background variables *gender*, *race/ethnicity*, and *school* were significantly associated with factor 1 (attitudes toward holism). Specifically, female students, white students, and students from North American and New Zealand medical schools had more positive attitudes toward holism than did male students, black students, Asian students, and students from Hong Kong and United Kingdom medical schools.

Factor 2 (*attitudes toward the effectiveness of integrated medicine treatments*) was significantly predicted by the background variable *gender* and was reflected in both indicator variables (i.e., whether students had previously visited a CAM practitioner and students' willingness to undertake a special study module in CAM). Female students had more positive attitudes toward the effectiveness of CAM treatments than male students did. Individuals with more positive attitudes toward the effectiveness of CAM were more likely to have previously visited a CAM practitioner and to be willing to undertake a special study module in CAM.

Factor 3 (*attitudes toward introspection and the doctor–patient relationship*) was significantly associated with the background variable *school* (see Figure 1). Specifically, those from New Zealand and North American medical schools were more likely to have positive attitudes toward introspection and the doctor–patient relationship than were students from Hong Kong and United Kingdom medical schools.

In addition, although the background variable *age* was not associated with any of the IMAQ factors, it did have a statistically significant direct relationship with one of the indicator variables (i.e., whether students had previously visited a CAM practitioner), with older students being more likely to have visited a CAM practitioner than younger students. Furthermore, in addition to the background variable *school* being associated with factors 1 and 3 of the IMAQ, it also had statistically significant direct relationships with both indicator variables (i.e., whether students had previously visited a CAM practitioner and students' willingness to undertake a special study module in CAM) and item 7 of the IMAQ (i.e., "The spiritual beliefs of patients play an important role in their recovery"). More specifically, students from medical schools in the United Kingdom, Hong Kong, and New Zealand were more likely to believe that spiritual beliefs did play an important role in recovery than did students from North American schools (and in particular students from the Canadian school). Students from the New Zealand and Asian medical schools were more likely to

have previously visited a CAM practitioner than were students from the United Kingdom and North American medical schools, and students from United Kingdom medical schools were less likely to be willing to undertake a special study module in CAM than were students from any of the other schools.

Discussion

Validity and reliability of the IMAQ

When we tested Schneider's two-factor structure for the IMAQ, the fit of this model to our data was unsatisfactory. This is probably because Schneider et al. and we used different methods of analysis in our studies. In this study, we were able to validate the three-factor model and establish the internal consistency of the IMAQ factors with two large samples of medical students, one from North America ($n = 265$) and the second from the United Kingdom ($n = 236$). This is how we identified our three factors. Although the RMSEA and SRMR fit indices for this model with both sets of data indicated a good fit, our CFI indices were less satisfactory, showing that there was some disparity between the two sets of data and the model. However, there was no deterioration in fit on cross-validation with the United Kingdom sample, so we considered the model to be a satisfactory approximation on which to base further analyses.

The internal consistencies of the three factors were determined for the North American and United Kingdom samples separately and ranged from $\alpha =$. 4,103 (factor 1, United Kingdom) to $\alpha =$. 7,087 (factor 3, North America). Only one of the six Cronbach's α coefficients found met the minimum threshold of .7 suggested by Bland and Altman (see Table 2).[31] These reliability coefficients are substantially lower than those reported by Schneider et al. ($\alpha = .89$) and Lie and Boker ($\alpha = .83$).[20] These differences probably result from the dissimilar number of items used to determine internal consistency. For example, internal consistency declines with a decrease in the number of items on a factor.[32–34] Both Schneider et al.[28] and Lie and Boker[20] examined the reliability of the entire 29-item tool, whereas we looked at the reliabilities of each factor separately (with eight, ten, and five items, respectively). These smaller numbers of items could account for the low reliabilities found, for example, for factor 1 (with eight items) compared with factor 2 (with ten items). Second, internal consistency declines with an increase in sample size,[32–34] and as already stated, our sample sizes were much larger than the sample size (i.e., 100) considered adequate for reliability analyses.[35]

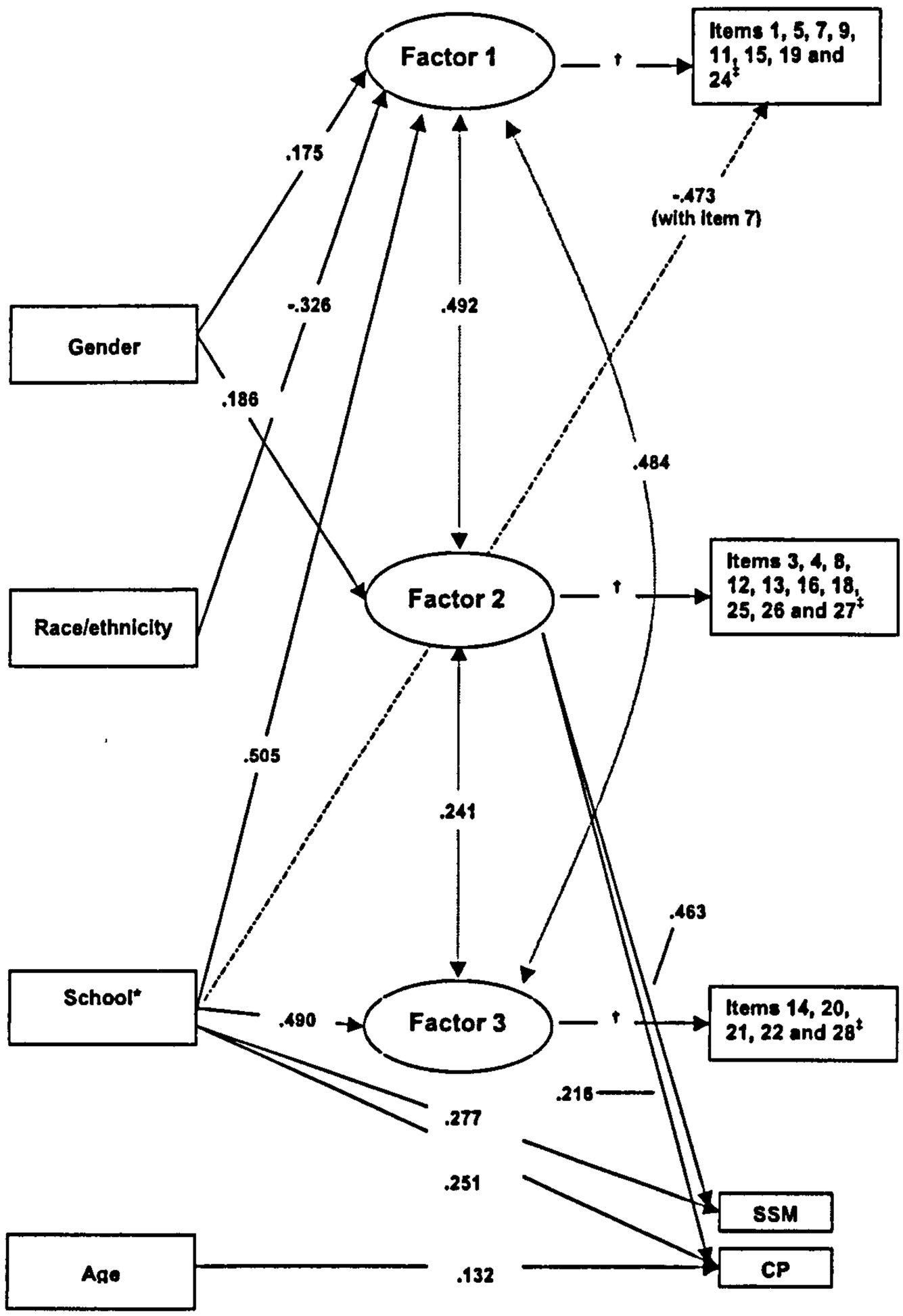

Figure 1 The relationship of the factors of the revised Integrated Medical Attitude Questionnaire to background and indicator variables from this study. A three-factor model was tested using confirmatory factor analysis.
*The background variables *school* and *race/ethnicity* were incorporated in the model through dummy coding. The individual dummy variables are not shown in the figure, to maintain clarity. The standardized path coefficients shown for *school* and *race/ethnicity* are the square root of the proportion of variance explained by the relevant set of dummy variables when taken together.
†See Table 2 for the standardized coefficients for paths to indicator variables.
‡The correlated residuals were .087 for item 7 with item 9; .254 for item 3 with item 12; .226 for item 4 with item 25; .192 for item 25 with item 26, and .109 for item 20 with item 22.

Relationship between attitudes toward holism and other student characteristics

We developed a MIMIC model from the CFA using the complete data set (also including data from New Zealand and Hong Kong, $n = 604$). This incorporated the extent to which background variables such as gender predicted students' ranking on the three IMAQ factors and also the association between students'

Table 2

Coefficients for Paths to Indicator Variables for the Three Factors Identified in This Study

Factor	IMAQ item*	Coefficient
1	1	−.314
1	5	.093
1	7	.409
1	9	.508
1	11	−.458
1	15	.261
1	19	.306
1	24	.416
2	3	.580
2	4	−.404
2	8	−.384
2	12	.500
2	13	−.496
2	16	.421
2	18	−.485
2	25	−.472
2	26	−.304
2	27	.574
3	14	.594
3	20	.403
3	21	.809
3	22	.263
3	28	.757

*IMAQ means Integrated Medicine Attitude Questionnaire.

attitudes and indicator variables such as willingness to undertake a special study module in CAM.

We found various statistically significant relationships between students' attitudes toward holism (as measured by the three factors) and various background and indicator variables. For example, *gender* predicted ranking on factors 1 and 2, meaning that female students had more positive attitudes toward holism and the effectiveness of CAM treatments. This result supports previous findings that there was higher interest in and higher use of CAM by women.[12,14,20,22]

Race/ethnicity predicted ranking on factor 1; white students had a more positive attitude toward holism compared to black and Asian students. This is initially counterintuitive given traditional views of medicine in Asian culture. However, black and Asian students choosing medicine as a career are likely to have a more positive view of orthodox than of heterodox systems, rebelling against therapies traditionally associated with their cultures and heritages and instead actively embracing Western medicine. For example, in discussing Hong Kong pharmacy students' attitudes toward CAM, Hon et al.[24] stated that despite Western and Chinese medicines being widely used by the public in Hong Kong, the students' pharmacy curricula mainly focused on Western (conventional) medicine.

Although student age was not associated with any of the IMAQ factors, it did have a direct relationship with whether students had previously visited a CAM practitioner or not. Older students were more likely to have visited a practitioner than were their younger peers. This relationship may not be because older students had more positive attitudes toward CAM but was probably because they had had more time to choose CAM for health-related problems. The same relationship of age and frequency of visits to CAM practitioners has been found in studies using general populations.[36,37] This finding differs from those in previous literature regarding medical students, which has suggested that younger students had more positive attitudes toward CAM than older students.[12,15] However, these finding may not be related to age per se but the stage of the medical school curriculum, as many studies have found medical students' attitudes becoming increasingly negative and cynical as the students progress through medical school.[38]

School predicted ranking on factors 1 and 3; students from New Zealand and North America had more positive attitudes toward holism and introspection and the doctor – patient relationship compared to students from Hong Kong and the United Kingdom. Significant and direct relationships also existed between *school* and both indicator variables (i.e., whether students had previously visited a CAM practitioner, and their willingness to undertake a special study module in CAM). Students from New Zealand and Hong Kong were more likely to have previously visited a CAM practitioner. It is difficult to explain this finding without knowing more about the local settings at all sites regarding CAM access and referral. Students from the United Kingdom medical schools were less willing to undertake special study modules in CAM than were students from other schools. Furnham and McGill[15] found statistically significant differences between students' attitudes toward CAM at a London medical school and a Newcastle medical school in the United Kingdom. Those authors failed to make any suggestions for this finding, but we assume that that these differences could be influenced by the different curricula.

The curricula of the United Kingdom and North American schools may indeed have been influences of this type. In the United Kingdom, the Peninsula Medical School has a problem-based learning curriculum and has a strong professionalism and humanism longitudinal theme, which permeates the entire five-year curriculum. Due to the perceived focus on the humanistic aspects of medicine at this school, students sometimes worry that they are not covering the biomedical sciences adequately and are therefore more inclined toward special study modules in biomedical sciences rather than holistic ones. Although Birmingham has a different curriculum, a similar picture emerges there, with students probably wanting to focus more on the biomedical aspects of medicine than those aspects focusing on holistic medicine such as behavioral sciences and professional development. In Auckland, a stronger professional development strand has been in place since 2001, and humanities options are available to balance the core biomedical science courses.

In the United States, Georgetown University Medical School has incorporated CAM-related topics in the medical school curriculum for the past four years. The first-year students who participated in this particular study were exposed to lectures on acupuncture, massage, and musculoskeletal manipulation within their gross anatomy course during the time period that we collected our study data. In addition to lectures in other core courses, all first-year medical students are offered the opportunity to participate in a mind–body medicine lecture and experiential course on a self-selection basis. Fifty students (about one-third of the class) participate in this activity every year. The early exposure of the Georgetown University students during their first semester in school to CAM-related topics

might explain the school-related differences observed in the study. In contrast, the University of Toronto medical school has a reputation for having a very rigorous science-based curriculum, despite attempts to increase the humanistic aspects of medicine and a growing focus on teaching "patient-centered" medicine.

Factor 2 (*attitudes toward the effectiveness of CAM*) had direct relationships with both indicator variables (i.e., whether students had previously visited a CAM practitioner and their willingness to undertake a special study module in CAM). These findings support those from previous studies, which were that students with past experience of using CAM had more positive attitudes toward CAM.[12,20,22] Hopper and Cohen[23] also found that previous CAM teaching related to more positive attitudes toward CAM in medical students.

Conclusions

Although our findings add to the emerging literature on medical students' attitudes toward holism and the relationship between holism and other student characteristics, our study is not without its methodological limitations, some of which have already been discussed. Despite its multischool nature and its large sample size, the overall response rate was low at 55.4%. Students volunteered to participate in this study, in accordance with ethics guidelines, and therefore constitute a self-selected group. It is possible that the students in our sample had more positive attitudes toward CAM than did students not participating in this study. However, we have only reported the relationships between students' attitudes and other variables, rather than presenting potentially biased data on medical students' attitudes per se.

The IMAQ should be seen as an instrument in development and needs further work. For example, trials should be made of new items, and additional items should be removed, such as item 7 (which is influenced by the geographical location of the school). These and other efforts could be guided by the factor structure presented in this report. However, it is clear that any attempt to distil people's attitudes toward holism and CAM into three factors is bound to be an oversimplification.

Even so, there do appear to be interesting relationships between medical students' attitudes toward holism and other characteristics such as gender, race/ethnicity, and school. The underlying reasons for such relationships are beyond this study and require further data collection. For example, why do black and Asian students, as groups, hold more negative attitudes toward holism than do white students? Why do students from the United Kingdom have more negative attitudes toward holism than do, say, North American students? Further research is required to elucidate the influences on such relationships, and qualitative methodologies may be most appropriate here, such as interviews or focus-group discussions. Without such future research, it may be difficult to tease apart the complex issues surrounding students' attitudes toward holism and CAM.

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The authors would like to thank all students who participated in this validation study. They also thank Dr. Adrian White and Professor Edzard Ernst for their help with the design of the project.

Katja Schmidt is supported by the Pilkington Family Trusts. The Georgetown University Study was funded by a grant from NIH NCCAM (AT 001193).

This project was carried out with the approval of all participating medical schools' ethics committees except in the case of the University of Hong Kong, which at the time did not need ethics approval for surveys carried out internally.

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Health Risks Over the Internet: Advice Offered by "Medical Herbalists" to a Pregnant Woman

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Keywords: Internet use – medical advice – pregnancy – medical herbalists.

Schlüsselwörter: Internetgebrauch – medizinischer Ratschlag – Schwangerschaft – medical herbalist.

Summary: Objectives: The aim of this study was to investigate Internet advice offered by "medical herbalists" to a pregnant woman regarding herbal treatment of morning sickness.
Study Design: Search engines were used to find relevant Web sites and all potential e-mail addresses were contacted. Herbalists were asked for advice regarding three specific medicinal herbs: ginger, raspberry and juniper.
Results: Eighty-three e-mail addresses were found and contacted. The response rate was 51%. Nineteen (45%) of all respondents recommended ginger, 9 (21%) of them without mentioning adverse effects. Seven (17%) respondents recommended taking raspberry; five (12%) without mentioning adverse effects. No respondent recommended taking juniper during pregnancy and 12 herbalists (29%) warned about using this herbal remedy during pregnancy.
Conclusions: Advice about herbal medicine is readily available over the Internet. The advice offered is misleading at best and dangerous at worst. Potential Internet users should be made aware of these problems and ways of minimizing the risk should be found.
(Wien. Med. Wschr. 2002;152;190–192)

Gesundheitsrisiken über das Internet: Ratschläge von "medical herbalists" an eine schwangere Frau

Zusammenfassung: Einleitung: Das Ziel dieser Studie war es, medizinische Ratschläge von „medical herbalists" (in aller Regel Nicht-Mediziner) zur pflanzlichen Behandlung von morgendlicher Übelkeit an eine Schwangere zu beurteilen.
Studiendesign: Anhand von Suchmaschinen wurden relevante Webseiten aufgesucht und potentielle E-mail-Adressen wurden kontaktiert. „Medical herbalists" wurden um Rat betreffs drei verschiedener medizinischer Pflanzen gefragt: Ingwer, Himbeere und Wacholder.
Ergebnisse: Dreiundachtzig E-mail-Adressen wurden gefunden und kontaktiert. Die Responserate betrug 51%. Neunzehn (45%) aller Studienteilnehmer empfahlen Ingwer, und 9 (21%) erwähnten keine Nebenwirkungen. Sieben Studienteilnehmer (17%) empfahlen die Einnahme von Himbeere, 5 davon (12%) ohne Nebenwirkungen zu erwähnen. Kein Studienteilnehmer empfahl die Einnahme von Wacholder während der Schwangerschaft und 12 „medical herbalists" (29%) warnten vor diesem Mittel.
Schlußfolgerungen: Ratschläge zum Gebrauch von Phytotherapeutika werden im Internet angeboten. Diese Empfehlungen sind häufig irreführend oder sogar gefährlich. Potentielle Internetbenutzer sollten auf dieses Problem hingewiesen werden. Wege zur Verringerung dieses Risikos sollten gefunden werden.

Introduction

CAM has become remarkably popular: its 1-year prevalence in general populations ranges from 65% (Germany) to 25% (UK) (9, 10). Most surveys agree that women use CAM more frequently than men (e. g. 8) and there is reason to believe that pregnant women feel particularly attracted to CAM, not least because it is promoted as free of adverse effects. Yet there is a large body of evidence that this notion is misleading (e. g. 7).

Consumers often obtain information on medical matters from the media and increasingly from the Internet (6). Given the likelihood that many pregnant women consult the Internet for advice on CAM, it seemed relevant to ask how reliable and safe such advice is. This investigation was aimed at shedding some light on to these issues. In particular, we wanted to know whether a pregnant woman is put at risk if she followed the advice obtained from medical herbalists offering recommendations over the Internet.

Material and Methods

We used the presently most popular search engines on the Internet to find useful e-mail addresses of medical herbalists world-wide. The following search engines were considered: www.excite.com, www.lycos.com, www.about. com, www.altavista.com, www.searchAOL.com, www.google.com, www.yahoo.com, www.askjeeves.com. We also used further sites recommended to us by various sources: www.scirus.-com, www.naturalhealthlink.com, www.onemedicine.com, www.healthandage.com, www.thorne.com/altmedrev/. The search terms were "medical herbalist" or "medical" + "herbalist". All sites thus found were visited. Web sites that did not provide an e-mail address were excluded. The study was conducted in May 2001. E-mail responses were collected between 14 and 23 May.

A letter was composed presenting a woman who is 12 weeks pregnant with her first child and suffers from neusea and vomiting in pregnancy (NVP). She asks the medical herbalist for advice on three specific herbs: ginger, raspberry and juniper (for full text of letter see appendix A). The letter seeks an explanation of symptoms, recommendations of other herbal remedies, and the effectiveness and safety of ginger, raspberry and juniper. Responses were assessed according to their advice on the effectiveness and safety of ginger, raspberry and juniper.

Results

Eighty-three sites with operative e-mail addresses were located and were sent our letter by e-mail (Appendix A). Forty-two responses were received (response rate = 51%). Eleven (26%) of these advertised herbal products. Six (14%) of the respondents attached information and price lists about their

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products. Forty-nine per cent of all respondents chose not to give any detailed advice – due to legal reasons, or lack of knowledge. Most of these 49% offered advice over the telephone or suggested making an appointment. Most replies came from the UK, 15 (36%); followed by the US, 10 (24%); Germany, 6 (14%); Australia, 2 (5%); and Canada: 2 (5%).

Table 1 shows the responses in relation to the three herbs. Nineteen (45%) of all 42 respondents recommended ginger as a herbal medication for morning sickness. None of them warned about possible adverse effects and 9 (21%) claimed that no such effects existed. Seven respondents (17%) recommended taking raspberry. Four respondents (10%) warned about adverse effects and suggested not taking raspberry before the last trimester of pregnancy. Five respondents (12%) claimed that there are no adverse effects involved with raspberry. Two respondents (5%) mentioned that raspberry is inappropriate for morning sickness, and one person (2%) explained that it helps to tone the uterus and prepare for contractions. No respondent recommended taking juniper during pregnancy. Twelve respondents (29%) warned about taking it – 6% said that large amounts of juniper can be "irritating on the kidneys", and three respondents (7%) advised that juniper is one of about 50 herbs NOT to be taken during pregnancy. Two per cent mentioned that juniper "affects the uterus" and another 2% said it "sounds too strong" for a herb to be taken during pregnancy.

Other herbs, vitamins and minerals were also recommended (Table 2). Further recommendations for treating nausea by changes in lifestyle are shown in Table 3. Six respondents (14%) attempted an explanation of what morning sickness is and why it might affect pregnant women. The "explanations" are summarized in Table 4. They suggest hormonal imbalances, stressful lifestyle, inadequate diet and emotional disturbances. One person (2%) provided references of clinical trials that support taking ginger for morning sickness. Seventeen percent of respondents admitted that they had no knowledge about herbal remedy use for NVP. Thirty-six percent were concerned about the legality of giving advice on the Internet. Twelve percent required more information before giving any advice, and 40% referred the e-mail sender to a medically trained alternative health practitioner, institutes, or governing bodies (e.g. Herb Line UK, Institute for Naturopathic Physicians).

Table 1. Responses in relation to the three herbs mentioned in the letter.

Responses	Ginger	Raspberry	Juniper
Use recommended	19	7	0
Warned about side effects	0	4	12
No side effect mentioned	9	5	0

Figures refer to numbers of respondents.

Table 2. Other herbal/vitamin/mineral remedies recommended by herbalists.

Remedy	Number of recommendations
Camomile	5
Peppermint	4
Black horehound	2
Melissa officinalis	1
Spearmint	1
Hops	1
Magnesium trisilicate	1
Bach flower remedies	1
"Morningmed relief"	1
Multipower/multivitamin	1

Table 3. Additional lifestyle recommendations by herbalists.

Nature of recommendation
• Eating last meal of day around 6 PM
• taking gentle walk 1 hour after dinner
• avoiding spicy food
• only sipping at drinks
• drinking frequent amounts through the day
• Drinking lots of water (2 L)
• storing herbal mixture in fridge for no longer than 3 days before preparing fresh
• trying mixture of meadow sweet, black horehound and camomile
• taking internally hydrosols (ginger root or peppermint)
• inhaling essential oils of ginger, peppermint or spearmint
• contacting natural health food stores
• contacting local qualified herbalist
• visit homeopath
• cut down or eliminate some of the foods in the nightshade family
• eat lots of vegetables and protein
• take folic acid and DHA

None of these recommendations were given more than once.

Table 4. Explanations for nausea given by herbalists.

Nature of explanation
• hormone surges but unsure about what determines it, who gets it and who does not
• can relate to high toxicity in body, prevention best through a liver cleanse before falling pregnant
• stress, diet and exercise involved with morning sickness but hard to predict who will suffer from it
• relates to individual health, changes in hormones during pregnancy
• hormone levels change, combined with low blood pressure
• could be an effect of state caused by emotional problem/ disturbance, not always evident to mother

Comment

The above data show that advice to lay people about herbal medicine is readily available over the Internet and raise concern about its accuracy and safety. Ginger is an effective treatment for nausea (16) but has been suspected to have emmenogogue (7) and abortifacient effects during pregnancy if taken in large amounts (4, 12, 15). From a cautious point of view, ginger should therefore be avoided during pregnancy. Nevertheless, 45% of respondents in this study recommended it without any mention of adverse effects. Juniper is not known to be effective for nausea but has emmenogogue effects (3, 5, 15). Its volatile oil can irritate the urinary tract which, in turn, can lead to reflex uterine stimulation (18). It is reassuring that, in our study, no respondent recommended juniper for NVP. Raspberry is thought to induce labour (17) due to its uterine stimulant activity (1, 2) and exhibits antigonadotropic activity *in vitro* (13). It is not known to be effective for nausea, yet 12% of all respondents recommended it for NVP. Little consensus exists amongst respondents about the optimal herbal treatment for NVP (Tables 1 and 2). Furthermore, no trial evidence exists for the ef-

ficacy of any of the additionally recommended herbal or other treatments for NVP (Tables 2 and 3). Similarly, most of the explanations offered for morning sickness lack a scientific rationale. Most respondents provided minimal cautionary information.

The lack of **quality control** on the World Wide Web has the potential to put patients at risk. *Eysenbach* and *Diepgen* have addressed the issue of quality control on the Internet and put forward a strategy of "distributed quality management" as a solution to the problem (11). They suggested decentralized control by third parties and users. Another suggestion was to self-label medical information by the author of the Web site in combination with a systematized critical appraisal of health-related information by third parties using a validated standard core vocabulary. Other researchers have addressed the issue of safeguarding **access to herbal remedies** (14). To quantify agreement about which herbal remedies might be regarded as unsafe, US researchers compiled a list of 113 potentially perilous herbals (PPHs) and compared it with various "negative lists" (NLs) of herbals from 9 different European countries. They found widespread international disagreement about which medicinal herb was classified as dangerous and about how access to these herbs is regulated.

Ethical considerations also need to be addressed. The main intention of this study was to mimic the process of a lay person seeking advice from a medical herbalist. The situation is comparable with what a pregnant woman or member of family could encounter when using the Internet for health care information. No patients were involved or put at risk. Nevertheless, this project entailed research on non-informed individuals (the herbalists). As there was no other way to conduct this investigation, we felt that this deception was permissible in the interest of gathering data generated to enhance patient safety. After data collection, we informed those who responded that they had received a fictitious e-mail which was part of a research project. In this way we tried to minimize our violation of informed consent. At no stage did or will we disclose the identity of the respondents to anyone outside this study. We would thus argue that our deception is justifiable and that health care professionals who use the Internet for offering advice can and should be challenged as to the validity of this advice.

Our study has several limitations. First, its sample size is too small for results to be generalizable. It is conceivable that other herbalists would have replied differently. Second, we asked for very specific advice. We chose NVP because we believed it involves a serious safety concern. Yet it is possible that the problem posed was exceedingly complex and that a simpler question would have generated more consistent answers. It is difficult to measure a medical herbalist's knowledge of NVP and CAM. On the other hand, one should point out that responsible health care professionals should abstain from giving advice if they feel that the problem is beyond their competence.

In conclusion, this preliminary investigation suggests that advice on herbal therapies obtained over the Internet for NVP can be misleading and might put patients at risk. We feel that this area, because of its implications for public health, requires further study and tighter regulation. Internet users should be made aware of these potential problems and we should find ways of minimizing the risks to our patients.

Acknowledgements

We would like to thank all participants of this e-mail survey for their co-operation. *Katja Schmidt* was supported by The Pilkington Family Trusts.

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Appendix A

Hello

My name is Katja Schmidt, I am pregnant (12 weeks/first child) and lately suffer from nausea. It is quite severe – I feel that the morning sickness affects my physical and mental state and therefore would like to ask you for advice. I've asked my doctor but he said he doesn't understand herbs.

Do you know why this affects me? A friend of mine is also pregnant but she is fine. Can I take anything for it? I am worried about taking any heavy medication (because of my unborn child) and therefore would like to use a herbal medication instead. Is there anything you can recommend? I have read somewhere that ginger, raspberry and juniper are good to take for morning sickness. Is that true? And are there any side effects?

I hope you will find some time to answer this e-mail.
Thank you very much!
Katja S.

Reflexologists' responses to a patient with abdominal pain—a survey on Internet advice

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SUMMARY. **Objective: To generate preliminary data on how individual reflexologists deal with patients seeking medical advice on the Internet. Design: E-mail survey involving reflexologists who were partly blinded for their advice on the Internet. Setting: Cyberspace. Participants: Two hundred and seventy-seven members of the Association of Reflexologists. Of 842 e-mails sent out we received 323 responses (38% response rate) of which 46 participants later withdrew their responses (14% withdrawal rate). Intervention: Participants were asked to advise a fictitious patient via e-mail who presented various health problems. Main outcome measure: Rating of responses according to safety and claims made by reflexologist sample. Results: Eighty-five percent of all respondents advised the fictitious patient to present the health problems to a medical professional. Fifty-eight percent expressed urgency to see a primary care physician or other health care professional and 95% pointed out that a diagnosis cannot and should not be made by a reflexologist. Twenty-nine percent of responders suggested a differential diagnosis or underlying causes for the patient's condition. Conclusions: In this survey reflexologists from the UK Association of Reflexologists have responded in an encouraging manner to a fictitious patient's request for health advice via electronic mail as only 5% (or possibly 15%) of reflexologists from this survey need to be more cautious about the advice they give their patients. We hope that our study will further encourage therapists to be more cautious giving Internet health advice in the future.**

INTRODUCTION

Reflexology is a therapeutic method that uses manual pressure applied to specific areas, or zones, of the feet and sometimes the hands or ears that are believed to correspond to areas of the body, in order to relieve stress and prevent and treat physical disorders.[1] It may be used together with other techniques by therapists of various disciplines. Some claimed benefits of reflexology include the acceleration of healing process by boosting and strengthening the immune system, restoring energy levels by relieving tension and improving the functioning of the body by releasing 'toxin build-up' and by providing deep relaxation.[1]

Common disorders that are treated with reflexology include asthma, back and neck pain, migraine and headaches, chronic fatigue, sinusitis, arthritis, insomnia, digestive problems such as irritable bowel syndrome and constipation, stress-related disorders and postmenopausal symptoms. Reflexology is considered a complementary therapy, and is often used alongside other forms of medicine. Some reflexologists have in the past claimed to be able to make a diagnosis. However, in one blinded study reflexologists' diagnosed conditions were no better than chance in identifying medical conditions.[2]

More and more individuals turn to the Internet for medical advice, as the Internet has become an important mass medium for patients seeking health information and health care services online.[3] When 12,000 Americans were asked about their use of Internet health resources 92% said their research was useful.[4] About 47% said that the online health information they found influenced their treatment decision. This begs the question as to the safety and appropriateness of such Internet advice. It has been suggested that almost no evidence exists that the Internet advice does any harm.[5] Our own research implies that this statement does not necessarily apply to CAM.[6,7] In previous studies of similar nature we

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doi: 10.1016/S0965-2299(03)00026-8

found, for instance, that some providers of complementary medicine were advising their clients against government policy regarding the measles, mumps and rubella vaccination.[6] No data are available on how many patients write to their own or any other reflexologist asking for advice on specific symptoms. In this study we wanted to generate preliminary data on how individual reflexologists deal with patients seeking medical by electronic mail over the Internet. Specifically, we asked the following research questions:

1. Do reflexologists respond to requests for clinical advice by e-mail?
2. Is the response rate lower if the request is identifiable as part of a research project?
3. Do reflexologists advise patients whether 'a liver is healthy' or not?
4. Can reflexologists identify by e-mail when a patient needs a medical opinion?
5. Do respondents make unconditional claims of therapeutic success?

METHODS

There are various reflexology groups and associations that provide practitioners' e-mail addresses on their websites. We decided to use the sample of members from the Association of Reflexologists (AoR). All e-mail addresses from one Internet-located database of reflexologists (http://www.aor.org.uk/) were used as the sample. The website has a link for searching the database and finding a reflexologist by name, town/county or postcode. The website does not officially state that practitioners will or will not give personal advice by e-mail. This database contains only registered members of the AoR. E-mail addresses were randomised according to a computer-generated list of random numbers and thus divided into two groups. Group A consisted of 519 e-mail addresses and group B of 520 e-mail addresses from the directory.

A letter (Appendix A) was sent to reflexologists in group A. In this letter, a (fictitious) patient reported that he suffered from abdominal pain, weight loss and low energy levels. These symptoms can be indicative of liver cirrhosis, liver secondaries or stomach cancer with liver metastases. Reflexologists in group B were asked for their advice as part of a research project. A vignette was included in the e-mail, which described the same fictitious case as in group A (Appendix A). Thus, members of group A and B were asked the same question, only in different contexts.

E-mails to group A were sent on 15 January 2002 and our closing date for responses was 29 January 2002. E-mails to group B were sent on 31 January 2002 (after group A, to avoid contamination between groups) and our closing date was 14 February 2002. After data collection, we informed all respondents from group A that they had received an e-mail from a fictitious patient as part of a research project. (In this way we tried to minimise our violation of the informed consent principle.) The letter also assured confidentiality, explained the intention of the project (to evaluate the quality and reliability of advice given via the Internet) and offered respondents the chance to withdraw their participation retrospectively.

Free text responses were categorised by the first author and checked by the second.

Responses were evaluated descriptively. SPSS version 9.0 was used to calculate confidence intervals for the response rate and various recommendations of reflexologists. Estimates are reported with 95% confidence intervals, and Chi-square statistical test is used for comparisons of proportions in response rates.

The ethics committee of the University of Exeter, School of Sport and Health Sciences gave ethical approval for the research protocol.

RESULTS

Of 519 e-mails sent to group A, 94 could not be delivered. Of the 425 e-mails that were delivered, we received 221 responses (response rate = 52%). One e-mail response could not be opened because it contained a virus. After retrospectively debriefing the participants and asking them for their consent, 28 participants withdrew their responses. Thus group A yielded 189 usable responses.

Of 520 e-mails sent in group B, 417 were successfully delivered and we received 102 responses (response rate = 24%), of which 14 later asked to withdraw from the study. Group B yielded 88 usable reflexologists' responses. Seven (8%) of those were categorised as 'non-responders' because they either did not answer any of the questions or wanted to discuss problems on the phone. One reflexologist responded but at the same time withdrew permission to use that response. The response rates were significantly different with χ^2 $(3, n = 842) = 67.53$, $P < 0.001$.

The majority of reflexologists in both groups declined to offer a diagnosis (Table 1): 65% in group A (95% CI, 0.58–0.72), and 61% in group B (95% CI, 0.51–0.71). Eighty-six percent in group A (95% CI, 0.8–0.9) and 84% in group B (95% CI, 0.86–0.98) suggested that the patient should see a doctor or other health professional, usually adding some degree of urgency (Table 2): 53% group A (95% CI, 0.46–0.6) and 69% in group B (95% CI, 0.59–0.79). Two reflexologists in group B gave a 'yes' to the question 'Can you say whether I have something wrong with my liver?'.

A few reflexologists answered the question as to whether a cure can be offered and some explained that their code of ethics does not allow reflexologists to claim to cure. One reflexologist was confident that reflexology could make the patient well again (Table 3).

Table 1 Reflexologists' responses to the issue of 'diagnosis'

Responses	Group A ($n = 189$)	Group B ($n = 88$)	All ($n = 277$)
Reflexologists not allowed to make diagnosis	24 (13%)	7 (8%)	31 (11%)
Reflexology is not a diagnostic tool	98 (52%)	47 (53%)	145 (52%)
No mention of diagnosis	58 (30%)	28 (32%)	86 (31%)
Can diagnose energetic imbalances	2 (1%)	1 (1%)	3 (1%)
Suggest condition concerns the liver	7 (4%)	3 (4%)	10 (4%)
Can diagnose	0	2 (2%)	2 (1%)

Table 2 Reflexologists' responses to 'seeing a primary care physician'

Responses	Group A ($n = 189$)	Group B ($n = 88$)	All ($n = 277$)
Advise to see medical doctor	162 (86%)	74 (84%)	236 (85%)
Urgency expressed to see medical doctor	100 (53%)	61 (69%)	161 (58%)
No mention of doctor	27 (14%)	12 (14%)	39 (14%)
Advise to see naturopath	0	1 (1%)	1 (0.4%)
Advise to follow instincts when deciding	0	1 (1%)	1 (0.4%)

Table 3 Reflexologists' responses to the claim to cure ('making me well again')

	Group A ($n = 189$)	Group B ($n = 88$)	All ($n = 277$)
Not claimed	29 (15%)	30 (34%)	59 (21%)
Not mentioned	151 (80%)	55 (63%)	206 (74%)
Possibly	9 (5%)	2 (2%)	10 (4%)
Yes	0	1 (1%)	2 (1%)

Some reflexologists attempted offering a differential diagnosis of conditions or possible underlying causes of a disease the patient might suffer from (Table 4). The conditions most frequently mentioned were stress, incorrect diet, liver problem, irritable bowel syndrome, digestive disorder and allergies. Two respondents suggested a diagnosis of stomach cancer.

CAM therapies that were recommended in addition included various diets, naturopathy, homeopathy and detoxification (Table 5).

Most reflexologists suggested that the patient must see a primary care physician in order to get a medical diagnosis and to rule out any serious condition. Some responders suggested blood tests. Three reflexologists (2%) asked for a referral from

Table 4 Possible conditions suggested by respondents

Primary		Possible underlying causes	
Allergy	4	Anxiety	1
Appendicitis	2	Depression	1
Bowel obstruction	1	Diet	8
Cancer	2	Exercise	1
Cirrhosis	2	Lifestyle	3
Coeliac disease	2	Stress	21
Colon	1		
Constipation	1		
Crohn's disease	1		
Cyst	1		
Digestive disorder	4		
Gall bladder	1		
Gall stones	1		
Hepatitis	1		
IBS	5		
Kidney infection	2		
Liver problem	7		
Pancreatitis	1		
Parasitic/fungal infection	1		
(Peptic) ulcers	3		
Stomach	1		
Tumours	1		

Table 5 Additional CAM recommendations

Acidophilus	1
Acupressure	1
Acupuncture	2
Aloe vera	2
Cooked millet 3× daily	1
Counselling	1
Craniosacral therapy	2
Detoxification	5
Dietary changes	9
Energy healing	1
Glasses of water 6× daily	1
Grapeseed extract	1
Green magic	1
Homeopathy	4
Kinesiology	1
Lemon and ginger tea	1
Mastic gum	1
Medical herbalist	3
Milk thistle	2
Naturopathy	5
Nutritionist	9
Pycnogelpine bark	1
Reiki	1
Supplements	2
Visceral manipulation	1
Vitamin B	1

the primary care physician to say that the patient may receive reflexology. Two responders (1%) suggested seeing a gastroenterologist. Two further respondents (1%) advised the patient to actively seek medical treatment.

DISCUSSION

This study investigated UK reflexologists' advice given to a patient suffering from abdominal pain, fatigue and weight loss. The symptoms presented were chosen to be alarming and to warrant urgent medical attention. Our study has shown that reflexologists are more likely to respond to an unsolicited e-mail by a patient than to a researcher approaching them. The response rate of the group who was covertly approached was more than twice as high as the other group.

It is reassuring to see that 85% of all respondents advise the (fictitious) patient to present the health problems to a medical professional. If our data were generalisable, which they are not, we would have to assume that one in six UK reflexologists does not advise seeing a doctor. This finding, however, needs to be viewed with caution.

It is also encouraging that 58% expressed some urgency in seeing a primary care physician or another health care professional and that 95% pointed out that a diagnosis cannot and should not be made by a reflexologist. However, 29% of responders seem to suggest a differential diagnosis or suggest underlying causes for the patient's condition. It should be noted that a number of reflexologists suggested that they could 'help the patient to heal themselves', which might by a patient be interpreted as claiming to cure. Most reflexologists in this study, however, reacted in a responsible manner.

There are several limitations to our study. The low response rate (especially in group B) limits the generalisability of our results. It was caused by interference from the AoR. The AoR stopped our research for approximately 1 week, advising AoR members to withdraw from our study if they had participated. Subsequently, after requesting and receiving a copy of the ethics approval the AoR sent another e-mail to all respondents recommending co-operation. Through this interference we incurred 55 withdrawals (39 group A and 16 group B) of which only 12 subsequently overturned their withdrawal. Moreover, our findings cannot be generalised to members of other reflexology societies. Additionally, summarising the results obscures the details of individual responses.

It might be distressing for professionals to be tested covertly by this method but it is more distressing for patients to be given unreliable health advice. The general principle should always be that practitioners need to be cautious about giving advice without knowing all details (i.e. via the Internet, telephone, etc.) and patients should be very cautious in asking for and accepting such advice.

Our research questions related to a possible area of risk to patients. We suspected that, without deception, we would not generate a truthful picture. This suspicion was confirmed by our findings that the response rate fell from 52% in the blinded group to 24% in the open group. The latter low response rate might have been exaggerated by the interference from the AoR. However, other studies have also shown a lower response rate in the open group (30%) compared to the blinded group (53%) in a study investigating acupuncturists' response to an unsolicited e-mail.[6] We would like to point out that very little harm was conceivable as a result of this project; in fact we hope that the publication of our results will encourage more cautious Internet health advice in the future, thus increasing patient safety.

There is a very large grey area between asking general health questions and confronting a health practitioner with a clinical problem.[8] Whereas e-mail advice replying to general health questions is giving general health information (which is not considered 'practising medicine'), answering an unsolicited e-mail which is asking about a specific clinical problem, can be regarded as medical practice. The UK General Medical Council advises medical practitioners on how to deal with providing advice and medical services online or by telephone.[9] They clearly state that standards of care may be compromised in online consultations because of the lack of a patient–doctor relationship. They also advise that practitioners who wish to provide online health advice need to consider whether such services will serve their patients' interests. Professional associations and organisations might need to be involved in advising their members accordingly.

The AoR has been noted as taking the lead in regulation and standard setting for UK reflexologists (own observation). Possibly, further Internet studies of a similar kind could explore whether members of other professional reflexology organisations respond in a different way, and how seriously patients consider advice given by practitioners outside the health service.

APPENDIX A.

Letter to group A

Dear reflexologist

By looking for reflexologists on the Internet I found your e-mail address. I'm 40 years old and suffer increasingly for about 6 months from stomach pains. I don't seem to have the energy to do anything and I think I'm losing weight. Even though I stopped drinking 3 years ago, I think I might have something wrong with my liver. Can you as a reflexologist tell whether I have? Can you make me well again? Do you think I should see my doctor even though I have completely lost faith in conventional medicine?

Letter to group B

Dear reflexologist

My name is Katja Schmidt and I am a member of the Department of Complementary Medicine, University of Exeter. I found your e-mail address at http://www.aor.org.uk/ on the Internet. I am currently working on exploring the field of reflexology. Would you please be so kind to read the following vignette and answer the questions involved?

"By looking for reflexologists on the Internet I found your e-mail address. I'm 40 years old and suffer increasingly for about 6 months from stomach pains. I don't seem to have the energy to do anything and I think I'm losing weight. Even though I stopped drinking 3 years ago, I think I might have something wrong with my liver. Can you as a reflexologist tell whether I have? Can you make me well again? Do you think I should see my doctor even though I have completely lost faith in conventional medicine?"

Thank you very much for your help.
Best wishes,
Katja Schmidt

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PERFUSION
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PERFUSION 15; 2002: 44–50

Internet advice by acupuncturists – a risk factor for cardiovascular patients?

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Summary
Background: **Acupuncture is often used for smoking cessation yet it has been shown to be no more effective than sham and not to be entirely free of risk. With more and more patients turning to the Internet for medical advice it seemed appropriate to determine the reliability of the advice given by acupuncturists over the Internet.**
Methods and results: **E-mail addresses were located through a pre-defined strategy and randomly divided into three groups. A letter was sent to groups A and B from a fictitious pacemaker patient asking about the safety and efficacy of electro-acupuncture treatment for smoking cessation. The difference between group A and B was that the patient in group B claimed to live in the acupuncturist's area. Group C was asked for their advice on electro-acupuncture for smoking cessation as part of a research project.**
The response rates in group A and B were similar (55 % group A, 53 % group B) whereas in group C it was significantly lower (30 %). Concerns with electro-acupuncture administered to a patient with a pacemaker were issued by 33 % of all acupuncturists. There are, however, significant differences between subgroups. When the question was asked in the context of a research project, the response was markedly more cautious.
Conclusions: **Recommendations, issued by acupuncturists regarding smoking cessation, are not based on the current evidence as to efficacy of this intervention and concerns about the potential harm of acupuncturists' advice emerge.**

Keywords: acupuncture, pacemaker, Internet

Zusammenfassung
Hintergrund: **Akupunktur wird häufig zur Raucherentwöhnung empfohlen, obwohl sie sich nicht effektiver als Scheinakupunktur erwiesen hat und nicht völlig frei von Risiken ist. Immer mehr Patienten nutzen das Internet, um medizinischen Rat zu erhalten. Es schien uns daher angebracht, die Zuverlässigkeit solcher Ratschläge zu untersuchen, die von Akupunkteuren über das Internet gegeben wurden.**
Methodik: **E-Mail-Adressen wurden mit einer zuvor festgelegten Strategie lokalisiert, randomisiert und in 3 Gruppen eingeteilt. Ein Brief von einem fiktiven Herzschrittmacherpatienten, in dem sich der Patient nach der Sicherheit und dem Nutzen der Elektroakupunkturtherapie für die Raucherentwöhnung erkundigte, wurde an die Gruppen A und B gesandt. Der einzige Unterschied zwischen den Gruppen A und B bestand darin, dass der Patient in der Gruppe B behauptete, in der Nähe des Akupunkteurs zu wohnen. Die Gruppe C wurde zur Elektroakupunktur für die Raucherentwöhnung als Teil eines Forschungsprojektes befragt.**
Ergebnisse: **Die Responsraten in Gruppe A und B waren sehr ähnlich (55 % Gruppe A, 53 % Gruppe B); in der Gruppe C lag sie dagegen bei 30 %. 33 % aller Akupunkteure äußerten Bedenken zur Anwendung der Elektroakupunktur bei einem Patienten mit Herzschrittmacher. Es bestanden jedoch signifikante Unterschiede zwischen den verschiedenen Gruppen. Wenn die Frage im Kontext eines Forschungsprojektes gestellt wurde, waren die Antworten deutlich zurückhaltender.**

Cigarette smoking continues to be the major cause of morbidity and mortality in many industrialised countries. The Joint European Societies recently found that the prevalence of smoking increased from 19.4 % (1994) to 20.8 % (1998) [1]. Every fifth coronary heart disease (CHD) patient continued to smoke despite myocardial infarction. Patients are more successful in quitting if they receive interventions from health care professionals [2]. A population survey in 1996 suggested that 15 % of respondents would use complementary medicine (CAM) to quit smoking [3].
It has been suggested that acupuncture releases endogenous opioid peptides which may assist in reducing opiate withdrawal syndromes [4]. Acupuncture, in particular electro-acupuncture, is often used for smoking cessation [e.g. 5]. Yet it has been conclusively shown to be no more effective than sham [6]. Moreover, it is not entirely free of risk [7]. One particular risk of electro-acupuncture is the interference of the electrical impulses with the function of a pacemaker [8]. This risk is well known and is cited in standard texts of acupuncture [e.g. 9, 10, and 11].
More and more individuals turn to the Internet for medical advice. When 12,000 Americans were asked about their use of Internet health resources 92 % said their research was useful [12]. About 47 % said the answer they found for their own enquiries influenced their treatment decision. This begs the question as to the adequacy of such Internet advice. It has been suggested that almost no evidence exists that the Internet advice does any harm [13].

*Katja Schmidt was supported by The Pilkington Family Trusts

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***Schlussfolgerung*: Empfehlungen von Akupunkteuren zur Raucherentwöhnung basieren nicht auf der Evidenz zur Effektivität dieser Intervention. Der Rat von Akupunkteuren erscheint nicht risikofrei zu sein.**

Schlüsselwörter: Akupunktur, Herzschrittmacher, Internet

We wanted to know how good advice of acupuncturists via the Internet is and used the model of a pacemaker patient wishing to give up smoking. We therefore sent a letter from a fictitious patient, a method previously applied [e.g. 14], in order to answer the following research questions:

1. Do acupuncturists recommend acupuncture for smoking cessation despite good evidence for the ineffectiveness of this approach?
2. Do acupuncturists take account of the risks associated with electro-acupuncture for a pacemaker patient?
3. Do the answers of acupuncturists differ according to
   a) patient or researcher asking the question
   b) professional qualification of the therapist
   c) location of the therapist (i.e. in the area of patient or not)?

Methods

All e-mail addresses listed on the website www.acupuncture.com/Referral/ were used to recruit our study sample. The directory included the following countries: Argentina, Australia, Austria, Belgium, Barbados, British West Indies, Brazil, Canada, China, Cyprus, Denmark, Egypt, Finland, France, Greece, Germany, Hong Kong, India, Ireland, Israel, Italy, Japan, Korea, Mexico, Netherlands, Norway, New Zealand, Pakistan, Portugal, Puerto Rico, Saudi Arabia, Singapore, South Africa, Spain, Sweden, Taiwan, United Arab Emirates, UK, USA and Viet Nam. E-mail addresses were randomised according to a computer-generated list of random numbers : and thus divided into three groups. Group A consisted of 288 e-mail addresses, group B of 288 e-mail addresses and group C of 289 e-mail addresses from the directory.
A letter (see Appendix) was sent to group A. In this letter, a (fictitious) patient reported to have been given a pacemaker after an acute myocardial infarction two months ago and asked about the safety and efficacy of acupuncture treatment for smoking cessation. A slightly different version of that letter was sent to group B (see Appendix). The difference was that the patient claimed to live in the acupuncturist's area. After collecting responses for group A and B we found that only five respondents from group A (4 %) and twenty-two respondents from group B (23 %) expressed their concern about using electro-acupuncture in the presence of a pacemaker. We therefore decided to send a follow-up e-mail to all respondents of group A and B in which the patient inquired specifically about the safety of electro-acupuncture (see Appendix). Responses to the initial and follow up question were used in the analysis. Group C was asked for their advice on electro-acupuncture for smoking cessation as part of a research project. A vignette was included in the e-mail, which described the same fictitious case as in group A and B (see Appendix). Thus, members of group A, B and C were asked the same question with the difference that group A and B were blinded to the fact that this was a research project.
E-mails to group A and B were sent on 18.07.2001 and our closing date for responses was 06.08.2001. E-mails to group C were sent on the 30.07.2001 (after group A and B to avoid contamination between groups) and our closing date was 08.08.2001. All responses were collected in the period between 18.07. – 08.08.2001. After data collection, we informed all respondents from group A and B that they had received an e-mail from a fictitious patient, which was part of a research project. (In this way we tried to minimise our violation of informed consent.) The letter also assured confidentiality and explained the intention of the project (to evaluate the quality and reliability of advice given via the Internet) and offered respondents the chance to withdraw their participation retrospectively.
Finally, we categorised respondents according to their qualification as an acupuncturist listed on the www.acupuncture.com referral webpage. Data were evaluated descriptively. SPSS version 9.0 was used to calculate confidence intervals for the response rate, the recommendations of acupuncture treatment and any mention of adverse effects. Estimates are reported with 95 % confidence intervals, and χ^2 statistical test is used for comparisons of proportions in response rates.

Results

The main professional groups were: *Licensed acupuncturist* (Licensed Acupuncturist, Acupuncturist with Diploma, Acupuncturist Physician, Registered Acupuncturist, Certified Acupuncturist), *medical doctors*, *DOM* (doctor of oriental medicine), *other qualification* (e.g. Bachelor of Acupuncture, PhD) and *no discernible qualification*. Table 1 shows the sample sizes and response rates for all three groups.

Group A

Group A consisted of originally 288 e-mail addresses, 62 addresses were returned with the note »user unknown«. Thus 226 e-mails were sent and received in group A. We received 125 responses (initial response rate = 55 %) (Table 2). No participant wished to withdraw from the study.
Most of the responses we received were from licensed acupuncturists (LAc). One hundred and fifteen respondents (92 %) recommended the use of acupuncture (95 % CI, 87 % to 97 %). Forty-four respondents (35 %) stated that acupuncture was safe if performed by a qualified acupuncturist (95 % CI, 27 % to 43 %). Twenty-two respondents (18 %) stated that acupuncture treatment involved few or. minimal risks (95 % CI, 11 % to 25 %). Five respondents warned about the application of electro-acupuncture for the patient (Table 3).
After sending our follow-up e-mail regarding electro-acupuncture (see above) we received 42 responses from respondents of group A (follow up response rate = 34 %) (Table 4). Most

Table 1: Sample size of groups A, B, C and all groups together

	Group A Blinded, general	Group B Blinded, local	Group C Unblinded	All groups
Sample size*	226	221	223	670
Number of responses received	125 (55 %)	117 (53 %)	67 (30 %)	309 (46 %)

*Defined as e-mails sent and received

Table 2: Group A – initial responses listed by profession (%) (MD = medical doctor, DOM = doctor of oriental medicine, CI = confidence interval)

	Licensed (n=112)	MD (n=3)	DOM (n=8)	Others (n=1)	No discernible qualification (n=1)	All professions (n=125)
Acupuncture recommended	94 (84)	2 (67)	7 (88)	1 (100)	1 (100)	105 (84) 95 % CI, 87 to 97
Acupuncture safe	39 (35)	1 (33)	4 (50)	0 (0)	0 (0)	44 (35) 95 % CI, 27 to 43
Risks involved in acupuncture	20 (18)	0 (0)	1 (13)	1 (100)	0 (0)	22 (18) 95 % CI, 11 to 25

Table 3: Group B – initial responses listed by profession (%) (MD = medical doctor, DOM = doctor of oriental medicine, CI = confidence interval)

	Licensed (n=95)	MD (n=7)	DOM (n=3)	Others (n=4)	No discernible qualification (n=12)	All professions (n=117)
Acupuncture recommended	79 (83)	6 (86)	3 (100)	3 (75)	8 (67)	99 (85) 95 % CI, 75 to 89
Acupuncture safe	21 (22)	1 (14)	0 (0)	1 (25)	2 (17)	25 (21) 95 % CI, 14 to 28
Risks involved in acupuncture	30 (32)	2 (28)	1 (33)	2 (50)	5 (42)	40 (34) 95 % CI, 25 to 41

Table 4: Group A – follow-up responses listed by profession (%) (MD = medical doctor, DOM = doctor of oriental medicine, CI = confidence interval)

	Licensed (n=37)	MD (n=1)	DOM (n=3)	Others (n=0)	No discernible qualification (n=1)	All professions (n=42)
Electro-acupuncture recommended	13 (35)	0 (0)	0 (0)	0 (0)	1 (100)	14 (33) 95 % CI, 17 to 45
Electro-acupuncture not recommended	14 (38)	0 (0)	2 (67)	0 (0)	0 (0)	16 (38) 95 % CI, 19 to 47
Concerns about pacemaker	17 (46)	0 (0)	1 (33)	0 (0)	0 (0)	18 (43) 95 % CI, 25 to 55

Table 5: Group B – follow-up responses listed by profession (%) (MD = medical doctor, DOM = doctor of oriental medicine, CI = confidence interval)

	Licensed (n=55)	MD (n=4)	DOM (n=1)	Others (n=1)	No discernible qualification (n=9)	All professions (n=70)
Electro-acupuncture recommended	8 (15)	3 (75)	0 (0)	0 (0)	1 (11)	12 (17) 95 % CI, 8 to 26
Electro-acupuncture not recommended	30 (55)	1 (25)	1 (100)	0 (0)	6 (67)	38 (54) 95 % CI, 42 to 66
Concerns about pacemaker	31 (56)	1 (25)	1 (100)	0 (0)	6 (67)	39 (56) 95 % CI, 44 to 68

of those responses were from LAc. Thirteen respondents (31 %) recommended using electro-acupuncture if a qualified practitioner is applying it (95 % CI, 17 % to 45 %). Fourteen respondents (33 %) recommended not using electro-acupuncture (95 % CI, 19 % to 47 %). Seventeen respondents (40 %) expressed their concern about the pacemaker (95 % CI, 25 % to 55 %).

Group B

In group B, 288 e-mails were sent; 67 e-mails could not be delivered because 'user unknown'. Thus 221 e-mails were sent and received in group B. One hundred seventeen responses were received (initial response rate = 53 %) (Table 3). Again, most responses we received from licensed acupuncturists. Four participants from this group wished to withdraw from the study.

Ninety-nine respondents (84 %) recommended acupuncture treatment if applied by a qualified acupuncturist (95 % CI, 75 % to 89 %). Twenty-five respondents (21 %) claimed acupuncture is a safe therapy if used by a qualified acupuncturist (95 % CI, 14 % to 28 %), forty respondents (34 %) mentioned that there are few to minimal risks involved (95 % CI, 25 % to 41 %). Twenty-two respondents (19 %) expressed their concern about the pacemaker.

After sending the follow up e-mail we received 70 responses (follow up response rate = 60 %) (Table 5). Twelve respondents (17 %) recommended the use of electro-acupuncture (95 % CI, 8 % to 26 %). Thirty-eight participants (54 %) recommended not using electro-acupuncture for the particular condition (95 % CI, 42 % to 66 %). Thirty-nine participants (56 %) expressed their concern about the pacemaker (95 % CI, 44 % to 68 %).

Group C

In group C, 289 e-mails were sent of which 62 were returned because 'user unknown'. Thus, 223 e-mails were sent and received. We received sixty-eight responses (response rate = 31 %) (Table 6). Most responses we received from licensed acupuncturists. One participant wished to withdraw from the study.

Table 6: Group C – initial responses listed by profession (%) (MD = medical doctor, DOM = doctor of oriental medicine, CI = confidence interval)

	Licensed (n=53)	MD (n=3)	DOM (n=4)	Others (n=2)	No discernible qualification (n=6)	All professions (n=67)
Electro-acupuncture recommended	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6) 95 % CI, 1 to 11
Electro-acupuncture not recommended	44 (83)	3 (100)	4 (100)	2 (100)	5 (83)	58 (87) 95 % CI, 77 to 93
Concerns about pacemaker	37 (70)	3 (100)	4 (100)	2 (100)	5 (83)	51 (76) 95 % CI, 65 to 85

Table 7: Responses according to their professional status (MD = medical doctor, DOM = doctor of oriental medicine)

	Licensed acupuncturist	MD	DOM	Other qualification	No discernible qualification
Number of initial responses received	177	13	15	7	19
Number of follow-up responses received (group A+B)	92	5	4	1	10
Recommendation to use electroacupuncture	25 (17 %)	3 (38 %)	0 (0)	0 (0)	2 (13 %)
Pacemaker concern mentioned	85 (59 %)	4 (50 %)	6 (75 %)	2 (67 %)	11 (69 %)
Recommendation to use acupuncture (group A+B)	173 (98 %)	8 (62 %)	10 (67 %)	4 (57 %)	8 (47 %)

Table 8: Additional co-interventions suggested by groups A, B and C (some co-interventions were recommended more than once)

Behavioural	Orthodox/Medical	Nutritional 1. Avoidance	2. Recommendation
Aromatherapy	Gum	Alcohol	Ardisia tablets
Behaviour modification Program	Nicotine gum	Caffeine	Chinese herbal supplements
Biofeedback	Nicotine patches	Smokers	Chinese teas
Breathing meditations	Zyban antidepressant	Soda pops	Coenzyme Q gel
Counselling		Sweets	Co-Q 10
Detoxification		Decrease sugar intake	Drinking water
Drainage techniques (homeopathic + biomedical)		Hot spicy food	Flaxseed
Ear seeds (wine treated vaccaria)			Flower essences
Enzyme therapy			Fruit + vegetables
Exercise			Grape-seed extract
Herbal therapy			Green tea
Homeopathic remedies			Hawthorne
Hypnotherapy			Lobelia tea
Join group			Lobelia tincture
Macrobiotics			Magnesium
Meditation			Minerals
Naturopathy			Nutritional advice
New hobbies			Olive oil
Prayer			Vegetarianism
Psychotherapy			Vitamin A&C
Relaxation			Vitamin B
Socialising pattern change			Vitamins C & E
Softlaser acupuncture			
Support groups			
Tai chi			
Telling others			
Thought field therapy			
Walks			
Yoga			

Four respondents (6 %) from group C recommended electro-acupuncture treatment (95 % CI, 1 % to 11 %). Fifty-eight respondents (87 %) recommended not using electro-acupuncture (95 % CI, 77 % to 93 %). Fifty-one participants (76 %) expressed their concern about the pacemaker (95 % CI, 65 % to 85 %).

Differences between groups

The response rates in group A and B were similar (55 % group A, 53 % group B) and group C had the lowest response rate (30 %) which was significantly smaller than groups A and B (χ^2 23.97, df 1, $p<0.001$). The respondents from group C had the lowest rate for recommending electro-acupuncture for the patient (6 %), followed by group B (17 %) and group A (33 %). This difference between groups A, B and C was significant (χ^2 13.87, df 5, $p<0.05$).. Similarly, concerns about the pacemaker were expressed by 51 (75 %) respondents in group C, followed by 39 (56 %) in group B and 17 in group A (43 %).
Our results show that 55 % (group A) and 53 % (group B) of acupuncturists responded to an e-mail from a (fictitious) patient and 30 % (group C) responded to a query from a researcher. These response rates were significantly (response rates in groups A and B significantly differed to group C – χ^2 23.97, df 1, $p<0.001$).

Discussion

One of our primary research questions related to the recommendations by acupuncturists to use acupuncture for smoking cessation. The evidence shows that this is no more effective than sham acupuncture [6] and considering safety concerns related to the presence of a pacemaker [8]. Our results show that 10 % of all acupuncturists (33 % of group A, 17 % of group B and 6 % of group C) would recommend electro-acupuncture in this particular situation. The respondents of group A significantly differed in their recommendation for electro-acupuncture treatment compared to group C. Thus, recommendations seem to vary according to blinding/deception. When a researcher approached acupuncturists openly, the response rate was 24 % lower than when

Appendix

Letter sent to Group A

Dear acupuncturist,
I found your e-mail address in the »International Acupuncturist Referral Directory« on the Internet. My name is Paul Stanfield, I am 53 years old and recovering from a heart attack, which I had 2 months ago. I now live with a pacemaker. I realise that I need to change a few things about my lifestyle. I am a heavy smoker and have tried everything to quit smoking. I want to get better and give up cigarettes for good. Can acupuncture help me? Are there any risks involved?
I hope you can give me some advice and have the time to reply.
Best wishes, Paul S.

Letter sent to Group B

Dear acupuncturist,
I live in your area and found your e-mail address in the »International Acupuncturist Referral Directory« on the Internet. My name is Paul Stanfield, I am 53 years old and recovering from a heart attack, which I had 2 months ago. I now live with a pacemaker. I realise that I need to change a few things about my lifestyle. I am a heavy smoker and have tried everything to quit smoking. I want to get better and give up cigarettes for good. Can acupuncture help me? Are there any risks involved? I hope you can give me some advice and have the time to reply.
Best wishes, Paul S.

Letter sent to Group C

Dear acupuncturist,
My name is Katja Schmidt and I am member of the Department of Complementary Medicine, University of Exeter. I found your e-mail address in the »International Acupuncturist Referral Directory« on the Internet. I am currently working on a research project in which I am looking at the role of acupuncture in dealing with smoking cessation. Would you please read the following vignette and answer the questions below?
Mr S. is 53 years old and recovering from a heart attack, which he had 2 months ago. He now lives with a pacemaker. He wants to change his lifestyle. He is a heavy smoker and has tried various methods to quit smoking. He wants to get better and give up cigarettes for good.
Would you think acupuncture is efficacious for smoking cessation in his case?
Do you think acupuncture involves risks for Mr S.?
Do you have any other comments?
Thank you very much for finding the time to answer and support my research project in this way. I appreciate you co-operation.
Sincerely, Katja Schmidt

Follow-up group A

Thank you very much for your reply to my e-mail (see below).
I have now spoken to my cousin who swears by electro-acupuncture for smoking cessation. Do you think this will work for me or does it involve any risk?
I will attach my previous e-mail in case you have forgotten what it was about.
Again, thank you very much
Best wishes, Paul S.

Dear acupuncturist,
I found your e-mail address in the »International Acupuncturist Referral Directory« on the Internet. My name is Paul Stanfield, I am 53 years old and recovering from a heart attack, which I had 2 months ago. I now live with a pacemaker. I realise that I need to change a few things about my lifestyle. I am a heavy smoker and have tried everything to quit smoking. I want to get better and give up cigarettes for good. Can acupuncture help me? Are there any risks involved?
I hope you can give me some advice and have the time to reply.

Follow-up group B

Thank you very much for your reply to my e-mail (see below).
I have now spoken to my cousin who swears by electro-acupuncture for smoking cessation. Do you think this will work for me or does it involve any risk?
I will attach my previous e-mail in case you have forgotten what it was about.
Again, thank you very much
Best wishes, Paul S.

Dear acupuncturist,
I live in your area and found your e-mail address in the »International Acupuncturist Referral Directory« on the Internet. My name is Paul Stanfield, I am 53 years old and recovering from a heart attack, which I had 2 months ago. I now live with a pacemaker. I realise that I need to change a few things about my lifestyle. I am a heavy smoker and have tried everything to quit smoking. I want to get better and give up cigarettes for good. Can acupuncture help me? Are there any risks involved? I hope you can give me some advice and have the time to reply.

being approached by a patient. However, acupuncturists did not significantly differ in their recommendation to electro-acupuncture according to their locality when comparing group A and B. In group C the proportion of recommendations for electro-acupuncture decreased to 6 %. This implies that acupuncturists tend to answer differently depending on the context in which they are being asked. These results imply that deception is a necessary prerequisite for conducting investigations into the safety of Internet advice.

Concerns about electro-acupuncture administered to a patient with a pacemaker were expressed by 62 % of all acupuncturists. There are, however, remarkable differences between subgroups. The least concerns about a risk were expressed in group A. The difference between group A and group C was significant (see confidence intervals). Group B may have issued more cautious recommendations as they had to consider the possibility of actually treating this patient. When the question was asked in the context of a research project, the response was markedly more cautious, and 85 % of respondents voiced concerns.

Our other research question, whether different groups of acupuncturists issue different recommendations, does not seem to be answerable on the basis of the data generated. Except for the group of LAc the subgroups are too small to provide reliable responses.

The expression of safety concerns varies according to the use of deception. There is a significant difference for groups A and B regarding the mention of risks of acupuncture treatment and for not recommending electro-acupuncture. It is, however, encouraging that the majority did not recommend electro-acupuncture and thus seems to be aware of the evidence regarding efficacy (Table 6). It is possible that some respondents did not recommend electro-acupuncture, because they generally do not apply it and not because of their belief in the evidence.

We are well aware of the ethical issues involved in this study. We wanted to determine whether Internet advice puts patients at risk with a view of minimising it. These special circumstances, we believed, allowed us to disregard informed consent in group A and B. We suspected that, with informed consent, the risk of obtaining a false picture was considerable. Thus we decided to conduct a comparison (group A and B vs group C) which, in fact, confirmed our suspicion (see above). By debriefing all respondents in group A and B, and offering the chance to withdraw retrospectively, we attempted to minimise the ethical problems. We felt that our breach of informed consent can be justified through our concern for patient safety.

This study has several limitations. In particular, the low response rate limits the generalisation of our results. Additionally, our descriptive statistics are sensitive to the totals from which they are calculated and it is important to describe the response spread across various qualifications as well as the average values of all respondents.

In conclusion, the recommendations issued by acupuncturists regarding smoking cessation are not based on the current evidence as to efficacy of this intervention and concerns about acupuncturists' attitude towards the potential harm of electro-acupuncture emerge. Thus, in this particular situation, Internet advice is not as sound as one would hope it to be.

Acknowledgements

We would like to thank Dr. Adrian White for his support in the design and analysis of the study. □

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Vol. **97** (2003) 104–105

respiratoryMEDICINE

LETTER TO THE EDITOR

Sir,

Are asthma sufferers at risk when consulting chiropractors over the Internet?

Classic chiropractic theory claims that vertebral subluxation blocks the flow of "innate intelligence" which, in turn, affects the health of asthma patients (1). Chiropractors often use spinal manipulation (SM) to correct such malalignments and treat asthma (2). Several clinical trials of chiropractic SM exist, but the most rigorous ones are clearly negative (3,4). Chronic medication with corticosteroids can lead to osteoporosis, a condition, which is a contra-indication to chiropractic SM (5). Given this background, we aimed to determine whether chiropractors would advise an asthma patient on long-term corticosteroids (5 years) to try chiropractic as a treatment for this condition.

All 350 e-mail addresses listed at www.interadcom.-com/chiro/html were randomised into two groups. A (deceptive) letter from a (fictitious) patient was sent to group A while group B was asked for advice on chiropractic treatment for asthma as part of a research project. Thus, groups A and B were asked the same question in different contexts: is chiropractic safe and effective for an asthma patient on long-term steroids. After data collection, respondents from group A were informed that the e-mail had been part of a research project.

Of 97 e-mails in group A, we received 31 responses (response rate = 32% (95% CI, 0.23–0.41)). Seventy-four per cent (23 respondents) recommended visiting a chiropractor (95% CI, 0.59–0.89). Thirty-five per cent (11 respondents) mentioned minimal or no adverse effects of SM (95% CI, 0.18–0.52). Three chiropractors responded that some adverse effects exist, e.g. risk of bone fracture, stroke. Two respondents noted that other investigations (X-rays, spinal and neurological examination) were required before chiropractic treatment. Three respondents suggested additional treatments and one warned about a possible connection between asthma and measles vaccine. Of 77 e-mails sent to group B, we received 16 responses (response rate = 21% (95% CI, 0.17–0.25)). Eleven respondents (69%) recommended visiting a chiropractor (95% CI, 0.46–0.91). Ten respondents mentioned minimal or no adverse effects of SM (95% CI, 0.39–0.87). Five chiropractors responded that adverse effects of SM exist (e.g. bone fracture). Five respondents suggested pre-testing of the patient to check bone density, allergy, diet, exercise level, hydration and blood. Additional treatments were recommended by three respondents. The pooled results of groups A and B suggested that the majority of chiropractors recommend chiropractic treatment for asthma and the minority mention any adverse effects (Table 1).

Our results demonstrate that chiropractic advice on asthma therapy is as readily available over the Internet as it is likely to be misleading. The majority of respondents from both groups (72%) recommended chiropractic treatment. This usually entails SM, a treatment modality which has been demonstrated to be ineffective in rigorous clinical trials (3,4,6). The advice may also be dangerous: the minority of the respondents of both groups (17%) caution of the risk of bone fracture. Our findings also suggest that, for the research question asked, a degree of deception is necessary. The response rate in group B was 12% lower than that of group A, and the answers received differed considerably between groups. In group A, 10% acknowledged the possibility of adverse effects, this figure was 33% in group B.

In conclusion, chiropractors readily provide advice regarding asthma treatment, which is often not evidence based and has the potential to put patients at risk.

Katja Schmidt was supported by The Pilkington Family Trusts

TABLE 1. Responses for efficacy and safety for groups A and B

	Group A (n=31) (%)	Group B (n=16) (%)	Groups A + B (n=47) (%)
Efficacy			
1. Chiropractic treatment recommended	23 (74)	11 (69)	34 (72)
2. Insufficient evidence for recommendation	2 (6)	2 (13)	4 (9)
3. Chiropractic treatment not recommended	6 (20)	3 (18)	9 (19)
Safety			
1. Minimal or no adverse effects mentioned	11 (35)	10 (63)	21 (45)
2. Adverse effects mentioned	3 (10)	5 (31)	8 (17)
3. No comments about adverse effects	17 (55)	1 (6)	18 (38)

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United Kingdom for six years and had not travelled abroad in the recent past or had contact with rubella. The mother was susceptible to rubella on routine antenatal testing at 12 weeks' gestation. The infant was born at 34 weeks' gestation with intrauterine growth restriction and thrombocytopenia but no other serious sequelae.

The infant and mother both tested positive for rubella IgM. The mother gave a clear history of a transient, non-itchy rash at 26 weeks' gestation. We could not find any social or community link between this mother and those in our two previous cases.

Rubella is highly infectious. In a recent case report from another London hospital rubella virus was nosocomially acquired by an infant being cared for in the same neonatal nursery as an infant with the congenital rubella syndrome.[2] As we know that at least three infants are excreting rubella virus in north west London, we now test for rubella IgM in all infants with severe intrauterine growth restriction (birth weight <3rd centile).

We believe that rubella infection may be underdiagnosed, given the recent decline in uptake of measles, mumps, and rubella (MMR) vaccination and the existence of at least five cases of congenital rubella infection in areas of London with large numbers of immigrant women from countries where rubella is endemic and childhood vaccination is not routine. A review of antenatal screening data from maternity units in north London showed that 23% of primiparous women of Sri Lankan origin were susceptible to rubella on routine antenatal screening testing in 1996-9 (P Tookey, personal communication).

A high index of suspicion and appropriate investigation of any suspicious rash in pregnancy are needed if the devastating effects of the congenital rubella syndrome are to be prevented from again becoming widespread in the United Kingdom. Clear guidelines on the management of, and exposure to, rash in pregnancy are contained in a report fom a working party of the Public Health Laboratory Service.[3]

Primary healthcare workers and midwives need to be aware of the need for targeted immunisation before pregnancy and for extra vigilance, particularly in women of childbearing age who have recently arrived from countries where rubella is endemic.

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Aspects of MMR

Survey shows that some homoeopaths and chiropractors advise against MMR

EDITOR—Vaccination for measles, mumps, and rubella (MMR) is highly controversial.[1] One of us (EE) found that some providers of complementary medicine have a negative attitude towards immunisation.[2] We therefore evaluated and compared the response of professional homoeopaths, chiropractors, and general practitioners to an inquiry about MMR vaccination.

We obtained the email addresses of the three health professions from these websites: www.homeopath.co.uk/directory, www.chiro-online.com/interadcom, www.internetgp.com/gpsites/alphabet.htm. We also visited the private homepages of homoeopaths and chiropractors on the internet. We sent a letter in which a mother asked for advice about the MMR vaccination for her 1 year old child to all the addresses. We explained to all those who responded that the query was, in fact, part of a research project, giving them opportunity to withdraw their answers. The study was approved by the local ethics committee.

We contacted 168 homoeopaths, of whom 104 (72%) responded, 27 (26%) withdrawing their answers. We contacted 63 chiropractors, of whom 22 (44%) responded, six (27%) withdrawing their responses. No general practitioners responded. The table shows that only a few professional homoeopaths and a quarter of the chiropractors advised in favour of the MMR vaccination. Almost half of the homoeopaths and nearly a fifth of the chiropractors advised against it.

These data suggest that some providers of complementary medicine are advising people against government policy. General practitioners, on the other hand, seem not respond at all to patients' emails on this delicate matter.

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Trying to find biological cause for autism does not make sense

EDITOR—Can vaccines cause autism?[1] Not really. Autism has no actual physical form; it is identified and diagnosed behaviourally, and most medical practitioners do not possess psychological competence. I am therefore not sure that something like autism is entirely contained in the medical sphere. I am a social psychologist and therefore interested in human interaction and its effects on behaviour. I am autistic myself and was not immunised with the measles, mumps, and rubella (MMR) vaccine.

Kurt Lewin, founder of group dynamics in social psychology, found that there are systems based around any individual that give rise to tensions between individuals.[2] These tensions operate like electrostatic fields and interact, resulting in behaviour (as people sense and perceive, and then construe[3]) that reorganises the tension system. The occurrence of "problem behaviours" might be seen as the end result of a system reorganising in such a way as to "force" a "leak" of behaviour at the point of least resistance.

The Finnish neuropsychologist Timo Järvilehto seems to support this idea from a social neuropsychological viewpoint.[4] His work accentuates the existing neurobiological substrate that can be said to underlie any person's behaviour but that none the less cannot possibly be the sole cause of that behaviour.

We cannot assume that autism is an "illness" with the same types of aetiological factors seen in, for example, haemorrhoids. Autism is best seen as a continual set of possible response states by the individual, concerned with inhospitable situational factors with which he or she has to deal. It is the best possible defensive response by the autistic person to the expectations and attitudes of the society into which he or she has been born. An autistic person may behave totally differently in any two different situations, which seems to support the notion of tension systems in that person's system that encompass organism and environment.[5]

I believe that biological causes for autism cannot be found, regardless of contributory factors. For this reason, I find the whole vaccine debate tiresome. The research should be oriented to discovering the types of interactions between the person and his or her environment are that bring about autistic states. Trying to find a biological cause for autism is akin to attempting to find a psychological basis for piles.

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Responses of three health professional groups to letter from mother asking for advice about vaccinating 1 year old child against measles, mumps, and rubella

Professional group	Response rate (% (No))	Withdrawal rate (% (No))	No (%) advising immunisation*	No (%) advising against immunisation*
Homoeopaths (n=168)	72 (104)	26 (27)	2/77 (3)	31/77 (40)
Chiropractors (n=63)	44 (22)	27 (6)	4/16 (25)	3/16 (19)
General practitioners n=111)	0	NA	NA	NA

*Directly or indirectly (of those who responded and did not withdraw). NA=not applicable.

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Vaccine 21 (2003) 1044–1047

Vaccine

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MMR vaccination advice over the Internet

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Received 24 June 2002; accepted 20 October 2002

Abstract

We wanted to investigate what advice UK homeopaths, chiropractors and general practitioners give on measles, mumps and rubella vaccination programme (MMR) vaccination via the Internet. Online referral directories listing e-mail addresses of UK homeopaths, chiropractors and general practitioners and private websites were visited. All addresses thus located received a letter of a (fictitious) patient asking for advice about the MMR vaccination. After sending a follow-up letter explaining the nature and aim of this project and offering the option of withdrawal, 26% of all respondents withdrew their answers. Homeopaths yielded a final response rate (53%, $n = 77$) compared to chiropractors (32%, $n = 16$). GPs unanimously refused to give advice over the Internet. No homeopath and only one chiropractor advised in favour of the MMR vaccination. Two homeopaths and three chiropractors indirectly advised in favour of MMR. More chiropractors than homeopaths displayed a positive attitude towards the MMR vaccination. Some complementary and alternative medicine (CAM) providers have a negative attitude towards immunisation and means of changing this should be considered.

Keywords: MMR; Vaccination; Internet advice; Complementary practitioner

1. Introduction

Complementary and alternative medicine (CAM) raises much public and professional interest and the predictions are that CAM will become even more popular in the future. In the United States the CAM usage in the general population has risen from 33% in 1990 to 42% in 1997 [1]. In the UK this number is smaller (20% in 1999) but also increasing [2]. The reason people turn to CAM are diverse, one is dissatisfaction with areas of the mainstream medicine, including immunisation.

Immunisation is presently a highly controversial topic. Many CAM practitioners are supporters of the 'anti-vaccination movement'. The measles, mumps and rubella vaccination programme (MMR) has been of recent concern among professionals, parents and the general public. This concern was caused by claims that the MMR vaccination could be related to autism, Crohn's disease and inflammatory bowel disease [3]. As a consequence, rates of MMR vaccination fell from 92% in 1996–1997 to 88% in 1998 [4]. In a survey for BBC Radio 5 Live, more than half of GPs surgeries reported that the uptake of the MMR vaccine had fallen [5].

Anti-vaccination groups and campaigns are gaining support, particularly in the USA and Western Europe [6]. Chiropractors, homeopaths and naturopaths often advise their clients against immunisation [7]. In a survey investigating US chiropractors' attitudes, one-third agreed that there is no scientific proof that immunisation prevents disease and that vaccinations cause more disease than they do prevent [8]. In an Australian survey 83% of all Sydney homeopaths did not recommend immunisation [9] and a German survey found that active immunisations against the 'classic childhood diseases', including MMR are used with more restraint among homeopathic physicians [10]. In another study of 117 Austrian homeopaths only 33 homeopaths rated immunisation as an important preventive procedure [11]. The chiropractic profession has also repeatedly expressed their negative view on vaccination [12]. The reasons for this are complex and rooted in the early philosophy of these approaches to healthcare. The early chiropractic philosophy considered most diseases to be a result of spinal nerve dysfunction caused by misplaced vertebrae. A minority of chiropractors is still accepting this concept [13].

On this background, the purpose of this survey was to investigate what advice UK homeopaths, chiropractors and general practitioners give regarding MMR vaccination.

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0264-410X/02/$ – see front matter
PII: S0264-410X(02)00628-X

2. Method

All e-mail addresses listed in UK practitioner referral directories online and private websites were extracted. Homeopaths' e-mail addresses we found at http://www.homeopath.co.uk/directory and at homeopaths' private homepages. Chiropractors' e-mail addressees we recruited from http://www.chiro-online.com/interadcom/engl_dc.html and at various chiropractors' private homepages. GPs' e-mails were extracted from http://www.internetgp.com/gpsites/alphabet.htm. We also intended to involve naturopaths. However, no database for UK naturopaths was accessible. Thus, only homeopaths, chiropractors and GPs were chosen.

All practitioners thus identified received the same query about MMR immunisation from a mother hesitating to give the MMR vaccine to her baby daughter (Appendix A). After 2 weeks of data collection (spring 2002), all respondents were informed that they had received an e-mail from a fictitious patient, as part of a research project. Confidentiality was assured, the intention of the project was explained and all participants were given the option of withdrawing from the project at this stage. Consent was implied through a non-response to the follow-up e-mail (Appendix B).

The following criteria were applied for evaluation of the remaining data: (1) Do practitioners respond to requests for vaccination advice by e-mail? (2) Do the respondents advise in favour of vaccination? (3) Are there statistically significant differences between the three groups regarding the nature of the advice given? Responses were categorised into (a) advising to have MMR (positive response), (b) advising not to have MMR (negative response), (c) indirectly advising to have MMR (for instance, using phrases, such as "If I had a child I would probably sway towards vaccinating it using the MMR vaccine") (positive response), (d) indirectly advising not to have MMR (for instance, stressing that own children were not vaccinated, or using phrases, such as "in principle I am against inoculation" or "I would most likely look at alternatives to vaccination") (negative response), (e) advising to obtain as much information as possible (neutral response), (f) no advice (neutral response) and (g) advising to have separate vaccinations for measles, mumps and rubella. Our local ethics committee gave ethical approval to the protocol of the project in April 2002.

The responses were analysed independently by two blinded researchers. χ^2 analyses were employed to statistically assess differences between groups using SPSS statistical software.

3. Results

One hundred and sixty eight e-mail addresses of homeopaths were contacted (Table 1). Of the 144 e-mails that were delivered we received 104 responses (response rate = 72%). Of those, one response arrived at a date beyond the deadline. Twenty-seven homeopaths (26%) wished to withdraw from the project after being debriefed about its nature. Of the 77 participating homeopaths, none advised the mother in favour of the MMR vaccination for her daughter, 3 (4%) openly advised against the MMR vaccination, 2 (3%) homeopaths indirectly advised to get the MMR, 28 (36%) indirectly advised not to have the MMR, 22 (29%) advised the mother to obtain as much information as possible before deciding, 14 (18%) gave no advice but offered their telephone number or a consultation with another homeopath, 5 (7%) advised to get individual vaccines and two homeopaths (3%) suggested neither to have the MMR nor any homeopathic vaccine but to treat the illnesses individually with a homeopathic remedy when they occur. Twenty-one different websites were recommended for further information.

Sixty-three e-mails to chiropractors were sent out, of which 50 were delivered. We received a total of 22 responses (response rate 44%). Six chiropractors (27%) withdrew their response. One chiropractor (6%) recommended getting the MMR vaccination, three (19%) indirectly advised not to have MMR, three (19%) more indirectly advised having the MMR and a further three (19%) advised to obtain as much information as possible before making a decision. Five chiropractors (31%) gave no advice and one (6%) suggested getting individual vaccines. Three websites were suggested by chiropractors for further information.

We sent e-mails to 111 GPs, of which one message was returned. We received no responses from GPs. We therefore decided to send the same letter to National Health Service (NHS) Direct and received the following reply "... (*we*) *are unable to provide advice on the MMR vaccine. We are able to give general information about the vaccine from accredited public health websites only. We cannot advise you on single dose vaccines, or where to obtain them.*" NHS Direct recommended four websites for more information.

Table 1

Professional group	Response rate (%)	Withdrawal rate (%)	Advise to immunise[a] (%)	Advise not to immunise[a] (%)
Homeopaths (n = 168)	104 (72)	27 (26)	2/77 (3)	31/77 (40)
Chiropractors (n = 63)	22 (44)	6 (27)	4/16 (25)	3/16 (19)
General practitioners (n = 111)	0 (0)	NA[b]	NA	NA

[a] Directly or indirectly (of those who responded and did not withdraw).
[b] NA: not applicable.

Using χ^2-test to compare responses between homeopaths and chiropractors, we distinguished between positive and negative attitudes towards MMR. There was no significant difference in negative attitudes between responses from chiropractors and homeopaths, X^2 $(1, n = 92) = 1.74$ ($P = 0.05$). However, there was a significant difference in positive attitudes between the two groups, X^2 $(1, n = 92) = 10.18$ ($P = 0.05$). Significantly more chiropractors displayed a positive attitude towards MMR vaccination.

4. Discussion

None of the practitioners involved in this study can be seen as representative of any organisation nor are they representative of their profession. When visiting websites of homeopaths' and chiropractors' organisations, no policy statements for guiding parents on the vaccination debate were found.

Our results confirm previous observations [5] that some CAM providers advise their patients against immunisation. The conclusiveness of our findings is limited by the small sample sizes and the low response rates. The sample sizes were determined by the number of e-mail addresses we were able to locate. The response rates were reduced through the option of withdrawal, which we felt was an ethical imperative. Initially, homeopaths showed a good response rate (72%) compared to chiropractors (44%). These figures were reduced to 53 and 32%, respectively, through subsequent withdrawals. Remarkably, GPs unanimously abstained from advising over the Internet, which resulted in a response rate of zero. No homeopath and only one chiropractor directly advised in favour of the MMR vaccination. Two homeopaths and three chiropractors indirectly advised in favour of the MMR. More chiropractors displayed a positive attitude toward the MMR when compared to homeopaths.

We are keenly aware of the fact that this study raises important ethical issues, it represents research on human subjects without informed consent. In order to minimise our ethical dilemma we fully debriefed all participants after responses had been received. This step does not, however, entirely solve the ethical problem of not obtaining informed consent. Informed consent would have rendered this project impossible. We (and our ethics committee) felt that identifying a potential safety issue in the interest of public health had sufficient potential benefit to outweigh the small risk, namely wasting practitioners time or alienating them. In fact, several respondents were appreciative of our project and accepted that it might contribute to participants' re-thinking their position on the MMR-vaccine and the nature of any advice given on the Internet. Others felt that a study such as ours could help CAM professions to be more accepted and to obtain a better status in healthcare. Unfortunately, we also received three official complaints about our investigation.

If one accepts, firstly, that MMR vaccination does more good than harm and, secondly, that some CAM providers are an obstacle in obtaining this net benefit, one must consider ways of changing the attitude of such practitioners. Obviously, this is much easier said than done. We believe that a strategy to achieve this aim should include a rational and open debate about the pros and contras of immunisation in the chiropractic and homeopathic literature. Moreover, the media would have an important role to play in objectively informing both, the general public and the growing population of CAM providers on the potential risks and benefits of (MMR) vaccination.

In conclusion, our study has confirmed previous investigations, suggesting that some CAM providers have a negative attitude towards immunisation, specifically MMR. With the raising popularity of CAM this could amount to a major threat to public health. Ways of rationally debating the issues with proponents of CAM should therefore be found.

Acknowledgements

Katja Schmidt was supported by The Pilkington Family Trusts.

Appendix A

Dear homeopath/chiropractor/GP,

My 1 year old daughter is coming up for MMR vaccination but I am not sure whether she should have the MMR at all. I want the best for her but there is so much about it in the news at the moment. My friend has been told by her therapist better not to get the MMR for her son. Can I ask your advice? Should I go ahead with the MMR, should I try separate vaccination or should I not vaccinate at all? Or perhaps, is there an alternative to vaccination?

I would very much appreciate your opinion.

Best wishes, Laura Phillips.

Appendix B

Dear homeopath/chiropractor/GP,

A few weeks ago you received an e-mail from a young mother asking you for advice on vaccination for the immunisation of her child. The patient 'query' you received was part of a research project investigating homeopaths'/chiropractors'/GPs' responses to this vignette. The aim of the project carried out by the Department of Complementary Medicine, University of Exeter is to investigate what sort of MMR advice is given via the Internet and to publish the results in a scientific peer-reviewed journal. This study is part of a wider research project about the safety of Internet advice and our protocol has received ethical approval by an independent ethics committee.

You can rest assured that confidentiality will be strictly observed and that at no stage will your identity be disclosed

to anyone outside this research project. If you have any questions, please do not hesitate to send me another e-mail.

This e-mail is a follow-up, asking you retrospectively for your informed consent. If we may use your original response you do not need to reply to this. We will then assume you agree. However, if you would like to withdraw from the study please reply to this e-mail and state that you would like to withdraw, in which case we will exclude your response from the report and completely remove it from our records. Responses received 14 days after we have sent the original e-mail will be discarded and counted as non-responses.

Thank you very much for your understanding.

Best wishes, Katja Schmidt.

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Int. J. Cancer: 107, 262–267 (2003)

Publication of the International Union Against Cancer

MISTLETOE FOR CANCER? A SYSTEMATIC REVIEW OF RANDOMISED CLINICAL TRIALS

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Mistletoe extracts are widely used in the treatment of cancer. The results of clinical trials are however highly inconsistent. We therefore conducted a systematic review of all randomised clinical trials of this unconventional therapy. Eight databases were searched to identify all studies that met our inclusion/exclusion criteria. Data were independently validated and extracted by 2 authors and checked by the 3rd according to predefined criteria. Statistical pooling was not possible because of the heterogeneity of the primary studies. Therefore a narrative systematic review was conducted. Ten trials could be included. Most of the studies had considerable weaknesses in terms of study design, reporting or both. Some of the weaker studies implied benefits of mistletoe extracts, particularly in terms of quality of life. None of the methodologically stronger trials exhibited efficacy in terms of quality of life, survival or other outcome measures. Rigorous trials of mistletoe extracts fail to demonstrate efficacy of this therapy.
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Key words: *mistletoe; alternative medicine; viscum album; cancer*

"Alternative" cancer cures remain in widespread use.[1] Particularly in continental Europe, mistletoe (*viscum album*) extracts (anthroposophical or herbal remedies) are amongst the most popular such therapies.[2] More than US $30 million is spent on mistletoe extracts annually in Germany and the yearly increase in sales has been estimated at 20%.[3] It is therefore important to ask whether mistletoe extracts are of benefit to cancer patients. Numerous clinical trials have attempted to answer this question with highly varying rigour and results, *e.g.*, the study of Majewski and Bentele.[4] Several reviews have summarised the clinical evidence, for example, references 5–10. The only *systematic* review of the subject concluded in 1994 that "the use of mistletoe extracts in the treatment of cancer patients [cannot be recommended] with an exception for patients involved in clinical trials."[10] This review included nonrandomised studies and may therefore have been open to bias. Moreover, it is now outdated as several new trials have emerged.

The current article is aimed at critically evaluating the evidence for or against mistletoe extracts as a treatment of cancer from all randomised clinical trials available to date.

MATERIAL AND METHODS

Systematic literature searches of Medline, Embase, BIOSIS, AMED (British Library), Scirusa, Clinical trials.com, CISCOM (Research Council for Complementary Medicine, London, UK) and the Cochrane Library (all from their respective inception to July 2002) were performed to identify all randomised clinical trials of mistletoe for any type of human cancer. The search terms were alternative medicine, cancer, controlled clinical trial, Eurixor®, Helixor®, Iscador®, lectin, malignancy, Mistel, mistletoe and derivatives. In addition, manufacturers of commercial mistletoe products and other experts were asked to contribute published as well as unpublished material, and our own extensive files were hand-searched. A manual search was also performed of the bibliographies of studies and reviews located through the computer searches and through scanning our own files.

All prospective, randomised clinical trials (RCTs) conducted with human cancer patients were considered. RCTs were excluded if they only reported nonclinical outcome measures, *e.g.*, immunological parameters, or failed to include an adequate comparison group (*e.g.*, one mistletoe preparation *vs.* another). Dual publications were only included once. All mistletoe preparations were considered, including pure mistletoe lectin preparations. No language restrictions were imposed. Both adjuvant and mono-therapy trials of mistletoe extracts were considered. Data extraction and validation were performed by 2 authors and checked by the third author using standardised, predefined criteria: study design, sample size, patient description, interventions, primary endpoints and main results. The scoring system developed by Jadad *et al.*[11] was used to evaluate methodological quality (Table I). Statistical pooling of data had been anticipated, however, due to the heterogeneity of the primary studies, this plan had to be abandoned.

RESULTS

Ten RCTs met our inclusion criteria. Key data are summarised in Table I and described in narrative form below.

Douwes and colleagues[12] randomised 60 patients with histologically verified metastatic colorectal carcinoma into 3 groups. Group A received only chemotherapy (5-fluoruracil and folinic acid), group B was treated with the mistletoe extract Helixor® (slow, insidious commencement up to a dose of 200 mg daily subcutaneous) plus chemotherapy and group C were treated with xenogenic peptides (Ney Tumorin®) plus chemotherapy. The frequencies of complete remission, partial remission, minimal response, tumour standstill and progression were similar in all groups. Mean survival time in groups A and B was about twice that of group C.

It is unclear which of these endpoints was the primary outcome measure; the text implies that remission rates were the primary and survival the secondary endpoints. The total number of chemotherapy cycles in each group was not adequately reported. It was not mentioned how many injections of Helixor® or Ney Tumorin® were actually administered and other concomitant biological treatments were administered but inadequately accounted for. Finally, this trial was not patient-blinded.

Dold *et al.*[13] assessed the effects of Iscador® (group A) compared to Polyerga® (group B), a glycopeptide extracted from the spleen of sheep, with a multi-vitamin "placebo" (group C) in 408 patients with histologically confirmed advanced nonsmall-cell carcinoma. Iscador® Q (oak tree) and Iscador® U (elm tree) were used both with Hydrargyrum D8 (dilution 10^{-8}). Patients were stratified according to clinical severity and stages groupings. The total drop-out rate was 17%, yet no intention-to-treat analysis was

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Received 3 February 2003; Accepted 14 March 2003

DOI 10.1002/ijc.11386
Published online 6 August 2003 in Wiley InterScience (www.interscience.wiley.com).

carried out. Median survival was 9.1 (95% CI: 6.8–10.7) months, 9.0 (7.1–11.5) months and 7.6 (6.0–8.9) months for groups A, B and C, respectively. Two-year survival was 11.5%, 13.9% and 10.1%, respectively. None of these differences was statistically significant. Quality of life (measured with the Karnofsky Index) was similar in all 3 groups. However, more patients in group A experienced improvement of their general well-being.

Even though this was a relatively rigorous trial, it is not flawless. The lack of patient-blinding renders the subjective endpoints of debatable value. The high dropout rate may have jeopardised comparability between groups. No intention-to-treat analysis was performed. There was no check of compliance, and the authors fail to mention the number of Iscador® injections that the patients actually received. The study was published in book form and has therefore not passed the usual peer-review process.

Salzer *et al.*[14] randomised 218 patients with histologically verified nonsmall-cell bronchial cancer to receive the mistletoe extract Iscador® (group A) or no treatment (group B) in addition to conventional care. The report lacks many methodological details essential for evaluation. The authors state that Iscador® is clinically "clearly advantageous, however, from a statistical point of view, there is no significant difference. . .." The Kaplan-Meier curves presented in the article suggest a better survival rate of the experimental compared to the control group, which becomes apparent after 2–4 years of therapy.

This report provides little data essential for critical evaluation. The most reliable hard endpoint is the rate of patients remaining free of recurrences, which does not show a statistically significant effect.

Lenartz and colleagues[15] randomised 35 patients with histologically verified glioma (stage grouping III or IV) to receive either a mistle lectin-1 (ML-1) standardised mistletoe extract (1 ng ML-1 per kg twice weekly for 3 months) or no such treatment in addition to conventional care (*e.g.*, surgery and radiation). A range of immunological parameters served as primary outcome measures and quality of life (Spitzer questionnaire) was quantified as a secondary endpoint. After 24 weeks of therapy, there was a difference between the 2 groups of about 1.5 points on the Spitzer scale. The authors report no statistical assessment (nor exact numbers with standard deviations) but note that there was "a considerable improvement for the verum group." Four years after their initial publication, a (not identical) team of authors reported the survival rates of this trial after a total follow-up of 50 months. No beneficial effect was noted in the total patient group. A subanalysis of stage grouping III/IV patients, however, demonstrated a significant prolongation of the overall survival in the therapy group (20.05 ± 3.5 months *vs.* 9.90 ± 2.1 months).[16]

This study has several obvious drawbacks. The clinical endpoints were employed as secondary outcome measures, and no evaluable results are presented for quality of life. Lack of patient-blinding, absence of adequate descriptions of randomisation or dropouts/withdrawals and the small sample size constitute further weaknesses. Most importantly, the 2 published reports of this study are highly inconsistent. In the first article,[15] the sample size is 35, while in the second,[16] it is 38. In the first article,[15] only stage grouping III/IV patients were mentioned, while in the second publication[16] the authors differentiate between analyses of all stages and one of stage grouping III/IV patients only.

Heiny and Albrecht[17] randomised 79 patients with advanced colorectal cancer into 2 groups. The control group received standard care (5-fluorouracil), while the experimental group received in addition Eurixor® (0.5–1 ng ML-1 per kg every 72 hr for 8 weeks, followed by 4 weeks no treatment and repeat of cycle). The results showed that significantly fewer patients in the experimental group suffered from mucositis stage III. Similarly, the average length of this complication was significantly shorter in this group. There were no significant differences for remission rates, length of remission, recurrence-free interval or survival time. The primary endpoint of this study was quality of life that was quantified with a visual analogue scale (VAS). This parameter significantly favoured mistletoe. After 7 weeks of therapy, the difference amounted to 18 *mm* on a 100 *mm* VAS.

This study is burdened with several problems. The authors state that 107 patients participated in the trial but only 79 were randomised. They note that the study was randomised but continue to explain that it followed a matched pair design. As the numbers in the 2 groups were not equal, a proper matching seems implausible. They also mention that quality of life was measured with a verbal rating scale but present the results of a VAS in mm. The study was not patient-blinded and subjective outcome measures could therefore be unreliable.

Kleeberg *et al.*[18] reported results for the EORTC Melanoma Cooperative Group (so far only) in the form of an abstract. Melanoma patients were randomised into 3 groups: low dose r IFN-α2 (iMU) or r IFN-γ (0.2 mg) both subcutaneous qod for 12 months or to placebo. All patients received standard care in addition. The German Association of Medical Oncology added a 4th group to this trial. It consisted of patients treated with Iscador® (subcutaneous twice per week) and monitored every second month with a quality of life measurement. Time to progression and length of survival were the primary outcome measures. Analysis was by intention to treat. Eight hundred thirty patients were followed for 5.5 years on average. Comparisons were stratified by melanoma stage grouping at randomisation. Compared to placebo, the relative risk in the Iscador® group for disease-free interval was 1.33 (95% CI 0.93–1.89). The authors conclude that "the clinical benefits of . . . Iscador are most likely not important." This study is difficult to evaluate because the abstract lacks sufficient detail.

A widely mailed document from Madaus, Germany described the following multicentre trial of Lektinol®, a ML-1 standardised preparation.[19] Two hundred seventy-nine women with breast cancer (T1-3 NO-N+ MO) were randomised after surgery into 4 groups: 5, 15 and 35 ng ML twice weekly for 15 weeks or placebo. The study was double-blind. Two hundred sixty-two patients were included in the intention-to-treat analysis. The treatment group receiving the intermediate dose showed a significant advantage in terms of quality of life (VAS, GLQ8 and Spitzer Scale). The 2 other experimental groups yielded results that were similar to those of placebo.

The results of this study look encouraging. Unfortunately it has not yet been published in a peer-reviewed journal (the manufacturer informed us that publication of this trial is not planned). As the frequency of local adverse reactions increased with increasing doses, patient-blinding may have been inadequate, which would seriously weaken the quality of life results. The short promotional text from the manufacturer may not be the best source of reliable information, and critical evaluation of these data is therefore not possible.

Grossarth-Maticek *et al.*[20] reported 2 RCTs including 49 and 17 matched pairs of patients with various cancers with various stage groupings. These patients received either Iscador® (no mention of host tree) or no such adjuvant therapy. Neither the dose, the type of Iscador® injected nor the treatment schedules were documented. The authors report significantly longer survival times (3.5 *vs* 2.5 years and 4.8 *vs.* 2.4 years, no standard deviations provided) for the experimental groups.

This study is either poorly reported or poorly conducted or both. A detailed commentary is available elsewhere and casts serious doubt on the rigour of this study.[21] The data provided are incomplete, confusing, contradictory and therefore of debatable value. Information is insufficient in respect of informed consent, study design, randomisation and treatment schedule. No entry has therefore been made of this study in Table I.

Steuer-Vogt and colleagues[22] studied a total of 477 patients with head and neck squamous cell carcinoma. Patients in the experimental group received subcutaneous injections of a mistletoe extract (Eurixor®) with a standardised amount of mistletoe lectin I (1 ng/kg bodyweight, twice weekly over a 60-week period). Treat-

TABLE 1 - RANDOMISED CLINICAL TRIALS OF MISTLETOE FOR CANCER[1]

First author (year)	Jadad score	Study design	Sample size	Patient description	Experimental intervention* (host tree)	Control intervention	Primary outcome measures	Main results	Comments
Douwes (1986)	3	Three parallel groups	60	Metastatic, colorectal CA, histologically confirmed	A) Helixor® (apple or fir) B) Ney Tumorin®	C) No such treatment	Remission rate, survival time	No significant inter-group differences	Survival favoured groups A and B
Dold (1991)	3	Multicentre, 3 parallel groups	408	Advanced, nonsmall-cell bronchial CA, histologically confirmed	A) Iscador® Q and Iscador® U with Hydrargyrum D8 (elm and oak) B) Polyerga®	C) Placebo (multi-vitamin)	Survival time, tumor growth, well-being	No significant inter-group differences in terms of survival, well-being favoured Iscador® therapy	Rigorous study but not free from flaws, subjective results (wellbeing), not reliable (no patient blinding), authors' conclusions negative
Salzer (1991)	2	Two parallel groups	218	Nonsmall-cell bronchial CA, histologically confirmed	A) Iscador® (unclear)	B) No such adjuvant therapy	Percentage of patients free from recurreaces, mortality	No significant inter-group differences (50 *vs.* 55%), mortality 59% *vs.* 56%	Report lacks essential details
Heiny (1991)	3	Two parallel groups	46	Advanced breast CA	A) Eurixor® (poplar)	B) Placebo injections	Leukocyte and platelet counts; quality of life and anxiety were secondary endpoints	Significant advantage for A in terms of wellbeing and anxiety	No patient blinding, thus subjective endpoints not reliable
Lenartz (1996 and 2000)	1	Two parallel groups	35	Glioma, all stage groupings (histologically confirmed)	A) Eurixor® (poplar)	B) No such adjuvant therapy	Leukocyte count and other surrogate variables; quality of life was a secondary endpoint; relapse free and overall survival was reported in a 2nd publication	"Considerable improvement in quality of life"; no survival differences in total sample, for stage grouping III–IV patients, a significant effect on survival was shown in the experimental group (20.1 *vs.* 9.9 months)	No test statistics for quality of life
Heiny (1997)	1	Two parallel groups	79	Advanced colorectal CA	A) Eurixor® (poplar)	C) No such adjuvant therapy	Quality of life	Significant inter-group difference in favour of mistletoe	Multiple problems raise concern about the validity of this study
Kleeberg (1999)	n.a.	Four parallel groups	830	Melanoma after curative resection of high risk primary (> 3 mm)	A) r IFN-α2	D) Placebo	Disease-free survival, length of survival, relapse rate	No differences that indicate efficacy of Iscador®	Trial so far only reported as an abstract

					B) r IFN-γ C) Iscador® (unclear)			
Schaefer (2000)	n.a.	Four parallel groups, double-blind	272	Breast cancer (T 1–3 NO-N+MO)	A) Lektinol® low dose	D) Placebo	Quality of life (and immunological variables)	Si
					B) Lektinol® intermediate dose C) Lektinol® high dose			
Steuer-Vogt (2001)	3	Two parallel groups, stratified for conventional therapy	477	Head and neck squamous cell CA	A) Eurixor® (poplar)	B) No such adjuvant therapy	Disease-free survival, 5-year survival rates, relapse rates, quality of life	I
Kleeberg (1999)	n.a.	Four parallel groups	830	Melanoma after curative resection of high risk primary (> 3 mm)	A) r IFN-α2	D) Placebo	Disease-free survival, length of survival, relapse rate	
					B) r IFN-γ C) Iscador® (unclear)			
Schaefer (2000)	n.a.	Four parallel groups, double-blind	272	Breast cancer (T 1–3 NO-N+MO)	A) Lektinol® low dose	D) Placebo	Quality of life (and immunological variables)	
					B) Lektinol® intermediate dose C) Lektinol® high dose			
Steuer-Vogt (2001)	3	Two parallel groups, stratified for conventional therapy	477	Head and neck squamous cell CA	A) Eurixor® (poplar)	B) No such adjuvant therapy	Disease-free survival, 5-year survival rates, relapse rates, quality of life	
Goebell (2002)	3	Two parallel groups	45	Superficial bladder CA (pTaG1-2)	A) Lektinol® (poplar)	B) No such adjuvant therapy	Recurrence-free survival, total number of recurrences during 18 months of follow-up	

[1]CA, cancer.–[a], treatment schedules are usually complex, conventional care was always given in parallel.–ML-1, mistletoe lectin 1.

ment cycles lasted 12 weeks followed by a mistletoe-free interval of 4 weeks. Three cycles were given in total. The primary endpoint was disease-free survival (DFS). Disease-specific survival (DSS) was a secondary endpoint. The adjusted hazard ratio for DFS was 0.959 (95% CI 0.725–1.268). Five-year survival and quality of life also did not significantly favour mistletoe. The authors concluded that "the used mistletoe preparation has no indication in the adjuvant treatment of patients with head and neck squamous cell carcinoma."

This study is probably the most rigorous mistletoe-trial published to date. It includes a formal power calculation, adequate follow-up and stratification for conventional treatments. One weakness is the lack of placebo and thus patient-blinding.

The most recent RCT of mistletoe was published by Goebell *et al.*[23] Forty-five patients with pTa G 1–2 bladder cancer were randomised after transurethral resection into receiving adjuvant therapy with 0.1 ml mistletoe lectin or no such therapy. The mistletoe treatment schedule commenced 2 weeks after surgery and involved twice weekly subcutaneous injections of 1 ml extract standardised for the galactoside-specific ML I for 3 months. Subsequently there were 3 months of no such injections followed by a second cycle. Recurrence-free interval and the total number of recurrences were the endpoints during 18 months of follow-up. Both variables did not differ significantly between groups: there were 30 and 31 recurrences, and the recurrence free intervals averaged 9.0 and 10.5 months, respectively. Similarly, secondary outcome variables did not demonstrate statistically significant or clinically relevant differences between the 2 groups.

Even though relatively rigorous, this study has several limitations: it did not report quality of life, it was neither placebo-controlled nor double-blind and, perhaps most importantly, its sample size was small.

DISCUSSION

The collective evidence reviewed above does not lend strong support to the efficacy/effectiveness of mistletoe extracts as a curative or supportive cancer therapy. In reviewing 11 controlled clinical trials, Kleijnen and Knipschild came to similar conclusions.[10] Only 4 of the 11 studies in their review were adequately randomised. In 1989, Kiene reviewed 46 clinical studies of mistletoe and arrived at a much more encouraging overall result.[8] This review included uncontrolled, historically controlled and retrospective studies. As it is important to eliminate selection bias in clinical trials; our emphasis was on randomised studies only. Apart from one study,[23] none of the included RCTs have carried out a power calculation to estimate how many participants are needed to be sure of finding something important. Numerous other weaknesses of the primary studies are mentioned above. The overall picture that emerges shows that those trials that are insufficiently vigorous to be conclusive do not demonstrate the effectiveness of mistletoe extracts.

One problem with our systematic review is that a diverse variety of mistletoe extracts (different mistletoe species, different forms of extraction and different host trees) and treatment regimen exist. These had to be assessed together for the purpose of this article. It is not always clear which extracts have been tested (Table I), and the number of trials on each extract is not sufficiently large to conduct separate systematic reviews. However, no clear evidence emerges from this review that one extract might be superior to another. "Claims about health effects must ideally be sustained ... for every single mistletoe extract."[10] and the burden of proof clearly rests with those who manufacture and promote these treatments. A further problem is that mistletoe extracts are used for most forms of cancer. For the purpose of this review, we therefore pooled the data relating to different types of malignancy. Again, the information currently available is too scant to allow subanalyses for different cancers. All one can therefore state with confidence is that the existing evidence does not imply that mistletoe extracts are more effective for one type of malignancy than for another.

Our systematic review was hampered by several other factors. Some trials of mistletoe appear in relatively obscure journals; even though our search strategy was thorough, we cannot be absolutely certain that all relevant RCTs were included. Many of the retrieved RCTs are poorly reported. Some have been published 2–4 times with considerable contradictions between these reports. Some manufacturers were less than helpful in assisting our efforts, even doubting our motivation in conducting this review. We therefore fear that unpublished trials, if they exist, may not have been included in our analysis. For obvious reasons, these would be studies with a negative result.

The treatment of cancer with mistletoe extracts was suggested by R. Steiner, the founder of anthropological medicine.[24] Steiner was guided by philosophy rather than science. Considering this history it seems surprising that mistletoe extracts do, in fact, possess several immunological effects that could be useful in the treatment of cancer. Most importantly, mistletoe extracts have been shown to increase the severity of tumour necrosis factor α, interleukin-1 and interleukin-6.[25] These could decrease cancer cell viability,[26] influence their migratory behaviour[27] and render cancer cells more sensitive to induction of apoptosis.[28] While these effects appear encouraging, one has to consider that they are based on *in vitro* experiments. Proponents of mistletoe therapy tend to extrapolate too optimistically from the preclinical findings to the clinical situation.[29] Furthermore, Gabius and Gabius have pointed out that several *in vitro*, *in vivo* and clinical studies suggest that interleukins can also stimulate (rather than suppress) the proliferation of certain cancer cells.[6] In other words, mistletoe therapy has the potential to harm cancer patients.

The notion that mistletoe extracts may not always be harmless is further supported by the fact that they are contra-indicated for patients with primary or secondary brain tumours, leukaemias or malignant lymphoma.[30] Adverse effects occur in up to 45%[31] and include local reactions at the site of injection, fever, elevation of intracerebral pressure, swelling of lymph nodes, thrombophlebitis, headache, circulatory problems and allergic reactions including anaphylaxis.[30] This high frequency of adverse effects renders placebo-controlled trials a near impossibility—a fact that deserves consideration when evaluating or planning future clinical trials in this area.

The issue arises of how to definitively answer the question whether mistletoe extracts are clinically effective. Obviously, we need high quality trials conducted by trustworthy experts and monitored according to GCP guidelines. No less than 30 different mistletoe preparations are on the German market.[31] As these vastly differ (for instance, in lectin content), each preparation should be tested and evaluated separately. As one cannot necessarily extrapolate from one type of cancer to another, each extract should be tested in each cancer for which it is claimed to be effective. The research effort thus needed is huge, and it seems unrealistic to expect the necessary data to emerge in the foreseeable future. The most reasonable alternative is therefore to insist that manufacturers' claims are supported by convincing data or they are not deemed acceptable.

In conclusion, the evidence from rigorous RCTs of mistletoe extract does not imply that this widespread and collectively costly therapy has any benefit for cancer patients.

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VOLUME 22 · NUMBER 21 · NOVEMBER 1 2004

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Efficacy of Coenzyme Q10 for Improved Tolerability of Cancer Treatments: A Systematic Review

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Submitted February 4, 2004; accepted August 23, 2004.

Supported by a grant from the British Medical Association (L.R.) and the Pilkington Family Trusts (K.S.).

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2221-4418/$20.00

DOI: 10.1200/JCO.2004.02.034

ABSTRACT

Purpose
The aim of this systematic review was to summarize and evaluate the evidence available for oral supplementation with coenzyme Q10 (CoQ10) to improve the tolerability of cancer treatments.

Materials and Methods
Searches for all published and unpublished controlled trials were carried out on seven databases. Manufacturers of CoQ10 were identified and contacted. Controlled clinical trials of monopreparations of CoQ10 administered orally to cancer patients were included. No language restrictions were imposed. Data were extracted independently by two authors according to predefined criteria.

Results
Six studies were included in the review, including three randomized clinical trials and three nonrandomized clinical trials. Patients in five of six studies received anthracyclines. The results suggested that CoQ10 provides some protection against cardiotoxicity or liver toxicity during cancer treatment. However, because of inadequate reporting and analysis, as well as questionable validity of outcome measures, the results are not conclusive.

Conclusion
Suggestions that CoQ10 might reduce the toxicity of cancer treatments have not been tested by rigorous trials. Further investigations are necessary to determine whether CoQ10 can improve the tolerability of cancer treatments.

J Clin Oncol 22:4418-4424. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Complementary and alternative medicine (CAM) has become an important issue among cancer patients. The inability of conventional medicine to treat all aspects of cancer and the patients' desire for an active role in the decision-making process regarding their treatments have been regarded as some of the contributing factors as to why CAM has become more popular over the last decades.[1-3]

A systematic review of surveys on the topic included 26 investigations, from 13 countries, published between 1977 and 1998. The average prevalence of CAM usage in cancer patients was reported to be 31%.[4] A more recent survey of 148 breast cancer patients in the state of Vermont reported considerably higher prevalence figures; 62.8% reported using at least one CAM treatment after surgery, with vitamins and nonfood supplements being the most frequently used.[5]

The widespread and well-documented use of CAM by cancer patients has led to a need for intensive research focused on the efficacy and safety of some of the CAM modalities. Coenzyme Q10 (CoQ10), also known as vitamin Q10, ubiquinone, or ubidecarenone, is one of the top 10 complementary therapies being promoted on the

Internet for cancer care.[6] A Danish survey of 769 cancer patients found that 18% used CoQ10.[7]

A coenzyme is an organic, nonprotein molecule that binds with a protein molecule to form an active enzyme. The formula of CoQ10 ($C_{59}H_{90}O_4$) is synthesized endogenously in humans and is also found in virtually all aerobic organisms.[8] The primary action of CoQ10 occurs in the electron transport chain for cellular respiration. It is a lipid-soluble quinone and is essential for the synthesis of adenosine 5′-triphosphate (ATP). It affects the function of all cells in the body in its role as a mobile electron transporter, assisting enzymes in the oxidation of nutrients in the mitochondria of cells to produce energy for growth and preservation.[9] CoQ10 is also metabolized to ubiquinol, which prolongs the antioxidant effect of vitamin E.[10]

CoQ10 is widely promoted for enhancing or modulating the immune system. Levels of immunoglobulin G in serum of patients treated with CoQ10 have been found to increase,[11] and in 1993, a small uncontrolled trial on healthy participants suggested that CoQ10 supplementation may help support immune responses by increasing immunoglobulin G and T4/T8 lymphocytes.[12] Other uncontrolled studies have suggested that CoQ10 may suppress tumor growth.[13-15] However, no controlled trials have been published assessing the use of CoQ10 alone as a prevention or treatment for cancer in humans.

CoQ10 is manufactured as a dietary supplement by the fermentation of beets and sugarcane with yeast and is taken widely in Japan. In the diet, it is primarily derived from meat and poultry.[16] After absorption in the gastrointestinal tract, CoQ10 is distributed to the liver and incorporated into very low–density lipoproteins.[9] Serum concentrations of CoQ10 have been found to increase after ingestion of CoQ10 both as a supplement and postprandially.[16] It is absorbed well but slowly from dietary and supplementary sources, with peak plasma levels occurring 5 to 10 hours after ingestion.[9]

Deficiencies of CoQ10 in humans occur with age, the use of certain medications, and with diseases including cancer.[17] The incidence of CoQ10 deficiency has been found to be significantly higher in cancer patients than in healthy controls.[18] In a study of 200 women hospitalized for breast cancer surgery, a CoQ10 deficiency was noted both in patients with malignant (80 patients) and nonmalignant lesions (120 patients).[19] Serum levels of CoQ10 may be depleted by 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (including lovastatin), which are usually used for lowering cholesterol.[17]

Anthracyclines, commonly used in chemotherapeutic regimens, have been shown to interfere with the energy-generating biochemical actions of CoQ10[20,21] and to generate free radicals, which affect cell growth and tumor production. CoQ10 is a free-radical scavenger, and its antioxidant activity and membrane-stabilizing properties help to protect against and repair damage to DNA caused by free radicals. The impact of free radicals on DNA is thought to be the link between free radicals and cancer formation.[22]

Anthracyclines are also known to cause cardiotoxicity.[23,24] Acute toxicity is usually manifested by changes in ECG, including arrhythmias, but delayed dose-related cardiomyopathy can also occur, resulting in congestive heart failure.[24] CoQ10 supplementation can have favorable actions in various cardiovascular conditions[8]; thus, studies have investigated the use of CoQ10 for reducing the adverse effects of cancer treatments and have particularly focused on the cardioprotective effect of CoQ10 in cancer patients treated with anthracycline antibiotics.

The aim of this systematic review is to summarize and critically evaluate the available evidence for or against the efficacy of supplementation with CoQ10 for improved drug tolerability in cancer patients.

MATERIALS AND METHODS

Electronic literature searches were performed to identify all controlled clinical trials in which CoQ10 was administered to cancer patients. The following electronic databases were searched from their inception until July 2003: the Allied and Complementary Medicine Database (inception 1985), the British Nursing Index (1994), CINAHL (1983), DH-DATA (1983), EMBASE (1966), MEDLINE (1966), and the Cochrane Central Register of Controlled Trials. The search terms used were cancer or oncolog$ or carcinogen$ or tumo$r and ubiquinone or ubidecarenone or coenzyme Q10 or CoQ10 or CoQ 10 or CoQ-10 or Co-Q10. Additional hand searches were carried out on the bibliographies of the obtained articles and on our departmental files.

Twenty-eight manufacturers from five countries were sent letters requesting details of any clinical trials they may have conducted with CoQ10 on cancer patients. Three manufacturers replied, all stating that they had not conducted trials of this nature.

No restrictions were placed on the language of publication. Studies were included only if they were controlled trials in which monopreparations of CoQ10 were administered orally to cancer patients in addition to standard cancer care. Studies were excluded if they measured CoQ10 levels rather than clinical effects of CoQ10 supplementation. Reviews were also excluded after the bibliographies were searched for more trials. Figure 1 shows the inclusion and exclusion process.

Papers were translated in house by other researchers where necessary, and data was extracted independently from each study by two reviewers (L.R., K.S.) according to predefined criteria. The methodologic quality of studies was assessed using the Jadad score.[25] The Jadad score is calculated by assessing the following three criteria: methods of blinding, randomization, and reporting of dropouts and withdrawals. The maximum number of points that can be achieved on the Jadad score is 5. The heterogeneity of the studies precluded statistical pooling of the results. Therefore, they were tabulated and described narratively.

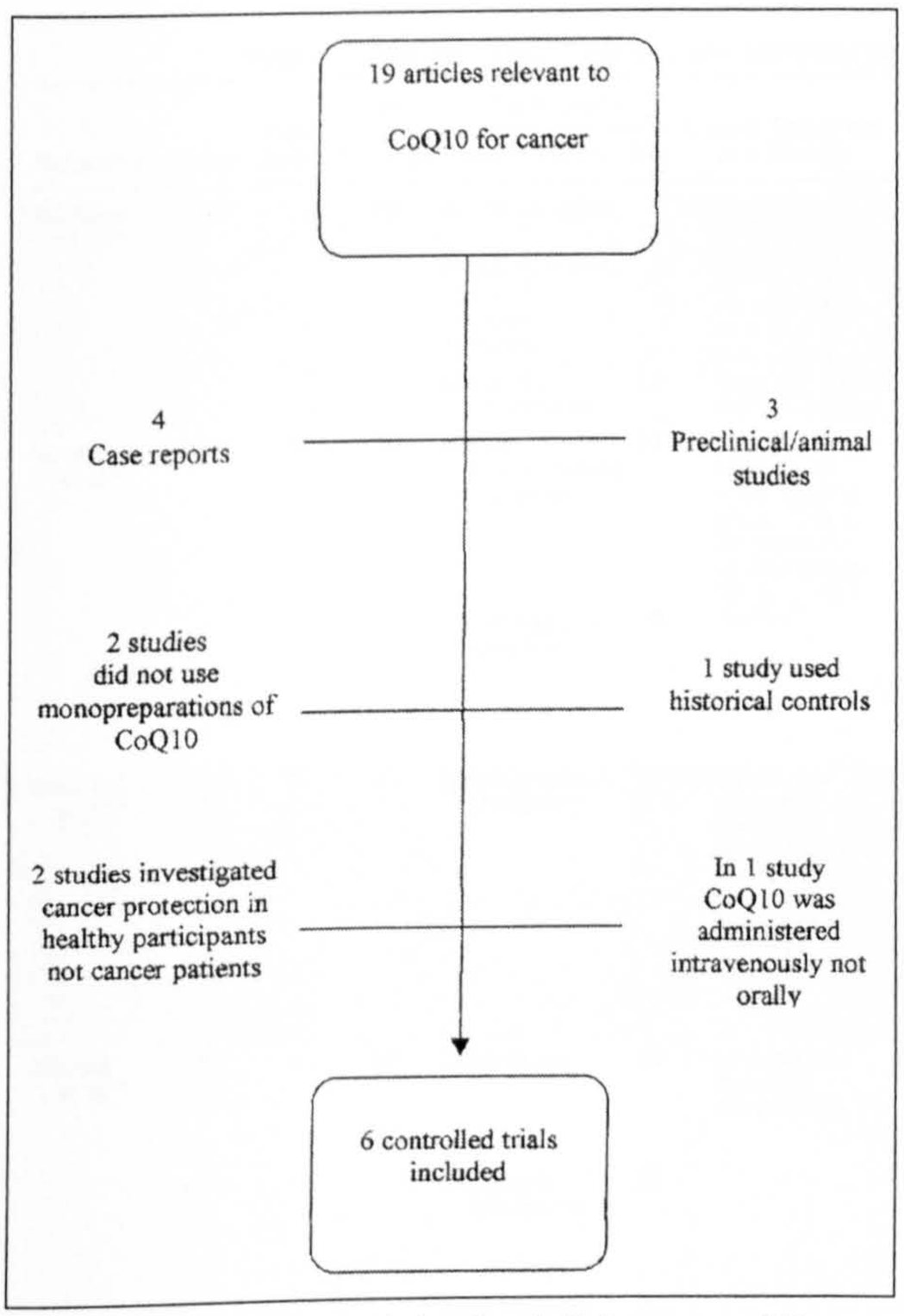

Fig 1. Flowchart of excluded studies. CoQ10, coenzyme Q10.

RESULTS

Nineteen studies were retrieved in the literature searches. Six trials met our inclusion criteria. Two studies were excluded because of the administration of combined treatments consisting mainly of CoQ10, vitamin C, vitamin E, beta-carotene, selenium, and zinc.[26,27] The extracted data of the six studies that met our criteria[28-33] are listed in Table 1.

The included studies were carried out in Japan,[28-30] Italy,[31,32] and the United States[33] between 1982 and 1996. Three of the studies were randomized controlled trials.[29-31] There was one placebo-controlled double-blind study.[28] All other studies were open trials in which the experimental group received CoQ10 plus standard care and controls received standard care only. Sample sizes ranged from 19 to 88 patients, and dropouts and withdrawals were mentioned in two studies.[32,33] All participants included in the studies had previously been diagnosed with various types of cancer. The ages of participants were reported in all but one study and varied widely across the studies (range, 1 to 71 years). One study included children.[31] Sex was not specified in two studies,[28,30] but all other studies included both male and female patients.

Studies examined the protective effect of CoQ10 against toxic adverse effects of cancer drug treatment and whether CoQ10 improved the tolerance of anthracyclines or other cancer treatments. This was assessed using various measures of heart function and toxicity in five studies[29-33] and using hair loss and liver enzyme levels in one study.[28] Cancer treatment included anthracyclines in all the studies except one, in which patients were treated with lovastatin.[33] The CoQ10 dosage ranged from 90 mg/d to 240 mg/d. Although daily recommended allowance has not yet been established for CoQ10, manufacturers advise a daily intake between 10 and 100 mg. No toxicity has been reported for daily intakes as high as 300 mg. However, safety has not been established in pregnant or lactating women.

The duration of treatment with CoQ10 varied according to an individual's cancer treatment. No adverse effects of CoQ10 were reported in any of the studies. None of the included studies recorded survival outcomes or measured changes in tumor responses. The individual studies are narratively described in the following paragraphs.

Akihama et al[28] investigated the protective effect of CoQ10 against hair loss and abnormalities of liver enzymes during treatment with anthracycline antibiotics in a double-blind, placebo-controlled trial. Nineteen participants diagnosed with acute leukemia, blastic crisis of chronic myeloid leukemia, or malignant lymphoma were included. Eight participants received 120 mg/d CoQ10. No significant differences were found in hair loss between the experimental group and the placebo group. It was suggested that this might be a result of low absorption of CoQ10 when administered orally. Serum levels of AST increased significantly in the placebo group ($P < .01$) but not in the treatment group.

Iarussi et al[31] conducted a randomized controlled trial of the protective effect of CoQ10 on anthracycline cardiotoxicity. Ten of 20 children with acute lymphoblastic leukemia or non-Hodgkin's lymphoma were given 100 mg of CoQ10 twice daily. Myocardial function was measured using echocardiography. Measurements were taken at baseline, at a cumulative dose of 180 mg/m^2, and at the end of treatment. A significant reduction in percentage of left ventricular fractional shortening was noted in both the CoQ10 and the control groups between baseline measurements and the end of treatment with anthracyclines. In the control group, a reduction in percentage of left ventricular fractional shortening appeared earlier than in the experimental group. However, in the experimental group, no significant changes in left ventricular fractional shortening were found. A significant reduction in interventricular septal wall thickening was noted in the control group only. No significant changes were found in left ventricular posterior wall thickening in either group. The authors suggest that CoQ10 had a protective effect on left ventricular global function and

Table 1. Controlled Clinical Trials of Orally Administered Coenzyme Q10 for Improved Tolerance of Cancer Treatments

Reference	Design	Jadad Score	No. of Patients	Participants: Type of Cancer	Participants: No.	Cancer Treatment and Dosage	CoQ10 Dosage	Primary Outcome Measures	Within-Group Results	Between-Group Results
Akihama et al[28]	CCT	2	19	Acute leukemia	6	Anthracycline antibiotics: doxorubicin (n = 11) or daunomycin (n = 8); cumulative dose: 50-100 mg	120 mg/d for 2-6 months	Hair loss; serum level of AST and ALT liver enzymes	Both enzymes levels raised in the placebo group ($P < .01$); no significant differences in CoQ10 group	No significant differences in hair loss or enzyme levels between groups; no protection against hair loss
				Blastic crisis of chronic myeloid leukemia	2					
				Malignant lymphoma	11					
Iarussi et al[31]	RCT	2	20	Acute lymphoblastic leukemia	17	Anthracylines; cumulative dose: CoQ10 group, 240 ± 20 mg/mg^2; control group: 252.0 ± 20.1 mg/mg^2	100 mg bid, duration not stated	Cardiotoxicity/myocardial function (echocardiography): % LVFS; SWT; LVPWT	Significant reduction in % LVFS in both groups: CoQ10 group: $P < .05$; control: $P < .002$ (change earlier in control group); significant reduction in SWT in control group ($P < .01$); NS changes in LVPWT	LVFS reported to be significantly lower in CoQ10 group, but no statistics reported
				Non-Hodgkin's lymphoma	3					
Lucarelli et al[32]	CCT	1	30	Hematologic neoplasm	30	Complex cytostatic therapy: anthracyclines: daunoblastin, doxorubicin, 50-80 mg for 3-5 days	30 mg Ubiten tid for 30 days	SBP; DBP; ECG: QRS voltage; frequency of repolarization alterations; heart rate	Increase in SBP in CoQ10 group significant at $P < .05$; increase in DBP in CoQ10 group only; ECG remained normal in CoQ10 group; QRS lowered in two patients in control group	No between-group results reported
Okuma et al[29]	RCT	1	80	Lung cancer	30	Chemotherapy including doxorubicin	90 mg/d, 1 week before chemotherapy until chemotherapy completed	Cardiotoxicity (ECG); QRS voltage; QTc duration	CoQ10 group remained stable	QRS voltage lower in control group at measurements 1, 2, and 3 ($P < .01$); QRS duration longer in control group at last treatment ($P < .05$); QTc duration was significantly longer in control group at measurements 5, 6, and 7 ($P < .05$) and at measurement 8 ($P < .01$)
				Malignant lymphoma	30					
				Patients with nine other types of solid tumour cancers	20					
Takimoto et al[30]	RCT	1	40	Lung	33	FAC therapy every 3 weeks: day 1, 500 rad irradiation of cobalt 60; day 2, 500 mg flurouracil + 50 mg doxorubicin + 500 mg cylcophosphamide	90 mg/d; duration not stated	Myocardial intoxication; CTR	CTR and pulse rate increased in control group (no statistics reported)	Significant difference in CTR increase between control and CoQ10 group ($P < .01$); CTR increased significantly more in control group; NSD in pulse rates; NSD in QRS voltage
				Breast	6					
				Thyroid	1					
				All treated with doxorubicin				Pulse rate; ECG: QRS voltage		
Thibault et al[33]	CCT	1	88	Hormone-independent prostate	38	Lovastatin administered at four different dose levels: (30, 35, 40, or 45 mg/kg/d)	240 mg/d ubiquinone in four doses administered with lovastatin; duration not stated	Toxicity: National Cancer Institute Common Toxicity Criteria + musculoskeletal toxicity (myalgias); drug activity: cholesterol concentrations; Serum HMG-CoA reductase inhibitory activity	Declined rapidly in both groups (CoQ10 did not affect drug activity)	CoQ10 did not decrease the incidence of musculoskeletal toxicity but significantly reduced its severity ($P < .01$); NSD between groups; NSD between groups
				Primary CNS	24					
				Breast	7					
				Colorectal	4					
				Ovary	4					
				Sarcoma	3					
				Lung	2					
				Others	6					

Abbreviations: CoQ10, coenzyme Q10; CCT, controlled clinical trial; CTR, cardiothoracic ratio; NSD, no significant difference; QRS, deflections in an ECG that represent ventricular activity of the heart; QTc, correction of time from ECG Q wave to the end of the T wave corresponding to electrical systole; RCT, randomized controlled trial; % LVFS, percentage of left ventricular fractional shortening; SWT, septum wall thickening; LVPWT, left ventricular posterior wall thickening; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant; FAC, fluorouracil, doxorubicin, cyclophosphamide; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A.

was effective in protecting myocardial function during therapy with anthracyclines.

In an open, controlled, clinical trial, Lucarelli et al[32] investigated the effect of CoQ10 on toxic cardiopathy from antiblastic therapy with the anthracycline duanoblastine. Fifteen of 30 patients diagnosed with hematologic cancers took 30 mg CoQ10 tid (Ubiten; Italfarmaco, Milan, Italy) for 30 days. Blood pressure, ECG readings, and heart rate were obtained at the beginning and the end of treatment. Systolic blood pressure measurements were taken at rest and after gentle exercise; after gentle exercise, the measurements were not significantly different in the treatment group compared with the control group, but when they were measured at rest, they increased significantly in the treatment group at the end of treatment ($P < .05$). This was attributed to an improvement in general health. The diastolic pressure increased slightly in both groups and was reported to be significant in the experimental group. The authors suggest that a positive effect of CoQ10 was demonstrated by improvements in general health and less cardiotoxicity. The ECG remained stable in more patients in the treatment group than in the control group. Nine patients in the CoQ10 group had a normal ECG reading at the beginning of treatment, and six had a normal reading at the end of treatment; whereas in the control group, seven patients had a normal reading at the beginning of treatment, and four had a normal reading at the end of treatment. No statistical analysis of this difference was reported. No significant alterations in heart rate or blood sugar were found in either group. Repolarization alterations were more frequent in the control group. No adverse effects attributable to CoQ10 were reported.

In a 13-center, randomized, clinical trial, Okuma et al[29] examined the protective effect of CoQ10 in 80 patients treated with chemotherapy including doxorubicin. Patients suffered from 10 different types of cancer, including 30 patients with lung cancer and 30 patients with malignant lymphoma. CoQ10 was administered to 39 patients at a dose of 90 mg/d beginning 1 week before chemotherapy and continuing until the treatment with doxorubicin was completed. Serial ECGs were recorded immediately before and after each administration of doxorubicin. QRS voltage decreased in the control group but increased in the CoQ10 group at treatments 1, 2, and 3. QRS duration became significantly lower in the control group than the CoQ10 group ($P < .05$). QTc duration was significantly longer and QRS voltage decreased in the control group. In patients taking CoQ10, both variables remained stable.

In 1982, Takimoto et al[30] carried out a randomized, open study investigating the effects of 90 mg/d CoQ10 on myocardial toxicity during therapy consisting of an irradiation of cobalt and an infusion of doxorubicin, cyclophosphamide, and fluorouracil. Forty patients suffering from lung, breast, and thyroid cancer received doxorubicin, cyclophosphamide, and fluorouracil every 3 weeks for 4.4 ± 3 months (experimental group) or 5.8 ± 3 months (control group). Twenty patients in the experimental group received CoQ10. Patients in the CoQ10 group showed a significant increase in their cardiothoracic ratio when compared with the control group. There were no differences between the two groups in heart rate and ECG measures, such as QRS, ST segment, T-wave, and arrhythmia frequency.

In 1996, Thibault et al[33] investigated the effect of 240 mg/d CoQ10 on 88 cancer patients enrolled onto an open, controlled, clinical trial primarily designed to measure the tolerability of lovastatin when administered at progressively higher doses to achieve antiproliferative activity. Patients suffered from various forms of cancer. Patients were treated with four different doses of lovastatin, which was administered qid for 7 days in monthly cycles. CoQ10 was administered to 56 of 88 patients to prevent lovastatin-induced myotoxicity in stage 2 of the study. Of the 56 patients, only 27 had previously been treated with lovastatin during stage 1 of the study. The remaining 32 patients were treated with lovastatin only during stages 1 and 2. The activity of lovastatin was determined using biochemical measurements of pharmacologic parameters. Musculoskeletal toxicity was assessed, and toxicity was graded according to the National Cancer Institute Common Toxicity Criteria. Tumor responses were also monitored. CoQ10 had no effect on the activity of lovastatin; cholesterol concentrations declined significantly in both groups, with no significant intergroup differences. The administration of CoQ10 did not decrease the incidence of musculoskeletal toxicity, but its severity was significantly reduced. It is unclear whether the analysis was carried out with just the 27 patients in the CoQ10 group who had previously received lovastatin or whether all 56 patients who received CoQ10 were included.

DISCUSSION

These results indicate that CoQ10 may provide some protection against toxicity associated with cancer treatments. However, weaknesses in the design and reporting of all the studies create ambiguity. The overall methodologic quality and reporting of the trials was poor. Between-group analyses, which are necessary to detect a therapeutic effect in controlled clinical trials, were absent from two studies.[31,32] Sample sizes were small, with the exception of two studies,[29,33] and power calculations were absent from all reports. Only one trial was a placebo-controlled and double-blind study,[28] but it was not clear whether this study was randomized. None of the studies scored over 2 points out of 5 on the Jadad score.

Certain aspects of methodology and statistical analysis were inadequately reported in all trials. The statistical values were lacking from all the studies, and few mentioned

whether baseline differences or withdrawals had occurred. None of the studies reported an intent-to-treat analysis. Only two studies mentioned the manufacturer of the CoQ10 used in the trial, and neither identified the actual preparation used (Table 1). Although we aimed to include only monopreparations of CoQ10, we cannot be certain whether emulsifying agents (which can include vitamin E) were present.

Treatment controls varied across and within the trials. Individual differences in patient requirements prevent standardization of the type, dose, and duration of cancer treatments within trials of this nature. These and further variations in types of cancer and outcome measures made it impossible to submit these data to a formal meta-analysis.

Despite this high level of heterogeneity, there were some common features between the studies. In five of six studies, anthracyclines were administered to patients as part of their chemotherapy regimen, and half of the studies measured ECG to assess cardiotoxicity. Between-group analyses revealed significant changes in QRS voltage, QRS duration, QTc duration,[29] and cardiothoracic ratio[30] in the control groups compared with the treatment groups. Thus, CoQ10 may have a stabilizing effect on the heart, but more definite conclusions cannot be drawn to because of insufficient reporting of data.

It was unclear in some studies precisely when the outcome measures were taken. Arrhythmia occurs during administration of anthracycline antibiotics or within several hours of treatment. Disturbances in electrocardioarrhythmia, such as lowered voltage of QRS complex, usually disappear spontaneously within hours or weeks after the completion of chemotherapy.[34] Therefore, the timing of measurements is critical for diagnosing acute toxicity.

There is also controversy over the validity of different monitoring techniques for detecting cardiotoxicity.[24,34,35] It has been suggested that ECG and echocardiography are limited in their ability to detect early reversible cardiac damage or disturbances and that radionuclide angiocardiography provides more accurate measurements of left ventricular function.[34] The transient nature of ECG changes makes detection difficult, requiring 24-hour continuous ECG.[34] However, this was not carried out in any of the trials included in this review.

The effectiveness of the dosages of CoQ10 administered in the studies reviewed here could not be evaluated. Only one study[33] measured and reported pre- and post-treatment plasma levels of CoQ10. A significant increase in serum requires supplementation with approximately 100 mg/d CoQ10,[17] but three studies administered a dose of only 90 mg/d. Optimum levels of CoQ10 have not been determined, and plasma levels are intrinsically variable within a patient. Many factors have been linked with the bioavailability of CoQ10, such as the CoQ10 preparation used, the age, sex, race, diet, and nutritional status of an individual, and the stomach content and alcohol consumption.[36,37] Significantly increased plasma levels of CoQ10 occurred (without supplementation) after treatment with doxorubicin in a recent study.[38] Studies measuring CoQ10 levels before and after courses of anthracycline chemotherapy are lacking.

No adverse effects of CoQ10 were reported in any of the trials. CoQ10 is structurally similar to vitamin K and possesses procoagulant effects. Case reports have suggested that CoQ10 may interact with the anticoagulant effects of warfarin therapy, and concurrent use may cause a diminished response.[39,40] Caution is also advised in selecting a brand of CoQ10 supplement; ConsumerLab (White Plains, NY) reported in January 2004 that one of the 32 products investigated contained no detectable CoQ10 and another exceeded its concentration by 75%.[41]

CoQ10 was not found to interfere with standard treatments in the clinical trials included in this review. It is uncertain whether the cytoprotective and antioxidant activities of CoQ10 may decrease the efficacy of chemotherapeutic agents, such as anthracyclines, which work by inducing oxidative stress. There is no biologic rationale for the selective protection of healthy cells, and interactions between antioxidants and cancer treatments vary according to tumor type and the type and dosages of antioxidant and chemotherapy.[42] A nonsystematic search of preclinical studies revealed conflicting preclinical evidence regarding whether supplementation with CoQ10 benefits or inhibits chemotherapeutic treatments. A preclinical study of doxorubicin concentrations in mice advised caution with concomitant use of CoQ10 and doxorubicin.[43] However, a more recent preclinical study found that CoQ10 treatment had no significant effect on the pharmacokinetics of doxorubicin.[44]

Balancing the benefits and risks of chemotherapy and other cancer treatments is a continuous concern for oncologists and cancer patients and their caregivers. Potential benefits and risks from adjuvant therapies also require careful consideration. Despite encouraging suggestions from clinical trials that CoQ10 might reduce the toxicity of cancer treatments, such effects have not been tested rigorously. There is still much uncertainty over the interactions between CoQ10 and anthracyclines. Further investigations are necessary to determine whether supplementation with CoQ10 is appropriate for improving the tolerability of cancer treatments.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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PSYCHO-ONCOLOGY
Psycho-Oncology (in press)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.889

A SYSTEMATIC REVIEW OF GUIDED IMAGERY AS AN ADJUVANT CANCER THERAPY

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SUMMARY

Aim: The aim of this paper is to summarise and critically evaluate the evidence available from controlled clinical trials regarding the use of guided imagery as a sole adjuvant therapy for cancer patients.

Methods: Electronic searches for controlled clinical trials were carried out in eight databases and two clinical trial registers. Trials that featured guided imagery as a sole adjuvant therapy were included. No language restrictions were imposed. Data were extracted and validated independently by two researchers.

Results: Six randomised clinical trials were included. Detailed results were available for four studies only. Poor reporting and heterogeneous populations, interventions and outcome measures across trials precluded statistical pooling of results. The methodological quality was on average low. Three studies reported significant differences in measures of anxiety, comfort or emotional response to chemotherapy for patients who received guided imagery over the control groups. Two studies showed no differences between guided imagery and other interventions in any of the outcome measures.

Conclusion: Guided imagery, as a sole adjuvant cancer therapy may be psycho-supportive and increase comfort. There is no compelling evidence to suggest positive effects on physical symptoms such as nausea and vomiting. The data seem sufficiently encouraging for the use of guided imagery as an adjuvant cancer therapy to merit further research.

INTRODUCTION

Guided imagery has recently been identified as one of the 10 most frequently recommended complementary cancer therapies on the Internet (Schmidt and Ernst, 2004). It is a technique used to harness the power of the mind to form mental representations of objects, places or situations, which are perceived through the senses (Post-White, 2002). The term 'visualisation' is often used interchangeably with imagery. Although visual images are most commonly evoked, sounds, smells, tastes and sensory or affective feelings may also be induced.

Guided imagery refers to the use of imagination to invoke one or more of the senses. It involves the 'guiding' of an individual through experiences in the mind, in order to access physical, emotional and spiritual dimensions to affect bodily change (Achterberg, 1985). In a guided imagery session a practitioner or other individual leads the participant through an imagery technique or script. This can take place in group or in one-to-one sessions. Recordings of spoken scripts on audiotapes are also commonly used, allowing an individual to practise in a location of their choosing. Individuals may also use imagery without the guidance of a script. Gentle background music often accompanies imagery sessions to help maintain a relaxed state and to free the mind from other thoughts.

Imagery techniques are frequently used to bring calmness and a sense of space to alleviate anxiety and pain (Spiegel, 1993; Lang and Patt, 1994) and are claimed to encourage the receptivity of treatment and facilitate the process of recovery (Simonton *et al.*, 1978). Guided imagery techniques encourage people to feel a connection between their mind and their body and can aid

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Received 13 April 2004
Accepted 1 November 2004

in facilitating feelings of empowerment in order to help individuals manage certain difficulties in their lives. Studies have suggested that guided imagery may influence physiological outcomes such as white blood cell count in medical patients including cancer patients, (Donaldson, 2000), narcotic medication requirements (Tusek *et al.*, 1997a,b) and other immunological effects (Gruber *et al.*, 1993; Walker *et al.*, 1997). Psycho-neuroimmunological theories propose that the psychological response to guided imagery may down-regulate the hypothalamic–pituitary–adrenal-axis, resulting in a reduced stress response, increased immune function and sense of well-being (Post-White, 1998). However, immune responses to emotional stress are complex and heterogeneous (Post-White, 2002).

Guided imagery techniques vary, but generally involve guiding the imagination towards places (environment or situation) in which the patient feels calm, safe, content, happy and relaxed. Similar to meditation, guided imagery encourages individuals to free their mind of interfering thoughts, release their concerns from daily life and become absorbed in the session (Post-White, 1998). Scripts have been developed to address particular conditions or problems, which may introduce the participant to new experiences and enable them to break out of inflexible or negative thought patterns (e.g. Post-White, 2002).

Guided imagery interventions in oncology have focused on four areas: efficacy in pain management, influence on surgical outcomes, improvement in quality of life and changes in immunity (Lee, 1999). Specific techniques for cancer patients may involve directing their thoughts to locations of the tumour or metastases. The images evoked may vary according to the technique or the individual's preference, from visualising a healing light shining on the tumour or affected area of the body, to the immune system or cancer treatment attacking and destroying cancer cells. Scripts may address concerns over treatments, provide positive thoughts and encourage new coping behaviours for managing pain, anxiety and nausea (Post-White, 2002).

The boundaries between the different types of mind body therapies are not easily defined, and therapies are therefore often discussed collectively (Astin *et al.*, 2003). Guided imagery is often used to aid hypnosis, or meditation, or combined with other techniques such as progressive muscle relaxation, but the technique can also be used alone. Relaxation is not always thought to be necessary for guided imagery (Post-White, 2002) although many relaxation or guided imagery sessions incorporate elements of each practice and use similar techniques. Previous reviews of guided imagery trials have included combined interventions (Wallace, 1997; Luebert *et al.*, 2001) but did not include all randomised-controlled trials of guided imagery with cancer patients available to date. We would argue that the therapeutic effects of guided imagery as a sole adjuvant intervention should be evaluated in order to clarify its role in other therapeutic regimens.

A systematic review can be viewed as a scientific and systematic examination of the available evidence in a specific topic (Bigby and Williams, 2003). The aim of a systematic review is to systematically and thoroughly assess the best possible scientific evidence about the effects of a healthcare intervention (Cochrane Library, 2004). The method of this systematic review was based on Cochrane Collaboration principles. Our aim was to summarise and critically evaluate the evidence from clinical trials for or against the use of guided imagery as a sole adjuvant intervention with cancer patients regarding any physical or psychological change. We asked the following research questions:

Are there benefits to cancer patients from the use of guided imagery as a sole adjuvant therapy? What does the evidence from controlled clinical trials suggest regarding the effectiveness of imagery as an adjuvant cancer therapy? What outcome measures have been tested and are they appropriate? What is the methodological quality of the studies?

METHOD

Systematic literature searches were performed to identify all randomised controlled clinical trials in which an imagery intervention was applied to cancer patients. The following electronic databases were searched from their inception until March 2004: the Allied and Complementary Medicine Database (inception 1985), the British Nursing Index (1994), CancerLit, CINAHL (1983), Current Controlled Clinical Trials Register (inception 1998), DH-DATA (1983), EMBASE (1966), ISI Web of Science (inception 1975), MEDLINE (1966), National Research Register (inception

2000) and PSYCHINFO (1987). The search terms used were cancer or oncolog$ or carcinogen$ or tumo$r and imagery or visualisation or visualisation. Reference lists of reviews and our departmental files were hand-searched for additional trials.

Studies were required to include a control group. No restrictions were placed on the language, place or year of publication. The terminology used in the primary reports was used to determine and distinguish between the types of therapies. Articles were included if they specified the use of guided imagery, imagery or visualisation with cancer patients as a sole adjuvant intervention to standard or palliative cancer care or as a sole supportive intervention in cancer patients who were not concurrently undergoing treatment. There were no restrictions placed on the site or stage of cancer. Studies in which the guided imagery intervention was described as occurring in a support group environment, or as guided imagery combined with any other therapy or coping package, such as hypnosis, relaxation therapy, music therapy, cognitive behavioural or any other coping package were excluded.

Data were extracted independently from each paper by two reviewers (L.R., K.S.) and verified by a third reviewer (E.E.) according to pre-defined criteria. The methodological reporting of the studies was assessed using the Jadad score (Jadad *et al.*, 1996). The Jadad score was calculated by assessing three criteria: blinding and description of the method of blinding, randomisation and description of the method of randomisation and reporting of dropouts and/or withdrawals. The maximum number of points that can be achieved on the Jadad score is 5. In guided imagery it is impossible to blind patients, as it will be obvious whether an intervention was received or not. However, one point was given for blinding if the outcome assessor was blinded. The validity of each trial was assessed according to a previously published score ranging from 0 (minimum validity) to 3 (maximum validity) where one point was given for a positive answer to each one of the following questions: (1) Was the study sample relevant? (2) Was the intervention appropriate? (3) Was the outcome measure suitable? (Ernst, 2002). The heterogeneity of populations, interventions and outcome measures across trials precluded statistical pooling of results. Results were therefore tabulated and described narratively.

RESULTS

The literature searches located 103 articles investigating guided imagery for cancer patients. From these, 97 studies did not meet the inclusion criteria. The remaining six trials were included in the review. Figure 1 summarises the exclusion process. Examples of some of the more relevant but nevertheless excluded trials are six RCTs that assessed the effects of guided imagery in combination with relaxation techniques in cancer patients (Burish *et al.*, 1991; Gruber *et al.*, 1993; Arathuzik, 1994; Richardson *et al.*, 1997; Walker *et al.*, 1999; Xie-Zhong, 2001). Five RCTs combined guided imagery with progressive muscle relaxation in the experimental group (Burish and Lyles, 1981; Lyles *et al.*, 1982; Syrjala *et al.*, 1995; Liu *et al.*, 2001; Baider *et al.*, 2001). Two RCTs combined guided imagery with music therapy (Xie-Zhong, 2001; Burns, 2002). One other RCT combined guided imagery with hypnosis or meditation in the experimental group (Rapkin *et al.*, 1991; Targ and Levine, 2002).

Furthermore, four ongoing or completed RCTs in the UK were located from the National Research Register (http://www.update-software.com/national/), of which the majority are combined interventions. These assess the efficacy of guided imagery in cancer patients undergoing surgery for colorectal cancer (completed project R Molloy, Department of Surgery, Gartnavel General Hospital, Glasgow; http://www.update-software.com/national/); evaluate the benefits of guided imagery and relaxation in cancer patients through a comparison of immune-targeted and non-specific imagery (ongoing project, M Spencer, Consultant in General Adult Psychiatry, Rydon House, Taunton (http://www.update-software.-com/national/); assess the Psycho-neuroimmunological effects of relaxation and guided imagery alone and in combination with other interventions in patients with colorectal cancer (ongoing project, P Mack and L Walker, Institute of Rehabilitation, Hull; http://www.update-software.com/national/) and assess Quality of Life and psycho-neuroimmunological effects of reflexology, relaxation and guided imagery in patients with lung cancer (Lesley Walker).

Only four of the included studies were published in their entirety. Two studies were published as abstracts only (Post-White, 1996; Kwekkeboom, 1999). The authors were contacted but due to unpublished material the results from these studies

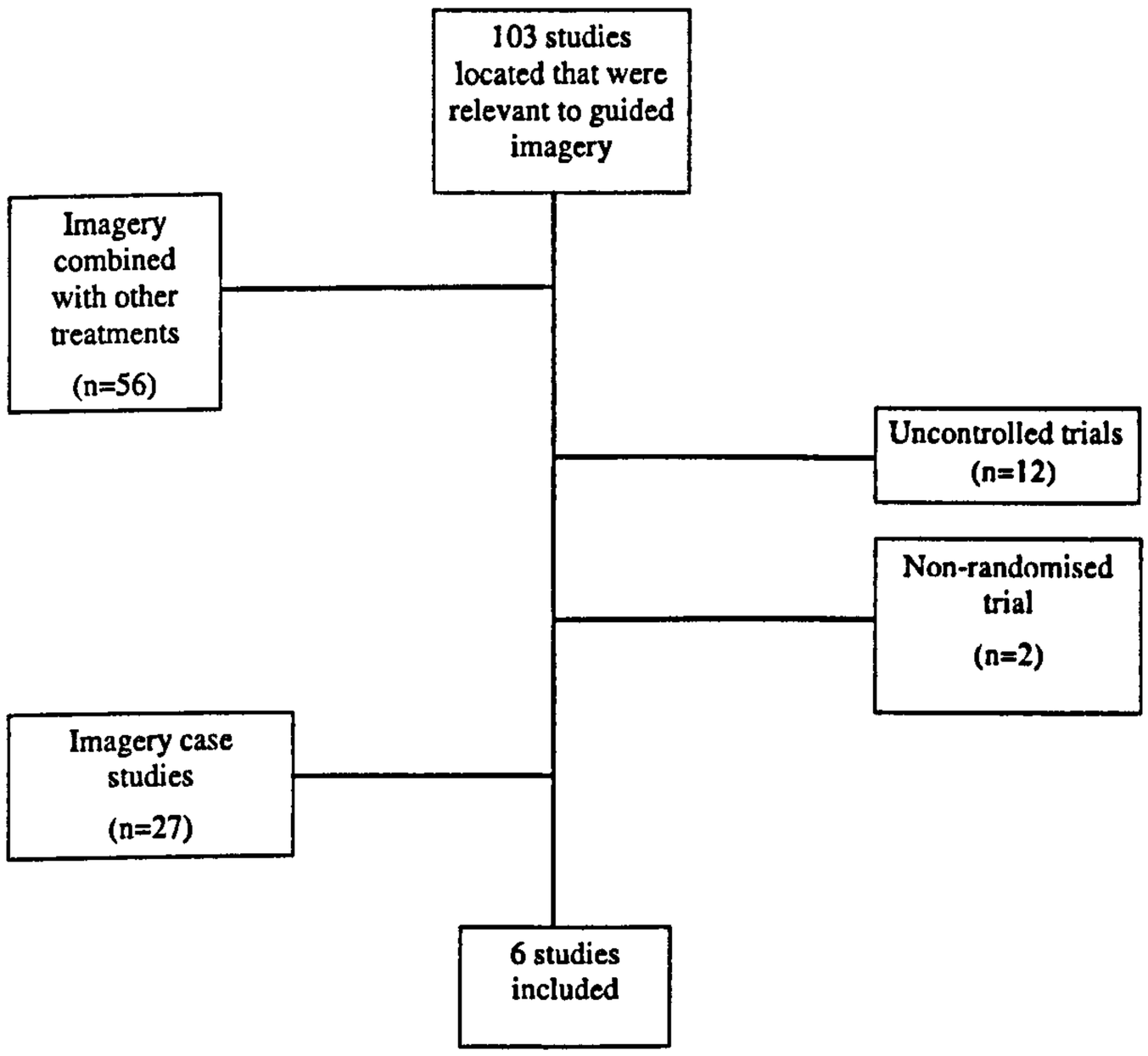

Figure 1. Flowchart of excluded studies including cancer patients.

were not available and could therefore not be evaluated. These studies are discussed narratively only. The extracted data from all included trials are presented in Table 1.

Five included studies were carried out in the USA between 1990 and 1999 and one was undertaken in Israel in 2002. All six studies were randomised controlled clinical trials, but none were outcome assessor blinded. All six trials adopted a parallel group design. In all trials patients in the experimental group received an imagery intervention additional to standard cancer care or palliative care. Patients in the control groups received standard care only, except in one study (Sloman, 2002), in which all patients received palliative care and the control condition was an 'attention' control where a nurse or practitioner spent an equivalent amount of time with patients but provided no specific therapeutic intervention. Three studies compared the guided imagery intervention with a standard care control only (Troesch *et al.*, 1993; Kolcaba and Fox, 1999; Kwekkeboom, 1999), whereas three studies included other intervention groups such as progressive muscle relaxation, hypnosis, support or a combination of guided imagery and one of the above named interventions (Feldman and Salzberg, 1990; Post-White, 1996; Sloman, 2002).

Sample sizes ranged from 30 to 75 cancer patients. Dropouts and withdrawals were mentioned in three studies (Troesch *et al.*, 1993; Kolcaba and Fox, 1999; Kwekkeboom, 1999). All participants had previously been diagnosed with cancer and cancer types included newly diagnosed cancer, advanced primary or metastatic cancer, and early stage I or II breast cancer (Table 1). The ages of participants were reported in three studies (Troesch *et al.*, 1993; Kolcaba and Fox, 1999; Sloman, 2002) and varied across the studies from 27 to 81 years. Gender was specified in all but one study (Troesch *et al.*, 1993); two studies included both males and females, and in three studies participants were all female.

A variety of self-report measures were used to assess the effect of guided imagery, including anxiety, depression, quality of life, comfort, pain, nausea and vomiting, and overall chemotherapy experience. These outcomes were assessed using

Table 1. Randomised controlled clinical trials of guided imagery as a sole adjuvant cancer therapy.

Reference	Jadad score [validity score]	Number, gender and age of participants randomised	Type of cancer, standard cancer treatment and dosage	Interventions (description, duration)	Primary outcome measures	Time at which measurements were taken	Between group results
Feldman and Salzberg (1990)	1 [3]	60 male and female adult cancer out patients. No further information given.	No detail given about types of cancer. Patients received chemotherapy and antiemetic medication. Patients had received at least 1 cycle prior to study.	Training sessions beginning on the first day of a treatment cycle of either: (1) Hypnosis + imagery (2) Hypnosis during chemotherapy or (3) Guided Imagery (structured images, described by experimenter) while awaiting chemotherapy (4) Standard treatment control.	Adverse effects of chemotherapy using: State-Trait Anxiety Inventory (STAI—Form Y1), physiological and self-report measures	Baseline and during training sessions 1 and 2; before, after and 24 h following each cycle of chemotherapy	No significant differences in anxiety, nausea or emisis between interventions over time. Significant group by time interaction $F(6,112) = 2.40$, $p = 0.03$ for post-chemotherapy anxiety. Significant group difference in anxiety between interventions and control: $F(1, 178) = 7.14$, $p = 0.008$.
Kolcaba and Fox (1999)	2 [3]	53 Females Age 37–81	Stage I or II breast cancer, beginning localised radiation therapy (RT)	(1) Guided Imagery tape: 10 min > once/day during RT and for 3 weeks afterwards. Tape recorded by a therapist, with music background. Script developed by researcher, to address all aspects of comfort. (2) Standard treatment control.	Comfort during radiation therapy. (a) State anxiety inventory (SAI) (b) Radiation therapy comfort questionnaire	(a) Baseline only (b) (i) baseline (ii) 3 wks after radiation started (iii) 3 wks after radiation ended.	Significant difference in comfort across time: Mean square 2.38, $F = 4.33$, $p < 0.05$ Significant effect size at time 2: $T = 2.14$; $D^2 = 0.55$, $p < 0.05$
Sloman (2002)	1 [3]	56 Participants: 26 Female 30 Male Age: 27–79 yr Mean: 54.6	Advanced cancer: 21 pts with primary cancer; 35 pts with metastases. Receiving palliative care at home including morphine.	30 min sessions with trained practitioner or nurse, followed by practice with tape twice per day (for intervention groups) and follow up with nurse twice per week. (1) Progressive muscle relaxation (PMR); (2) Guided imagery (GI) audio tape; (3) PMR + GI; (4) Attention control.	Anxiety and Depression: Hospital Anxiety and Depression Scale (HAD); Quality of Life (QoL): Functional Living Index—Cancer Scale.	Pre-test–post-test (3 weeks after initial session)	No significant differences in anxiety between intervention and control No significant differences in depression or Quality of Life between treatments, but all differed significantly from control No significant differences in depression or Quality of Life between treatments, but all differed significantly from control Group effect on depression $F = 4.639$, $p < 0.01$ Group effect on Quality of Life $F = 4.979$, $p < 0.01$

Table 1. (Continued)

Reference	Jadad score [validity score]	Number, gender and age of participants randomised	Type of cancer, standard cancer treatment and dosage	Interventions (description, duration)	Primary outcome measures	Time at which measurements were taken	Between group results
Troesch *et al.* (1993)	2 [3]	30 participants. Age: 33–80 yr Mean age: 63 yr	Newly diagnosed patients commencing chemotherapy with cisplatin based antineoplastic drug protocol.	(1) Guided imagery: verbal instruction by researcher followed by practise with 20 min 'positive experience' tape 3 times: 60 min before chemo session (in the clinic); the following morning before breakfast, and the following evening at bedtime. (2) Standard treatment control	Chemotherapy adverse effects: (a) Nausea and vomiting: INV-2 Self-report tool (b) 2-part Chemotherapy experience survey (CES) about overall experience of chemotherapy: I word pairs; II: visual analogue scale.	3 cycles of chemotherapy. (a) 4 h prior to chemotherapy and 12, 24, 36 and 48 h afterwards. (b) After the third cycle of chemotherapy	No significant differences in occurrence of nausea and vomiting No significant differences in perceptions of distress associated with symptoms. Significant difference in emotional response: chemotherapy experience significantly more positive in the GI group: CES part I ($p=0.0326$). CES part II: ($p<0.0001$).

validated questionnaires, such as the State Trait Anxiety Inventory (STAI), the Hospital Anxiety and Depression Scale (HADS), the Functional Living Index Cancer Scale (FLICS), Post-chemotherapy State Anxiety Scale (PCSTAS), and the Rhodes Index of Nausea and Vomiting Form 2, and non-validated tools such as the Chemotherapy Experience survey, and the Radiation Therapy Comfort questionnaire. One abstract only study additionally measured immune function (Post-White, 1996). Two studies investigated physiological outcomes such as heart rate and occurrence of nausea and vomiting (Feldman and Salzberg, 1990; Troesch *et al.*, 1993). In three studies, patients were undergoing chemo- or radiotherapy; in one study patients were undergoing surgery and in another trial patients were receiving palliative care but had no other intervention. Additional cancer treatments included pain medication such as morphine and other antiemetic medication. In one study, published as an abstract only, patients had completed treatment; thus, imagery was strictly a supportive rather than an adjuvant therapy. This study was included as it met all other inclusion criteria but results were not available, and therefore it was not included in the evaluation (Post-White, 1996). All four studies published in full state that guided imagery training sessions were held either once or up to three times during duration of the trial, and duration of sessions varied from 12 to 60 min (Feldman and Salzberg, 1990; Troesch *et al.*, 1993; Post-White, 1996; Sloman, 2002). No adverse effects of guided imagery were reported in any of the studies. The included studies are narratively described in the following section.

SUMMARIES OF INCLUDED STUDIES

Feldman and Salzberg assessed the effects of guided imagery on adverse reactions to cancer therapy in a randomised clinical study (Feldman and Salzberg, 1990). Sixty cancer outpatients who had recently received at least one cycle of chemotherapy were randomised into one of the following groups (a) guided imagery, (b) hypnosis, (c) hypnosis-imagery or (d) standard care. The intervention groups received training sessions, in which an experimenter briefly introduced the intervention before inducing a trance by describing

structured images before administering chemotherapy. Measurements were taken before, after and 24 h following each administration of chemotherapy using the STAI and self-reports of anxiety, nausea and emesis. Results showed a significant group by time interaction for all groups for the post-chemotherapy STAI, $F(6,112)=2.40$, $P=0.03$. Additionally, significant group differences between the three intervention groups and the control group for the STAI were detected, $F(1, 78)=7.14$, $P=0.008$. No significant differences were shown between the three different interventions or between the control group and hypnosis-imagery group, the guided imagery group or the hypnosis group alone. This study achieved one out of five Jadad points. No blinding of the outcome assessor or method of randomisation was reported.

Kolcaba and Fox studied the effects of GI on comfort in a randomised clinical study of 53 women with early stage breast cancer who were about to undergo radiation therapy (Kolcaba and Fox, 1999). The State Anxiety Inventory was used as a baseline measure of anxiety. The primary outcome measure was the Radiation Therapy Comfort questionnaire. This instrument together with the guided imagery script was developed for the study by the authors to address all aspects of comfort. The script included references to the machinery and physical environment involved in the treatment, and to a healing white light. Measurements were taken three times: (1) at baseline, (2) three weeks after radiation therapy commenced and (3) three weeks after radiation therapy ended. The results indicated that in both groups overall comfort increased over a 6-week time period. Significantly higher levels of comfort were reported in the guided imagery group compared to the control group, $F(1, 51)=4.33$, $p<0.05$ over the three measurement points. The strongest effect occurred at measuring three weeks after radiation therapy commenced ($D^2=0.55$, $p< 0.05$). This study received two points on the Jadad score for methodological quality of the study. No blinding of the outcome assessor was reported.

Kwekkeboom carried out a randomised clinical trial to assess the role of imaging ability in the use of GI for cancer related pain (Kwekkeboom, 1999). Seventy-five women undergoing surgery for breast or gynaecologic cancers were randomised to receive either a GI intervention additionally to standard cancer care or only standard care control. The standard care control also allowed the use of analgesic medication. The GI intervention consisted of a 12-min relaxation tape with nature and relaxation images. Pain severity, distress and interference were the primary outcome measures. No significant differences were reported regarding the therapeutic effect of GI. Full results for this study were not available, as it was published only as dissertation abstract. Therefore, results could not be evaluated and the Jadad scoring system could not be applied to this paper.

Post-White *et al.* investigated the psycho-immune response to imagery and support in 73 female breast cancer survivors who had completed treatment for breast cancer within the past two years (Post-White, 1996). Participants were randomly assigned to an imagery group ('guided' imagery not specified), a support group or a standard care control group. Intervention groups met weekly for one and a half hours over a period of 8 weeks. Emotional state, fatigue, quality of life and immune responses were measured, however, no statistical analysis was reported. Again, this study is currently only available as a dissertation abstract. Therefore, the results could not be evaluated and the Jadad scoring system could not be applied to this paper.

In a randomised clinical trial, Sloman investigated the effect of guided imagery on quality of life, anxiety and depression in patients with advanced cancer (Sloman, 2002). All 56 participants were receiving palliative care in their homes and were on pain medication. Participants were randomised into four groups (a) guided imagery, (b) progressive muscle relaxation (PMR), (c) PMR and guided imagery or (d) attention control whereby nurses endeavoured giving patients an equal amount of attention as patients in the intervention group. Participants initially received a 30 min session with a trained practitioner or nurse, followed by practice with an audiotape twice per day (for the intervention groups) and follow up sessions with the practitioner twice per week. Pre-test versus post-test comparisons were carried out three weeks after the initial session with the practitioner. Outcome measures included the Hospital Anxiety and Depression Scale, and the Functional Living Index—Cancer Scale. There were no significant differences in the anxiety scores between any of the groups. Comparisons of mean depression and quality of life scores showed that none of the three treatment groups significantly differed from each other but that each treatment

group was significantly different from the control group for both depression and quality of life (no statistics available). A significant overall group effect of the three interventions was reported for depression ($F=4.639$, $p<0.01$) and quality of life ($F=4.979$, $p<0.01$). The methodological quality of the study achieved one point on the Jadad score. No blinding of the outcome assessor or method of randomisation was reported.

Troesch *et al.* investigated the influence of GI on chemotherapy-related nausea and vomiting in a randomised clinical trial of 28 newly diagnosed cancer patients receiving the antineoplastic agent Cisplatin as a part of their chemotherapeutic regimen (Troesch *et al.*, 1993). Patients were randomised into the experimental group, which received GI, or the control group, which received standard care alone. The experimental group was given instructions on the GI intervention from the researcher, followed by 20-min sessions using a positive experience GI audiotape. Participants practised with the tape three times: 60 min before their chemotherapy session in the clinic, at home the following morning before breakfast and in the evening of the same day at bedtime. The study investigators assessed nausea and vomiting with the Rhodes Index of Nausea and Vomiting Form 2, which measures patients' perceived duration, frequency and distress of dry heaves. Data from hospital records were collected using the Subject Demographics and Emetic Response Tool. This included nurses' documentation of the frequency and severity of nausea and vomiting. However, complete results were not reported. Findings showed no statistically significant differences between the groups at any of the five measured times during chemotherapy administration. The Chemotherapy Experience survey was used to evaluate participants' overall perceptions of the chemotherapy. The GI group expressed a significantly more positive experience with chemotherapy compared to the control group ($P=0.0326$). Two points were given to this study on the Jadad scale. No blinding of the outcome assessor was reported.

DISCUSSION

Results from both the two-armed trials showed benefits in the guided imagery intervention groups compared to standard care control groups; significant effects were found in emotional response to chemotherapy (Troesch *et al.*, 1993) and comfort during radiotherapy (Kolcaba and Fox, 1999). Significant effects were also reported for all interventions in both the four-armed trials, in which treatment groups included hypnosis or relaxation techniques and combined interventions in addition to guided imagery alone (Feldman and Salzberg, 1990; Sloman, 2002). These studies showed positive group effects for all intervention groups on depression, quality of life and anxiety over a control or attention control group, but there were no significant differences between interventions. One four-armed study also reported significant differences between each intervention, and the control in both depression and quality of life, but no statistics were reported (Sloman, 2002). Guided imagery did not have a significant effect on physical symptoms, such as nausea or vomiting. A low incidence of symptoms at baseline may provide a reason for this in one study (Feldman and Salzberg, 1990).

Collectively, these data suggest that guided imagery may be beneficial as a psycho-supportive adjuvant therapy for cancer patients. Several caveats, however, apply. Certain aspects of reporting were inadequate in all trials. The often-low scores on the Jadad scale present a possible tendency toward bias. Details of the subject matter in the guided imagery scripts were only reported in three studies (Troesch *et al.*, 1993; Kolcaba and Fox, 1999; Kwekkeboom, 1999) and, with the exception of one study (Kolcaba and Fox, 1999), explicit descriptions of the intervention procedures and duration were lacking. The often poor reporting of the studies available for review renders firm conclusions problematic.

The stages at which patients practised the interventions in their treatment regimen varied, as did the amount of time spent practising and the timing of measurements. Two studies reported time effects, for post chemotherapy anxiety and for comfort during radiotherapy (Feldman and Salzberg, 1990; Kolcaba and Fox, 1999). A recent meta-analysis suggested that the effect size of guided imagery increased over the first five to seven weeks but decreased at 18 weeks. (Van Kuiken, 2004). The authors also found that more detailed reporting of imagery practise and outcome measures is needed in further trials.

Most studies presented here incorporated the use of audiotapes with guidance by a nurse, practitioner or experimenter The use of audiotapes

is often favoured over face-to-face sessions with a practitioner in order to reduced costs. From a research perspective, this also has the benefit of reducing any context effect or influence of a personal interaction on the perceived benefit of the guided imagery technique itself. However, adherence to the intervention may be harder to achieve or assess in this situation. Only one study (Kolcaba and Fox, 1999) described monitoring patients' compliance with carrying out the interventions as required by the study. The use of a support group or attention control in one study (Sloman, 2002) is commended as an attempt to control for context effects.

There were no adverse effects reported in any of the trials, but there was a lack of reporting in all but one study (Sloman, 2002) about whether any opportunities were given for comments or follow up discussions with a practitioner. It has been noted that ambiguous sensations can be evoked during guided imagery, which people may interpret very differently (Graham, 1990). The opportunity for patients to discuss their feelings and the issues raised by guided imagery, may help people acknowledge and interpret their feelings (Post-White, 2002). This may also influence their perceptions of the therapy session and contribute to the effectiveness of the intervention. This, again, highlights the importance of careful planning, conducting and reporting of trials.

Confounding variables such as sleep, diet and exercise together with imaging ability and expectations about the intervention may influence the results of clinical trials (Kwekkeboom *et al.*, 1988) and measuring feelings and perceptions is fraught with difficulty. Many studies that have investigated the effectiveness of imagery lack the scientific rigour of randomised controlled trials. Physiological measures provide objective and reliable measurements, which usually satisfy rigorous scientific enquiry, however, individuals' needs and reasons for using imagery may vary greatly from one another and cannot always be reflected by such measures. The impact of an intervention on quality of life issues such as the experience of treatment, perceived relaxation or anxiety, or a sense of control can only be assessed by self-reports. It is therefore important that outcome measures employed to quantify such effects are adequately validated. A social desirability effect, whereby patients report positive responses to please the experimenter may contribute to positive results (Krosnick, 1999) particularly, when questionnaires are not validated, as in two of the included trials (Troesch *et al.*, 1993; Kolcaba and Fox, 1999). The sensitivity of frequently used diagnostic scales such as the HADS is also uncertain when employed in different clinical populations (Love *et al.*, 2002). The HADS has been found to be less accurate for those with progressive disease (Ibbotson *et al.*, 1994), yet this is the population it was applied to in one study (Sloman, 2002).

There is no single standard method or script for guided imagery treatment and there is currently no evidence to suggest that one form of guided imagery is more effective than another (Post-White, 2002). Techniques employed in the reviewed studies were, where described, varied, and the nature of the therapy allows practitioners and participants to modify their practise to suit circumstances and individual requirements. Due to the highly personalised and experiential nature of the therapy, patients are currently faced with a 'trial and error' approach to selecting a technique, and are dependent on the good judgment of a well-trained and experienced practitioner.

In the two four-armed trials, no differences were found between the results of groups who received other interventions and those who received guided imagery as a sole adjuvant intervention; nor were there differences between the GI groups and those who received hypnosis or progressive muscle relaxation, in addition to GI. These results suggest there may be no differences between guided imagery as a sole intervention than when combined with other interventions such as relaxation or hypnosis for outcomes such as anxiety, depression or quality of life.

The relatively small number of studies that have investigated the effect of guided imagery as a sole adjuvant therapy may be a reflection of practice. Boundaries between the various types of mind body therapies are blurred and combinations of techniques are frequently employed according to the practitioner and the user. However, for a clear evaluation, individual therapies, (ideally individual techniques) also need to be assessed in isolation. Given the widespread use of guided imagery and its popularity, sample sizes were small and lacked sufficient power to produce widely applicable results.

Questions regarding individual differences and the influence of imagery content on effect size and immune response, as raised by Post-White and Fitzgerald (2002) still remain to be answered.

Further research comparing different interventions, techniques (such as 'pleasant' imagery and 'targeted' imagery) and procedures (such as the timing of practise and number of sessions) and accompanied by qualitative data may reveal richer data regarding the suitability of techniques. This will enable the practitioner to address the individual needs of cancer patients from general quality of life or to a more direct approach to dealing with, for example, treatment related anxiety or adverse effects. The use of more sensitive tools and a combination of qualitative and quantitative methods might reveal subtle but important differences experienced by cancer patients. Limitations of this review include the difficulty involved in defining 'imagery' for the inclusion/exclusion criteria; and this was doubly problematic when the reporting of imagery techniques was unclear and lacked details regarding whether an intervention was adjuvant to standard oncological treatment. Even though our search strategy was thorough, we cannot be certain to have located all relevant trials. As the number of included studies is small, missing even one or two studies could alter the conclusion of this review. Furthermore, one-third of the included studies were only available in abstract form, which prevented any evaluation of their results.

In conclusion, guided imagery as a sole adjuvant cancer therapy may be psycho-supportive and increase comfort. There is, however, no significant evidence from trials to suggest positive effects on physical symptoms such as nausea and vomiting. The paucity and low methodological quality of the primary data allow only tentative conclusions. However, the evidence available to date seems sufficiently encouraging for the use of guided imagery and merits further study.

ACKNOWLEDGEMENTS

Liz Roffe was supported by a grant from the British Medical Association. Katja Schmidt was supported by the Pilkington Family Trusts.

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European Journal of Pain 9 (2005) 437–444
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Acupuncture for the relief of cancer-related pain – a systematic review

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Received 3 March 2004; accepted 6 October 2004
Available online 11 November 2004

Abstract

Aims: This systematic review summarises the existing evidence on acupuncture for cancer-related pain.

Methods: Literature searches were conducted in seven databases. All clinical studies of acupuncture, electroacupuncture and ear acupuncture in cancer patients with the main outcome measure of pain were included. Data were extracted according to pre-defined criteria by two independent reviewers and methodological quality was assessed using the Jadad scale.

Results: Of the seven studies included, one high quality randomised clinical trial of ear acupuncture showed statistically significant pain relief in comparison with placebo ear acupuncture. All the other studies were either non-blinded ($n = 2$) or uncontrolled clinical trials ($n = 4$). Most investigations suffered from methodological flaws such as inadequate study design, poor reporting of results, small sample size and overestimation of the results.

Conclusions: The notion that acupuncture may be an effective analgesic adjunctive method for cancer patients is not supported by the data currently available from the majority of rigorous clinical trials. Because of its widespread acceptance, appropriately powered RCTs are needed.

Keywords: Acupuncture; Cancer; Pain; Randomised clinical trial; Systematic review

1. Introduction

The use of complementary and alternative medicine (CAM) including acupuncture for chronic cancer-related pain control has become common and widespread (Ernst and Cassileth, 1998; Thompson and Filshie, 1999). In the UK, about 85% of chronic pain services offer acupuncture (Woollam and Jackson, 1998). Health care professionals in Ontario, Canada, working with cancer patients selected acupuncture as the top CAM modality that they would like to learn more about (Sellick and Zaza, 1998).

Acupuncture is a common treatment for many painful and non-painful conditions in traditional Chinese medicine (Ernst et al., 2001). It involves inserting fine needles into the skin at precise locations (acupuncture points) to treat various diseases or symptoms and improve health. There is good evidence for the use of acupuncture for low back pain (Ernst and White, 1998), acute dental pain (Ernst and Pittler, 1998), recurrent headache (Melchart et al., 1999) and for the prevention of nausea and vomiting associated with chemotherapy, pregnancy or post-surgery (Vickers, 1996; Lee and Done, 1999).

The manipulation of acupuncture needles has been suggested to stimulate the release of endorphins and enkephalins (Andersson and Lundeberg, 1995). Acupuncture might also influence the production and

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1090-3801/$30
doi:10.1016/j.ejpain.2004.10.004

distribution of many neurotransmitters and neuromodulators (Shen, 2001; Han, 2003).

While the use of acupuncture in conjunction with standard antiemetics to control chemotherapy-related nausea and vomiting is supported by good evidence (Vickers, 1996), fewer data are available on its role in palliation of chronic cancer-related pain (Weiger et al., 2002). Although several reviews of this topic are available (Filshie, 1988, 2000; Filshie and White, 2002), no systematic review has been published. Hence, in this systematic review, we aimed at critically evaluating the evidence for or against acupuncture as an adjunctive therapy for cancer-related pain.

2. Methods

Systematic literature searches were conducted in the following electronic literature databases all from their inceptions to February 2004: MEDLINE, EMBASE, CINAHL, AMED, PsycINFO, British Nursing Index and The Cochrane Library. In addition, two leading Korean journals (*The Journal of Korean Society for Acupuncture and Moxibustion* and the *Journal of Korean Oriental Medicine*) were searched for relevant studies. A combination of the following search terms was employed: acupuncture, electroacupuncture, cancer, neoplasm, tumor (tumour). Further handsearches were performed in our department's own files as well as in the reference lists of all located articles. The search attempted to identify all relevant studies irrespective of language.

All prospective clinical studies of manual acupuncture, ear acupuncture and electroacupuncture for cancer-related pain in human cancer patients were included. Other forms of acupuncture such as laser acupuncture, acupressure and moxibustion and studies using transcutaneous electrical nerve stimulation or other co-interventions of CAM modalities were excluded. Case series, case reports and abstracts with no details of intervention procedure were also excluded. Articles of acupuncture for postoperative pain in cancer patients were excluded, as the pain in this situation can be assumed to be due to surgery rather than cancer.

All articles were read in full and data were extracted independently by two authors (Lee and Schmidt) on trial methods, study design, participants, interventions, type of pain, pain outcomes and adverse effects. Taking account of the fact that it is virtually impossible for an acupuncturist to be blinded to the treatment, we used a modification of the Jadad scale (Jadad et al., 1996; White and Ernst, 1999). Points were awarded as follows: study described as randomised, 1 point; additional point for appropriate randomisation method, 1 point; inappropriate randomisation method, deduct 1 point; patient blinded to intervention (i.e., control procedure was indistinguishable from real acupuncture), 1 point; evaluator blinded to intervention, 1 point; description of withdrawals and dropouts, 1 point. The maximum points available were 5. Patient blinding was assumed where the control intervention was indistinguishable from acupuncture, even if the word 'blinding' did not occur in the report. Point for evaluator blinding was only given if specified in the text. Trials with 4 or 5 points were considered high quality. Uncontrolled studies can only achieve a maximum of one point on the modified Jadad scale, as randomisation and double-blinding are not applicable. The authors met to agree to a consensus and discrepancies were settled by discussion with the third author (Ernst).

3. Results

Seven studies meeting the inclusion criteria were included (Rico and Trudnowski, 1982; Xia et al., 1986; Xu et al., 1995; Filshie et al., 1996; Dang and Yang, 1998; Alimi et al., 2000, 2003): three of them were randomised clinical trials (RCTs) (Xia et al., 1986; Dang and Yang, 1998; Alimi et al., 2003), and four of them were uncontrolled studies (Rico and Trudnowski, 1982; Xu et al., 1995; Filshie et al., 1996; Alimi et al., 2000). Originally, 29 articles were located of which 22 were excluded for the reasons given in Table 1. Key data of included studies are summarised in Table 2.

3.1. Description of studies

The studies originated from China (Xia et al., 1986; Xu et al., 1995; Dang and Yang, 1998), France (Alimi et al., 2000, 2003), United Kingdom (Filshie et al., 1996) and United States (Rico and Trudnowski, 1982). Of the seven studies included, body acupuncture was used in four studies (Xia et al., 1986; Xu et al., 1995; Filshie et al., 1996; Dang and Yang, 1998), ear acupuncture in two (Alimi et al., 2000; Alimi et al., 2003) and electroacupuncture in one (Rico and Trudnowski, 1982), respectively. Cancer patient populations were heterogeneous and painful symptoms also varied from radiating back pain to neuropathic pain. Control groups were conventional therapies (Xia et al., 1986; Dang and Yang, 1998) or placebo acupuncture (Alimi et al., 2003).

3.2. Quality of studies

Of three RCTs included, one RCT with the highest methodological quality was given 5 points on the modified Jadad scale (Alimi et al., 2003) and the other two RCTs were given a point for randomisation (Xia et al., 1986; Dang and Yang, 1998). All uncontrolled

Table 1
Reports of excluded studies of acupuncture for cancer-related pain

Author (year)	Reason for exclusion	Direction of pain-related outcome
Mann et al. (1973)	Case series of heterogeneous patient population ($n = 18$)	Positive
Peng et al. (1974)	Case series ($n = 4$)	Positive
Wen (1977)	Case series ($n = 29$)	Positive
Filshie (1984)	Retrospective audit and heterogeneous patient population ($n = 156$)	Positive
Filshie and Redman (1985)	Retrospective audit and heterogeneous patient population ($n = 183$)	Positive
Poulain et al. (1985/1997)	Duplicated RCT of acupuncture for postoperative pain in cancer patients ($n = 250$)	Positive
Chen (1990)	No pain-related data or statistics provided ($n = 34$)	No pain-related outcome measure
Yu (1992)	No clinical study	
Aung (1994)	Combined therapy of acupuncture with Qi-Gong and meditation ($n = 344$)	Positive
Bauer (1994)	Case series of TENS ($n = 3$)	Positive
Li et al. (1994)	Acupuncture for postoperative pain in cancer patients ($n = 16$)	Negative
Guo et al. (1995)	Combined therapy of acupuncture with analgesic herbal decoction ($n = 286$)	Positive
Ding (1996)	Case series ($n = 2$)	Not clear
Filshie et al. (1997)	Conference abstract with no details of intervention ($n = 67$)	Positive
Gadsby et al. (1997)	Acupuncture-like TENS ($n = 14$)	Negative
Mose et al. (1998)	Different form of acupuncture ($n = 29$)	Negative
Dillon and Lucas (1999)	Heterogeneous patient population ($n = 28$)	Positive
He et al. (1999)	Acupuncture for range of movement of shoulder after ablation and axillary lymphadenectomy in breast cancer patients ($n = 48$)	No pain-related outcome measure
Leng (1999)	Heterogeneous patient population ($n = 47$)	Positive
Balk and Gerszten (2003)	Historical control ($n = 18$)	Negative
Zhang et al. (2003)	Retrospective study without pain-related outcome measure ($n = 405$)	Positive

studies scored zero point as they failed to report withdrawals and dropouts (Rico and Trudnowski, 1982; Xu et al., 1995; Filshie et al., 1996; Alimi et al., 2000).

3.3. Outcomes

Visual analog scale (VAS) (Filshie et al., 1996; Alimi et al., 2000, 2003) and patient's verbal assessment (Rico and Trudnowski, 1982; Xia et al., 1986; Xu et al., 1995; Dang and Yang, 1998) were used as primary pain-related outcome measures. Also plasma leucine-enkephalin level was measured in one trial (Dang and Yang, 1998).

Alimi et al. conducted two studies; one uncontrolled study (Alimi et al., 2000) where a significant pain relief after ear acupuncture was reported ($P < 0.00001$), followed by a randomised, placebo-controlled trial which demonstrated a superior analgesic effect of ear acupuncture to placebo ear acupuncture (Alimi et al., 2003). Two-month body acupuncture treatment provided no significant analgesic effect in one RCT (Dang and Yang, 1998), while another RCT reported chest pain relief by two-week body acupuncture treatment (Xia et al., 1986). However, the authors mentioned patients' assessment of pain relief and did not provide adequate statistics (Xia et al., 1986). Two uncontrolled studies reported pain relief by body acupuncture (Xu et al., 1995) and electroacupuncture (Rico and Trudnowski, 1982), respectively, whereas one session of manual acupuncture showed no significant analgesic effect in Filshie's study (Filshie et al., 1996). Mild (Dang and Yang, 1998; Xia et al., 1986) or no adverse events (Xu et al., 1995) were reported but four studies did not mention them (Rico and Trudnowski, 1982; Xu et al., 1995; Filshie et al., 1996; Alimi et al., 2000).

4. Discussion

Perhaps the most important finding of this systematic review is that only regrettably few trials of acupuncture exist, a method often used for alleviating cancer-related pain conditions in clinical routine.

Numerous drawbacks of the primary studies were noted. Of the seven studies in this review, four studies are uncontrolled (Rico and Trudnowski, 1982; Xu et al., 1995; Filshie et al., 1996; Alimi et al., 2000). Uncontrolled studies are open to bias often leading to

Table 2
Summary of clinical studies of acupuncture for cancer-related pain relief

Author (year)	Design (Jadad score)	Type of cancer/pain	Groups and interventions	Outcome measures and results	Comments
Alimi et al. (2003)	Randomised, placebo-controlled, three groups (5)	Various/ neuropathic ± nociceptive pain, pain level ⩾30 on 100 mm VAS at D0, lasting ⩾1 month	•Acupuncture ($n = 29$) Individualised ear acupuncture implanted twice in 2 months (from D0 to D60) •Placebo acupuncture ($n = 30$) Ear acupuncture at non-acupuncture points •Placebo seed ($n = 31$) Auricular seeds at non-acupuncture points	Pain intensity on VAS significantly decreased in acupuncture group compared with placebo acupuncture on D30 ($P = 0.02$) and D60 ($P < 0.001$)	Sample size calculated No adverse events reported
Alimi et al. (2000)	Uncontrolled (0)	Various/ neuropathic ± nociceptive pain, pain level ⩾30 on 100 mm VAS at D0, lasting ⩾1 month	•Acupuncture ($n = 20$) o Individualised ear acupuncture implanted o 1 session in 5–35 days	Pain intensity on VAS significantly decreased in all patients on D60 ($P < 0.00001$)	Stable analgesic consumption Adverse events not described
Dang and Yang (1998)	Randomised, unblinded, three groups (1)	Stomach cancer/abdominal, chest, back pain	•Acupuncture ($n = 16$) Filiform needle for 2 months •Point injection ($n = 16$) Filiform needle + point injection •Control ($n = 16$) Conventional analgesics	Analgesic effect on 3-point Likert type scale •Effect during the first 10 days o Transient; acupuncture < control ($P < 0.05$) o Long-term; acupuncture < control ($P < 0.01$) •Effect during the last 10 days o No significant differences in transient and long-term effects	Difference in plasma leucine-enkephalin level before and after treatment; acupuncture > control ($P < 0.05$) Adverse events not described
Filshie et al. (1996)	Uncontrolled (0)	Various/type of pain not specified	•Acupuncture ($n = 20$) o 1 session o LI4 or ST36 and two studs on sternum	No significant differences in VAS	Significant improvements at 90 min post-acupuncture on VAS scores of breathlessness ($P < 0.005$), relaxation ($P < 0.005$), and anxiety ($P < 0.001$)
Xu et al. (1995)	Uncontrolled (0)	Various/abdominal pain	•Acupuncture ($n = 92$) o ST36 bilaterally o 14 sessions in 2 weeks o De-Qi elicited	No pain for at least 1 month in 32.6% ($n = 30$); much of pain relief in 55.43% ($n = 51$); no effect in 11.95% ($n = 11$) in verbal assessment of pain relief by patients	No pain for at least 1 month in 100% of slight pain group, 36.58% of moderate pain group, and 0% of severe pain group

Xia et al. (1986)	Randomised, unblinded, two groups (1)	Lung, oesophagus, stomach cancer/chest pain	•Acupuncture (n = 38) o P6, ST36 and other points according to symptoms o 1 course for 30 days followed by 7–10 days rest •Control (n = 38) Radiotherapy or chemotherapy only	Chest pain disappeared or alleviated in verbal assessment of pain relief by patients, but no formal statistics provided	Fewer adverse events of dizziness, fatigue, poor appetite, etc. were reported in acupuncture group compared with control group
Rico and Trudnowski (1982)	Uncontrolled (0)	Various/radiating back pain	•EA o 6–8 Hz, 6 V, once daily for 6–7 days (n = 10) o 6–8 Hz, 6 V, 1–2 days followed by 5–10 days of rest and reapplication (n = 12)	Excellent (n = 10); good (n = 3); fair (n = 2); poor (n = 3); unsatisfactory (n = 4) in verbal assessment of pain relief by patients	Erythema, sleepiness, nausea, etc. were reported

EA, electroacupuncture; n, number of patients; VAS, visual analog scale.

false-positive results. Absence of adequate statistical comparison, use of unreliable or subjective outcome measure such as verbal assessment of pain relief by patients, variability of therapeutic protocols and poor quality of reporting further undermine the minimal evidence available. Of three RCTs included in this systematic review, only one trial scored 5 points on the modified Jadad scale (Alimi et al., 2003). The other two trials did not satisfy basic methodological criteria; i.e., patient and assessor blinding, describing of withdrawals and dropouts (Xia et al., 1986; Dang and Yang, 1998). The positive effects reported in these studies could thus be due to observer bias or patient-practitioner interaction (Xia et al., 1986). Failure to describe an appropriate randomisation method, using subjective outcome measures or inadequate statistics and poor reporting of intervention details cast further doubt on the credibility of the reported results (Xia et al., 1986; Dang and Yang, 1998).

Our research question was whether acupuncture is effective for the relief of cancer-related pain. Consequently, we evaluated only pain-related primary outcome measures, e.g., pain intensity on VAS. One might argue that there are other benefits from acupuncture treatment such as improving tolerance against conventional therapies and anxiolytic/relaxing effects (Filshie et al., 1996; Johnstine et al., 2002). Acupuncture also alleviates chemotherapy-related nausea and vomiting (Vickers, 1996; Weiger et al., 2002). Judging from the results of the studies in our review, however, its usage for analgesic purposes is not evidence-based. Most patients in the primary studies had failed to respond to conventional analgesic therapies (Rico and Trudnowski, 1982; Xu et al., 1995; Alimi et al., 2000, 2003). Nevertheless, patients in five studies continued conventional analgesic medication during acupuncture treatment (Xia et al., 1986; Filshie et al., 1996; Alimi et al., 2000, 2003), and it was not mentioned in one study whether the patients were given other analgesic treatments in addition to acupuncture (Rico and Trudnowski, 1982). Only in one study, no supplementary analgesics were given (Xu et al., 1995).

One could argue that the effects of acupuncture should be differentiated according to the nature of pain. For instance, the previous evidence suggests that acupuncture was not more effective than placebo in relieving pain caused by HIV-related peripheral neuropathy (Shlay et al., 1998). Although data on types of pain were extracted in this review, poor reporting and a dearth of data precluded such analyses. In acupuncture practice, the precise details of therapy are usually determined by characteristic manifestations of pain, patients' physical condition and other accompanying symptoms. By contrast, the underlying mechanism of pain is rarely a crucial factor. Nevertheless, it would certainly be a relevant research question to ask whether the nature of pain

correlates in any way with the therapeutic response to acupuncture.

In spite of evidence from laboratory experiments reporting a biological basis of acupuncture analgesia (Ulett et al., 1998) and the clinical use of acupuncture by patients with painful conditions, the effectiveness of acupuncture remains controversial. One theory on how acupuncture modulates pain is that the effects of acupuncture analgesia are partly mediated by activation of a cascade of endorphins and monoamines (Sims, 1997). A recent systematic review of acupuncture for chronic pain syndromes such as low back pain, neck pain, fibromyalgia and osteoarthritis, concluded that there is limited evidence that acupuncture is better than no treatment (waiting list) and inconclusive evidence that acupuncture is more effective than placebo, sham acupuncture or standard care (Ezzo et al., 2000). The authors also found that low-quality trials are significantly more likely to yield positive results than high-quality studies ($P = 0.05$) (Ezzo et al., 2000). In our review, the methodologically best trial showed promising results: ear acupuncture provided a superior analgesic effect compared with placebo ear acupuncture and placebo ear seeds in cancer patients with neuropathic and/or nociceptive pain (Alimi et al., 2003). Another poor-quality RCT failed to show a significant difference in analgesic effect of acupuncture in stomach carcinoma patients when compared with conventional analgesics both in short and long-terms (Dang and Yang, 1998). This trial lacks detail in reporting of methodological features such as carcinoma staging and co-intervention of point injection with human transfer factor (Dang and Yang, 1998). Although Xia et al. (1986) showed in their RCT some advantages for chest pain in lung and oesophageal cancer patients receiving acupuncture treatment, the trial methodology was too weak to draw any meaningful conclusions.

Our systematic review has several weaknesses. Due to a dearth of high-quality primary studies in this field, no informative conclusion could be drawn. One of the basic requirements for conducting a systematic review is a large body of original studies. Systematic reviews can only be as good as the clinical studies that it contains (Bigby and Williams, 2003). The message that our systematic review delivers to readers is therefore limited. Many cancer patients continue to explore CAM not as an "adjunct" in support or palliation, but as a "cure" (Ernst, 2002). This may cause more serious harm to cancer patients than to those with other diseases (Wilkinson et al., 2002). Until more information is available, this review provides a useful evidence for healthcare professionals to responsibly advise cancer patients on the uncertainty of the analgesic effect of acupuncture.

To establish the role of acupuncture in the pain management of cancer patients, we obviously need more clinical trials with adequate design and power. Considering the logistical difficulties of doing a clinical trial with cancer patients (e.g. ethical issues, variability of symptoms, loss to follow-up), a very large randomised, open study which addresses effects of acupuncture as an adjunctive on clinically relevant outcomes, especially any sparing effect of acupuncture on use of invasive, and potentially harmful conventional therapies, could be one of the realistic approaches. Utilising either an individualised or a standardised approach to intervention in an acupuncture trial is also an issue. Balancing the need for replicability and generalisability in research with the acupuncture treatment in a manner that is compatible with actual clinical practice to maximise its therapeutic effects is a continuing challenge (Smith, 2004). The research effort required is considerable and therefore it seems unrealistic to expect convincing data to emerge in the near future. Several RCTs are in progress at present (http://clinicaltrials.gov/show/NCT00034034; http://clinicaltrials.gov/show/NCT00060021). It is only after we obtained sound evidence that the widespread use and general acceptance of acupuncture among cancer population can be justified. There is no convincing evidence that acupuncture prolongs survival or alleviates symptoms in patients with malignancy except chemotherapy-related nausea and vomiting (Vickers, 1996). In certain circumstances it could be prudent to avoid acupuncture for cancer: e.g., thrombocytopaenia and anticoagulant therapy (Weiger et al., 2002).

5. Conclusion

In conclusion, the notion that acupuncture may be an effective analgesic adjunctive method for cancer patients is not supported by the data currently available from the majority of rigorous clinical trials. Because of its widespread acceptance, appropriately powered RCTs are needed.

Acknowledgements

Hyangsook Lee was supported by the Brain Korea 21 Project in 2003 and Katja Schmidt was supported by the Pilkington Family Trusts. The authors thank Dr. Jacqueline Filshie and Prof. Hyejung Lee for their helpful comments.

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BMC Cancer

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Ukrain – a new cancer cure? A systematic review of randomised clinical trials

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Published: 01 July 2005

BMC Cancer 2005, 5:69 doi:10.1186/1471-2407-5-69

Received: 17 March 2005

Accepted: 01 July 2005

This article is available from: http://www.biomedcentral.com/1471-2407/5/69

Abstract

Background: Ukrain is an anticancer drug based on the extract of the plant *Chelidonium majus* L. Numerous pre-clinical and clinical investigations seem to suggest that Ukrain is pharmacologically active and clinically effective. We wanted therefore to critically evaluate the clinical trial data in the form of a systematic review.

Methods: Seven electronic databases were searched for all relevant randomised clinical trials. Data were extracted and validated by both authors, tabulated and summarised narratively. The methodological quality was assessed with the Jadad score.

Results: Seven trials met our inclusion criteria. Without exception, their findings suggest that Ukrain has curative effects on a range of cancers. However, the methodological quality of most studies was poor. In addition, the interpretation of several trials was impeded by other problems.

Conclusion: The data from randomised clinical trials suggest Ukrain to have potential as an anticancer drug. However, numerous caveats prevent a positive conclusion, and independent rigorous studies are urgently needed.

Background

Ukrain (NSC-631570) is a semi-synthetic compound derived from the common weed, greater celandine (*Chelidonium majus* L.). This plant contains a range of alkaloids, most notably chelidonine, also known as benzophenanthridine alkaloid. A leaflet distributed to patients at the Bristol Cancer Help Centre, United Kingdom, describes Ukrain as " the only known product, which at present does not also destroy healthy cells, and which reduces tumors and boosts the immune system..." [1]. Ukrain is most commonly administered intravenously and consists of one molecule thiophosphoric acid conjugated to three molecules of chelidonine. It has drug licenses in several states of the former Soviet Union.

Research on Ukrain started about 20 years ago. Meanwhile, numerous in-vitro studies [2-37] animal experiments [38-83], case reports [84-97], and case series [98-108] have emerged. Collectively, these data suggest that Ukrain has anticancer activity in a wide range of cell lines, which could be of clinical value. Whether or not this translates into clinical effectiveness and whether or not Ukrain does indeed cure some type of cancer or improves their prognosis can best be decided on the basis of randomised clinical trials (RCTs). This systematic review is aimed at summarising and critically evaluating all such studies.

Methods

Electronic literature searches were conducted in the following databases: MEDLINE (1966 to date, via Pubmed), EMBASE (1974 to date), CINAHL (Cumulative Index to Nursing and Allied Health Literature, 1982 to date), AMED (Allied and Complementary Medicine Database, 1985 to date), PsycINFO (1987 to date), DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) and The Cochrane Central Register of Controlled Trials (CENTRAL). The following search terms were used: 'Ukrain', 'chelidonium', 'greater celandine', 'cancer', 'neoplasm' or 'tumour'. Further handsearches were performed in our unit's own files as well as in the reference lists of all located articles. The producer of Ukrain was also contacted. No restrictions regarding the language of publication were imposed.

We included all RCTs of Ukrain as a treatment for any type of human cancer. Ukrain could be used as a sole treatment or as an adjunct to conventional therapy. Any type of intervention was permitted in the control groups. The clinical endpoints had to be survival or parameters indicative of tumour burden. Non-randomised studies or RCTs that did not quantify clinical endpoints were excluded [e.g. [109-117]], as were duplicates [118].

All articles were read in full by both authors and data relating to design, diagnosis, number of subjects, treatments for experimental and control groups, outcome measures and results were extracted independently by both authors. The methodological quality of each trial was assessed using the Jadad score, unless the study was only available in abstract form [119]. It evaluates methodological quality using three items assessing random allocation, double-blinding and the reports of withdrawals and drop-outs and a maximum of 5 points can be given if all criteria are met. The authors agreed to a consensus on the assessed data and cases of discrepancy would be settled by discussion. Because of overt clinical heterogeneity, a meta-analysis was deemed unreasonable. Descriptive summaries of the data are presented in the following text.

Results

Our search strategy identified 7 RCTs [120-126]. The majority of these studies was published in two different journals between 1995 and 2002 by 4 different groups of authors from the Belarus and Germany. Key data from these studies are summarised in Table 1 and will be discussed below.

Susak et al published an RCT in which 108 colorectal cancer patients received either Ukrain as a monotherapy or 5-fluororacil for an unspecified time duration [126]. The results suggest that this was followed by non-progression of the malignancy in 88.8% of the patients in the experimental group compared to 27.7% in the control group. This study is only reported in abstract form. Numerous methodological details are therefore not accessible and its methodological quality cannot be reliably assessed.

One year later, the same research group published a similar clinical trial, this time including 96 colorectal cancer patients [120]. Forty-eight patients received Ukrain as a monotherapy and 48 patients received 5-fluorouracil and radiation. The survival rate differed substantially between the two groups. Two-year survival was 78.6% in the experimental group compared to 33.3% in the control group. This study was not blinded but applied an appropriate method of randomisation.

Bondar et al treated 48 histologically verified rectal cancer patients either with X-ray radiotherapy, chemotherapy and surgery (control group) or with Ukrain and surgery (experimental group) [121]. Before and after these treatments, the authors measured 19 different laboratory parameters including two tumour markers. In addition, the Karnofsky Index, tumour dimensions, and recurrences were monitored. All of these variables strongly favoured Ukrain therapy over conventional treatment. This study has, however, numerous limitations. For instance, the method of randomisation was not explained; the authors merely stated that "all patients were subdivided into two randomised groups". Moreover, "tumour dimensions" were mentioned as an outcome measure but neither the methodology of measurement nor the results were provided. The recurrence rates are expressed as percentage figures and no test statistics seem to have been applied.

Uglyanitsa et al conducted a study with 28 patients suffering from bladder cancer [116] aiming "to evaluate the efficacy of Ukrain". Patients were allocated to three groups treated with a total dose of 100 (group 1), 200 (group 2), or 300 mg Ukrain (group 3). Two weeks later tumour regression was verified through cytoscopy and ultrasound. Complete and partial regression was noted in 0/4 patients of group 1, 1/4 patients of group 2, and 2/6 patients of group 3. This study lacks many characteristics of a rigorous trial; its stated aims (to evaluate efficacy) cannot be achieved with the study design, which essentially was that of an equivalence or dose-finding study.

Zemskov and colleagues published a "pilot study" with 42 patients suffering from pancreas cancer who had refused chemotherapy [122]. They were randomised to receive either Vitamin C alone or with Ukrain (total dose 100 mg/patient). The primary endpoint (survival) strongly favoured the Ukrain group. The analysis seems to include 4 protocol violations (the description is unclear). Even though the randomisation procedure is mentioned ('closed envelopes') it seems unusual that precisely 21

patients ended up in both groups. The results are surprisingly good – much better than with any other treatment for that condition.

Uglyanitsa et al randomised ("by lottery") 75 breast cancer patients into three groups of 25 patients each [123]. They received either no specific treatment, a total dose of 50 or 100 mg Ukrain 5–7 days before mastectomy. The authors note that Ukrain rendered the primary tumour and the affected regional lymph nodes larger, harder and "more clearly defined". They interpret this as Ukrain-induced tumour sclerosis. According to the investigators' judgement, these changes facilitated surgery and the operative success. In addition, Ukrain was associated with remarkable symptomatic improvements, e.g. better appetite, more sleep, less weakness. The report is unclear in several respects. For instance, no details about statistical analyses are provided, the outcome measures seem subjective, no information regarding investigator blinding is given, and the randomisation procedure seems suspect.

Zemskov and colleagues randomised 42 patients with pancreatic cancer who had refused conventional therapy [124]. They received either Ukrain (total dose 100 mg/patient) with Vitamin C or Vitamin C alone. The results confirmed this group's earlier findings [122]. Survival was remarkable in the Ukrain treated patients and symptoms responded well to this treatment. There are, however, numerous puzzling details. Why do the authors call their second study a "pilot study"? Why did their ethics committee consent to this "placebo"-controlled trial in the knowledge of the surprisingly positive earlier results? How could a proper randomisation again result in two equally sized groups of 21? In the discussion, the authors describe their earlier results as though this trial was conducted against 5-FU which, in fact, is not the case [122].

Gansauge et al reported a study of 90 patients with pancreatic cancer treated either with 1000 mg gemcitabine/m^2 or 100 mg Ukrain or the combination of both regimens [125]. Survival rates suggested that Ukrain was superior to gemcitabine alone. A direct comparison of the 12 month survival rates revealed large differences compared to the data from Zemskov et al [124] (29% vs 76% in the Ukrain-treated groups). The randomisation procedure was not explained and, again, the equal group sizes are remarkable.

Conclusion

Collectively, these RCTs seem to suggest that Ukrain is an effective therapy for a range of cancers. In conjunction with the numerous encouraging case reports [84-97] case series [98-108], and non-randomised clinical trials [109-121] these data look impressive at first glance. Yet several important caveats need to be considered.

None of the RCTs in this systematic review is without serious methodological limitations. The Jadad score [119] of most RCTs was low. Their sample size was usually small, and a sample size calculation to define the number of patients required was lacking in most cases. Even though most RCTs were non-inferiority studies by design and purpose, their statistical approach was that of a superiority trial. The majority of RCTs were conducted in Ukrainian research institutes and published in only two different journals. In several trials, there are clear signs of involvement of the manufacturer of Ukrain. Most RCTs have generally been poorly evaluated and reported, which possibly reflects the poverty of clinical science in Eastern Europe. Independent replications are not available. The only German study [125] has also been heavily criticised: its sample size (30 patients in each group) is minute, the report lacks statistical detail and there is an inequality of treatment cycles between groups [127]. It was also noted that this study (the only RCT not published in the same two journals as all the other RCTs) was published in a journal for which the senior author served as editor [127]. No RCTs were found showing negative or near neutral results; this might suggest the existence of publication bias for which we did, however, find no definite proof.

Greater celandine (*Chelidonium majus* L), which forms the basis of Ukrain, was traditionally used for liver and gallbladder complaints, loss of appetite and gastroenteritis. None of these indications is supported by trial evidence. The main alkaloid from this plant, chelidonine, has antispasmodic, weak central analgesic and papaverine-like effects. In animal experiments, an alcoholic extract of greater celandine increased bile flow, caused non-specific immune stimulation and acted as a hepatoprotectant [128]. The oral administration of greater celandine in humans has been associated with several cases of toxic hepatitis [129].

The mechanism of action of Ukrain as an anticancer drug (if any) remains elusive. Collectively, the preclinical studies are suggestive of antineoplastic and immunomodulatory effects. It has been postulated that the antineoplastic effect is due to the alkaloids interfering with the metabolism of cancer cells, diminished synthesis of DNA, RNA and proteins, the inhibition of cellular oxygen consumption, and the induction of programmed cell death in malignant cells [130].

Several reports of adverse reactions after greater celandine have been published. Most notably, toxic hepatitis has been associated with its oral use [129,131,132]. No case reports of adverse events have emerged of intravenous Ukrain therapy for cancer. The clinical trial data suggest that Ukrain might cause the following adverse effects: an increase in patients' body temperature (n = 26)

[120,123,125], general burning sensations (n = 3) [123] and bleeding (n = 4) [125]. Levels between 0–2 according to World Health Organisation toxicity criteria were noted in two trials [122,124] and toxicity criteria between 0–3 were observed in one trial [125]. The costs of Ukrain therapy are high; one course costs € 700 for the medication alone, and the total treatment costs have been estimated at € 3000 per week [133].

In conclusion, Ukrain is a plant-based anticancer drug that is supported by clinical and pre-clinical evidence in a range of malignancies. The data are, however, not free from problems. Before positive recommendations can be issued, independent replications with definite trials and larger sample sizes seem mandatory.

Competing interests

The author(s) have no competing interests to declare.

Authors' contributions

EE conceived of the review, participated in its design and coordination, the data extraction and helped to draft the manuscript. KS carried out the data extraction and helped drafting the manuscript. All authors read and approved the final manuscript.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2407/5/69/prepub

PERFUSION
ORIGINALARBEIT

PERFUSION 2004; 17: 136–144

Music therapy for patients with cardiovascular diseases – A systematic review

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Summary
Background and objective: **It has been suggested that patients recovering from acute myocardial infarction and acute cardiac disease may benefit from music therapy. This review is aimed to assess whether adjunctive music therapy is effective in patients suffering from various cardiac conditions.**
Methods: **Electronic literature searches were performed using Medline, the Cochrane Library, Embase, CISCOM, CINAHL, AMED, the British Nursing Index and Psychinfo. References of identified articles were checked for further potential trials. Randomised clinical trials of adjunctive music therapy that involved patients with cardiac conditions were considered. Music therapy was defined as passively listening to music in addition to standard care. Data on study design, experimental intervention, control intervention, primary outcome parameters, statistics and results were extracted in a standardised manner. To be included, studies had to quantify endpoints relevant for cardiac conditions.**
Results: **Twelve randomised clinical trials were included in the systematic review. Eight of these showed significant benefits in a range of endpoints of music therapy over no such treatment. Music therapy was seen as superior to no treatment in three studies measuring physiological outcomes. In six trials, music therapy was superior to the control condition for psychological outcome measures. In three of the included studies music therapy was not superior to the control condition in any of the outcome measures.**
Conclusion: **Collectively, these data suggest that music therapy shows some promise to lower patient anxiety, heart rate and possibly blood pressure of patients with cardiac conditions. The use of music therapy for cardiac patients warrants further rigorous investigation.**

Keywords: music therapy, alternative medicine, coronary heart disease

Zusammenfassung
Hintergrund und Ziel: **Musiktherapie soll die Rehabilitationsdauer nach Myokardinfarkt und anderen akuten Herzkrankheiten verkürzen. Dieses Review soll bewerten, ob Musiktherapie als Zusatztherapie bei diversen Herzkrankheiten effektiv ist.**
Methodik: **Die elektronischen Datenbanken Medline, Cochrane Library, Embase, CISCOM, CINAHL, AMED, British Nursing Index und Psychinfo wurden systematisch durchsucht. Die Bibliographien der so identifizierten Publikationen wurden zusätzlich nach weiteren Studien durchgesehen. Alle randomisierten klinische Studien, in denen Musiktherapie bei Patienten mit Herzkrankheiten eingesetzt wurde, wurden eingeschlossen. Musiktherapie wurde dabei als passives Hören von Musik definiert. Daten zum Studiendesign, den experimentellen Interventionen, den Interventionen in der Kontrollgruppe, den primären Zielparametern, den statistischen Analysen und den Ergebnisse wurden in standardisierter Form extrahiert. Um in das Review eingeschlossen zu werden, mussten für Herzkrankheiten relevante Endpunkte quantifiziert worden sein.**
Ergebnisse: **12 randomisierte klinische Studien wurden in das systematische Review eingeschlossen. Davon wiesen 8 Studien signifikante Vorteile der Musik-**

Each year, 1.5 million people in the US experience an acute myocardial infarction (AMI), suffer from acute coronary syndrome (ACS) or acute cardiac disease (ACD) [1]. The annual incidence of ACS in France is greater than 280 per 100.000 men and 60 per 100.000 women [2]. In the UK approximately 300.000 people experience a myocardial infarction each year [3] and in Australia this figure amounts to an incidence rate of 605 coronary events per 100.000 population aged 40–90 years [4]. Admission to coronary care units (CCU) is a psychological and physiological strain on the patient, which might affect adversely the prognosis and recovery time [5–8]. Anxiety is often observed in CCU patients, and known to cause increased blood pressure, heart and respiration rate, all of which lead to poor blood circulation and can cause fluctuation in skin temperature [9–11].

One intervention, which may relieve patients with cardiovascular conditions of some of the stresses they are suffering at coronary care units is music therapy. Music therapy (MT) has been subjected to a great deal of research during the past three decades and several journals are devoted to it (e.g. the Nordic Journal of Music Therapy, the British Journal of Music Therapy, the Journal of the American Association for Music Therapy and the Harp Therapy Journal). A recent flurry of interest in the effects of music on the human body and psyche has been observed in the media. Music therapy has been mainly employed as

* Katja Schmidt was supported by The Pilkington Family Trusts

therapie im Vergleich zur Kontrollintervention in einer Reihe von Endpunkten auf. Musiktherapie erzielte in 3 Studien bessere Ergebnisse bezüglich verschiedener physiologischer Messpunkte. In 6 Studien war Musiktherapie der Kontrollintervention in psychologischen Messpunkten überlegen. In 3 Studien war die Musiktherapie der Kontrollintervention in keinem der Endpunkte überlegen.
Schlussfolgerung: **Dieses systematische Review liefert Hinweise dafür, dass Musiktherapie bei Patienten mit Herzkrankheiten Ängstlichkeit vermindert sowie die Herzfrequenz und möglicherweise den Blutdruck senkt. Musiktherapie bei Patienten mit Herzkrankheiten sollte auch weiterhin intensiv beforscht werden.**

Schlüsselwörter: Musiktherapie, Alternativmedizin, koronare Herzkrankheit

a distraction stimulus for uncomfortable procedures at hospitals [12–15].
MT has been shown in a number of studies, including randomised, controlled trials (RCTs), to have beneficial effects in a variety of conditions including Alzheimer's disease [16], dementia [17] as well as pain and anxiety in critical care patients [18]. It has been proposed that MT can be adopted as a safe and inexpensive therapy for patients undergoing surgery, dental procedures, invasive endoscopic interventions and hospitalisations [19–21]. It has been suggested that patients recovering from AMI may benefit from MT [22, 23].
This systematic review is aimed at assessing the effectiveness of MT on clinically relevant outcome measures in cardiovascular patients by summarising and critically evaluating the evidence from published randomised clinical trials.

Methods

The following electronic databases were searched from their inception until August 2003: Medline, the Cochrane Library, Embase, AMED, CISCOM, CINAHL, the British Nursing Index and Psychinfo. The search terms varied for different databases. For Embase the search terms were 'music', 'music therapy', 'coronary artery disease', 'heart infarction' and 'heart muscle ischaemic disease'. The search terms for CISCOM were 'music and cardiology or cardiac', 'music and coronary', 'music and myocardial', 'music and heart'. The search terms for all other databases were 'clinical trial', 'music', 'music therapy', 'cardiac', 'cardiology' and 'coronary'. All search terms were employed singularly and in addition with each other as subject heading, key words and text words. Additionally, the department's personal files were handsearched. Bibliographies of identified articles were checked for further potential trials. No restrictions regarding language of publication were applied.
For the purpose of this systematic review, MT was defined as the passive listening to music. Participants either chose themselves which music they wanted to listen to or had to chose from a pre-selected variety of musical tapes provided by the investigators. For inclusion, trials had to be randomised and involve human patients with cardiac conditions. All studies were employing music therapy as an experimental intervention in addition to standard care. Only studies that quantified psychological or physical outcome measures relevant to cardiovascular conditions were included. Trials on healthy volunteers, case studies, traditional reviews, abstracts and studies involving solely the presence of background music were excluded.
It was impossible to define one uniform endpoint because of the diversity of outcome variables used in the primary studies. However, two specific research questions were asked: a) what is the therapeutic effect of MT on anxiety of coronary patients and b) what is the effect of MT on physiological variables, such as heart rate and blood pressure in coronary patients?
Key data from all RCTs were extracted in a standardised manner according to the following pre-defined criteria: study design, number of patients and clinical condition, settings, treatment intervention, other interventions and control intervention, and results from various outcome measures. Both data extraction and the assessment of methodological quality were performed independently by two reviewers. Discussions between the reviewers resolved any discrepancies.
Statistical pooling was originally envisaged but proved to be impossible due to the heterogeneity of the data. Thus, a narrative synthesis was conducted with a separate focus on anxiety and the effect of MT on physiological outcome measures. The criteria on which the validity and quality of the studies were based involve randomisation, blinding, and dropouts. The judgements of validity and quality of the studies was made by employing Jadad's scoring system to measure the likelihood of bias, for which a total of 5 points can be distributed [24]. In Jadad's scoring system one point is given inter alia for the double-blinding procedure of the subjects. However, this is impossible for MT, as the patients were able to detect whether they have been randomised to receive either MT, the control treatment, such as, for instance, white noise tapes or standard care. Thus, one point was given if single blinding of the clinician was assured.

Results

Twelve RCTs were included in the review (Table 1) [22, 23, 25–34]. The studies reported were published between 1988 and 2002. One study was observer-blinded [26]. Only two studies reported a sample size calculation [33, 34]. Patients were recruited from community hospitals [23, 25, 26, 30, 31, 34], cardiac care units [27–29, 33] and intensive care units [23]. Five trials reported dropouts [26, 29–32]. Four studies scored 3 out of 5 total points on the Jadad score [26, 30–32], three studies scored 2 points [25, 27, 29], whilst the remainder scored 1 point [22, 23, 28, 33, 34]. All studies differ in terms of treatment period, treatment modality, and study sample. The methodological quality of studies ranged from 3 points on the Jadad score to 1 point. Only 5 of all 12 included studies have described the method of randomisation and only one study has applied appropriate assessor-blinding [26].
The total sample size of patients from all 12 studies was 904. The individual study samples ranged from 35 to 140 patients. Study patients suffered from a range of conditions or underwent

Table 1: Controlled clinical trials of music therapy for cardiac symptoms

First author Year [ref]	Study design	Participants	Quality score	Duration of intervention	Intervention 1 (n)	Intervention 2 (n)	Control (n)	Outcome measures	Results intervention Group 1 mean (SD)	Results intervention Group 2 mean (SD)	Results control mean (SD)	Significance
Barnason 1995 [25] measure	RCT repeated bypass 3 groups	96 coronary artery grafting patients	2	30 minutes 1 session 33	30 min musical tape 29	30 min music video rest	30 min scheduled 34	STAI NRS (anxiety NRS (mood) blood pressure heart rate	31.8 (11.4) 1.75 (2.16) 7.72 (1.49) no data no data	33.1 (12.9) 2.32 (3.2) 6.29 (2.75) no data no data	34.7 (16.0) 2.56 (2.52) 6.55 (2.42) no data no data	NS, F(2,89)=0.51, p>0.05 NS, F(2,87)=not stated, p>0.05 significant, F(2,87)=4.33, p=0.016 NS NS
Blankfield 1995 [26]	RCT, single-blind 3 groups	95 coronary bypass patients	3	30 minutes 1 session intraoperatively and postoperatively 2x daily for duration of hospitalisation	30 min musical tape 32	30 min suggestion tape 34	standard care 29	days of post-operative stay morphine (mean mg) depression scale daily living activities cardiac symptom scale	6.5 (1.5) 15.6 (11.2) 3.0 (2.6) 3.7 (4.8) 2.1 (1.4)	6.5 (2.5) 21.7 (12.5) 3.3 (3.3) 3.0 (2.7) 2.5 (1.7)	6.6 (2.3) 20.2 (15.7) 2.8 (3.0) 4.0 (4.5) 2.3 (1.8)	NS NS NS NS NS
Cadigan 2001 [27]	RCT pre-test post-test 2 groups	140 patients with intravascular sheaths or IABP	2	30 minutes 1 session	30 min musical CD 65	none	standard care 75	POMS pain perception (VAS) heart rate systolic blood pressure diastolic blood pressure respiratory rate peripheral skin temperature	5.8 (2.8) 1.1 (1.9) 69 (13) 112 (16) 57 (11) 17.3 (3.4) 88 (5.8)	none	7.0 (3.2 0.88 (1.5) 71 (14) 121 (18) 61 (11) 19.1 (3.4) 88 (6.2)	significant, t=-2.3, p=0.021 NS, t=0.79, p=0.43 NS, t=-0.71, p=0.479 significant, t=-3.1, p=0.002 significant, t=-2.2, p=0.028 significant, t=-3.0, p=0.003 NS, t=-0.005, p=0.996
Elliott 1994 [28]	RCT, pre-test post-test 3 groups	56 acute myocardial infarction and angina pectoris patients	1	30 minutes 2 or 3 sessions	30 min musical tape 19	30 min muscle relaxation tape 18	standard care 19	STAI LAAS HADS-A HADS-D heart rate systolic blood pressure diastolic blood pressure	32.1 (6.3) 30.8 (17.0) 6.8 (2.9) 2.9 (2.6) 72 (13) 24 (20) 71 (12)	33.2 (10.0) 24.2 (15.1) 8.4 (4.7) 4.0 (3.2) 76 (16) 129 (36) 71 (12)	30.1 (10.4) 26.4 (23.7) 6.6 (3.9) 3.8 (2.9) 80 (19) 124 (12) 75 (10)	no between group analysis
Guzzetta 1989 [29]	RCT, pre-test post-test 3 groups	80 acute myocardial infarction patients	2	20 minutes 3 sessions	20 min relaxation induction and musical tape 26	20 min relaxation technique 27	standard care 27	heart rate peripheral skin temperature	64.58 (12.67) 93.04 (3.12)	70.52 (16.82) 93.73 (2.69)	76.81 (14.17) 88.63 (6.64)	significant, F(2,76)=48.56, p<0.001 significant, F(2,75)=42.61, p<0.001
Hamel 2001 [30]	RCT, pre-test post-test 2 groups	101 patients undergoing cardiac catheterisation	3	20 minutes 1 session	20 minutes musical tape 51	none	standard care 50	STAI heart rate systolic blood pressure diastolic blood pressure	37.84 (9.82) 64.43 (12.00) 133.53 (19.79) 72.78 (10.91)		44.34 (10.99) 67.56 (10.43) 139.72 (21.61) 75.52 (11.94)	significant, p=0.002 NS NS NS

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PAGE NUMBERING AS ORIGINAL

First author Year [ref]	Study design	Participants	Quality score	Duration of intervention	Intervention 1 (n)	Intervention 2 (n)	Control (n)	Outcome measures	Results intervention Group 1 mean (SD)	Results intervention Group 2 mean (SD)	Results control mean (SD)	Significance
Lueders-Bolwerk 1990 [31]	RCT, pre-test post-test 2 groups	35 acute myocardial infarction patients	3	22 minutes 3 sessions	22 min musical tape 17	none	standard care 18	STAI	31.17 (7.63)	none	39.61 (9.67)	significance, t=-2.87, p=0.07
Taylor-Piliae 2002 [32]	RCT repeated measure 3 groups	45 patients undergoing cardiac catheterisation	3	15–20 minutes 1 session	15–20 min musical tape information 15	15–20 min sensory 15	standard care 15	STAI POMS MUIS heart rate respiratory rate	39.4 (5.9) 16.13 (24.6) 99.67 (13.4) 68.31 (10.1) 17.33 (2.4)	40.0 (4.9) 3.73 (15.9) 96.93 (8.2) 64.53 (6.9) 17.47 (2.1)	38.33 (9.1) 12.0 (23.1) 103.2 (10.5) 65.47 (5.0) 18.27 (2.9)	NS NS NS NS NS
White 1992 [22]	RCT, pre-test post-test 2 groups	40 myocardial infarction patients	1	25 minutes 1 session	25 min musical tape	none	25 min uninterrupted rest	STAI heart rate	37.15 (7.97) 77.10 (13.6)	none none	42.2 (7.53) 80.5 (8.48)	significant, F=29.72 NS, F=0.205, p=0.653
White 1999 [23]	RCT, repeated measure 3 groups	45 acute myocardial infarction patients	1	20 minutes 1 session	20 min musical tape 15	20 min uninterrupted rest 15	standard care 15	STAI heart rate respiratory rate systolic blood pressure	31.7 (2.5 SE) 70.5 (3.9 SE) 15.7 (0.8 SE) 115 (4.0 SE)	37.9 (2.0 SE) 74.0 (2.7 SE) 17.3 (1.1 SE) 122 (5.0 SE)	42.0 (3.3 SE) 79.6 (5.4 SE) 18.3 (1.5 SE) 121 (2.6 SE)	significant, F=10.09, p<0.001 significant, F=3.46, p=0.04 significant, F=4.62, p=0.02 significant, F=2.64, p=0.04
Zimmerman 1988 [33]	RCT, repeated measure 3 groups	75 suspected myocardial infarction patients	1	30 minutes 1 session	30 min musical tape 25	30 min white noise tape 25	30 min scheduled rest rest 25	STAI heart rate systolic blood pressure diastolic blood pressure peripheral skin temperature	33.0 (11.6) 76.8 (16.3) 114.1 (24.1) 65.1 (12.6) 91.0 (4.7)	32.1 (12.5) 74.6 (19.0) 118.0 (17.6) 67.6 (7.0) 92.3 (4.4)	31.4 (9.7) 78.5 (17.4) 120.1 (17.4) 63.9 (14.0) 90.6 (5.1)	NS, F(2, 34)=0.34, p>0.05 NS NS NS NS
Zimmerman 1996 [34]	RCT, repeated measure 3 groups	96 coronary bypass patients	2	30 minutes 1 session	30 min musical tape 32	30 min musical video 32	30 min scheduled rest 32	VRS MPQ (PPI) RSQ	0.68 (1.3) 0.38 (0.78) no data	1.03 (2.08) 0.52 (0.9) no data	0.88 (1.8) 0.41 (0.82) no data	NS significant, F(2,93)=4.74, p<0.05 for day 2 significant, F(2,92)=3.18, p<0.05

various procedures and included coronary bypass [25, 26], acute myocardial infarction [22, 23, 29, 31, 33], and angina pectoris [28], patients after placement of intra-vascular sheaths or intra-aortic balloon pumps [27], patients waiting to undergo cardiac catheterisation [30, 32] and a group of acute myocardial infarction and coronary bypass patients [34]. In all RCTs, patients received standard care as a baseline treatment and the experimental groups received MT in addition. The following control or other interventions were employed: watching a musical videocassette [25, 34] (other intervention), a rest period without music [22, 23] (control intervention), a vocational suggestion tape [26] (other intervention), a muscle relaxation tape [28] (other intervention), sensory information input (other intervention) [32] or a blank tape [33] (control intervention), Benson's »respiratory one-method« relaxation technique [29] (other intervention) or no further therapy at all (control intervention) [27, 30, 32] Eight studies involved three groups [23, 25, 26, 28, 29, 32–34] in which the third group received either a rest period or standard care [23, 25, 32–34] or listened to a suggestion tape [26], a muscle relaxation tape [28] or practised a muscle relaxation technique [29].

The outcomes assessed in this review involved a wide range of physiological and psychological endpoints. The State Trait Anxiety Inventory (STAI) [35] was most frequently employed as main outcome measures [22, 23, 25, 28, 30–33]. Other outcome measures were heart rate, blood pressure, respiratory rate, skin temperature, pain perception, days of postoperative stay at hospital, the Daily Living Activity Scale (DLAS), the Linear Analogue Anxiety Scale (LAAS), the Numeric Rating Scale for mood and anxiety (NRS), the Cardiac Symptom Scale (CSS), the Profile of Mood States (POMS), and the Hospital Anxiety and Depression Scale (HADS).

Barnason et al carried out an RCT with a repeated measure design on 96 artery bypass patients [25]. Patients who were randomly assigned to the experimental group had to chose one out of 5 musical tapes of their preference and received one 30-minute session of MT. Patients assigned to a second intervention group watched a musical video and control patients received 30 minutes of scheduled rest. The music tapes were from the following selection: Country Western Instrumental, Fresh Aire by Mannheim Steamroller, Winter into Spring by George Winston, and Prelude and Comfort Zone by Steven Halpern. Outcome measures were taken at 10-minute intervals and included the STAI, NRS for mood and anxiety, blood pressure and heart rate. The final measure was taken after 30 minutes of MT and the results indicate that there was a statistically significant difference for the NRS (mood) for patients in the MT group, $F[2, 87]=4.33$, $p=0.016$.

The methodological quality of this RCT was fairly poor. The method of randomisation of participants was described and appropriate. However, no single-blinding of the investigator or mentioning of dropouts were reported.

Blankfield et al were investigating the effect of taped therapeutic suggestion and taped music therapy as adjuncts in the care of 66 coronary bypass patients [26]. In this RCT patients were randomly assigned to one of the three groups: 1 suggestion group, 2 music group and 3 control group. Patients in group 1 listened to a suggestion tape with background music (Dreamflight II by Herb Ernst). Patients in group 2 listened only to this background music and patients in group 3 received standard care. One session of the intervention lasted 30 minutes and was carried out once intra-operatively and post-operatively twice daily for the whole duration of hospitalisation. Patients were assessed in regard to their days of postoperative stay, morphine intake, and their scores on a 7-item depression scale, DLAS, and the CSS. Results showed that there were no significant differences between groups for any of the outcome measures and thus, the trial did not demonstrate any objective effect to any of the interventions.

The assessment of methodology indicated a satisfactory quality with 3 points for the Jadad score, as the RCT was randomised and single-blinded.

One hundred forty-five cardiac patients who were bed resting due to procedural sheaths or intra-aortic balloon pumps were enrolled in a RCT carried out by Cadigan et al [27]. Patients were randomly assigned to receive either a 30-minute music intervention or standard care. The music selection was a combination of symphonic music and nature sounds and had been selected by the researchers. Psychological outcome measures included the POMS, and pain perception; physical outcome measures that were assessed were heart rate, blood pressure, respiratory rate and peripheral skin temperature. There were statistically significant differences between the two groups for the POMS ($t=-2.3$, $p=0.021$), for systolic and dialostic blood pressure ($t=-3.1$, $p=0.002$ and $t=-2.2$, $p=0.028$, respectively), and for respiratory rate ($t=-3.0$, $p=0.003$) as the intervention group had a greater decrease in all of those measures.

The methodological quality of the trial was fairly poor, as there was no mentioning of single-blinding or dropouts.

Elliott et al investigated the effects of music and muscle relaxation on patient anxiety in 56 CCU patients [28]. Patients were randomised into one of the following groups: 1) the muscle relaxation group contained a verbal script using a combination of autogenic heaviness and a technique for inducing the relaxation response, 2) the music group listened to light classical music designed by Bonnie (Music Rx, Portland, Washington) [36] and 3) patients in the control group received standard care. The number of sessions were two or three within a period of 24 hours, depending on CCU bed supply and demand and the subject's clinical condition. Psychological and physiological effects were measured before and after the intervention with the STAI, HADS, LAAS, blood pressure and heart rate. Within-group analyses revealed that all groups had statistically significant differences in STAI anxiety scores from pre-test to post-test measurements. No between group analyses were carried out. Thus, we cannot draw any conclusions from this methodologically fairly poor RCT.

In another RCT [28] 80 myocardial infarction patients at a CCU were randomly assigned to one of the following groups: 1) patients assigned to the relaxation group practised Benson's 'respiratory one-method', 2) patients assigned to the music group selected to listen to music tapes containing either soothing classical music, soothing popular music or non-traditional music (defined as compositions having no vocalisation or metre, periods of silence and an asymmetric rhythm) and 3) patients in the control

group received standard care. All patients from the muscle relaxation and music groups participated in an initial session and then again in two more following sessions the next day. Heart rate and peripheral skin temperature were measured at baseline and after each session. Analyses of outcome measures suggest that for both outcome measures there were statistically significant differences between groups. There was a statistically significant difference for heart rate when the relaxation group and music group were compared to the control group ($F[2, 76]=48.56$, $p<0.001$). No difference, however, was found between the relaxation and music group. Groups also differed significantly in peripheral skin temperature, as the difference between the two intervention groups and the control group was statistically significant ($F[2, 75]=42.61$, $p<0.001$). Additionally, the music therapy was more effective in decreasing peripheral skin temperature compared to the relaxation group ($t(49)=2.99$, $p=0.004$).
The quality of the methodological design of this study was fairly poor. No single-blinding of the outcome assessor was reported nor was the method of randomisation adequately described.
The effects of a music intervention on anxiety were assessed in 101 patients waiting for cardiac cathederisation has been evaluated by Hamel [30]. In this RCT patients either received one session of the intervention (Trance-Zendance by Halpern) or standard care alone. Outcome measures such as STAI, heart rate and blood pressure were taken before and after the intervention and analyses revealed a statistically significant difference for the STAI score between the two groups ($p=0.002$). Thus, the music intervention had significantly decreased patients' anxiety.
The methodological quality of the clinical trial was satisfactory – the only point of criticism is that the study was not assessor-blinded.
The effects of relaxing music on state anxiety of 40 myocardial infarction patients was assessed by Lueders-Bolwerk [31]. Patients were randomly assigned to receive either 3 sessions of music therapy (Largo by Bach, Largo by Beethoven and Prelude to the Afternoon of a Faun by Dubussy) or standard hospital care. Five patients dropped out of the study as they were transferred to other hospitals. All patients filled in the STAI at baseline and after the final intervention. The results showed that patients in the music group had statistically significant lower scores on the STAI compared to the control group ($t=-2.87$, $p=0.07$).
This study is of satisfactory methodological quality and received 3 points on the Jadad scale.
Taylor-Piliae et al measured the effects of nursing interventions utilising music therapy or sensory information on patients' anxiety prior to cardiac cathederisation [32]. In this RCT patients were randomly assigned to either receive 1) music therapy, 2) a sensory information intervention or 3) standard CCU care. Anxiety (STAI), uncertainty (Mishel's Uncertainty in Illness Scale), mood states (POMS), heart and respiratory rates were measured at baseline, after the intervention session and post-cardiac catheterisation. Participants in the music intervention could chose to listen to either New Age music (Songs from a Secret Garden or Introduction to New World Music, Vol I), Chinese instrumental (Guzheng selections of Kwok Wai-Sze) or classical music (Symphony Nr 8 by Beethoven or Canon in D by Pachelbel). Post-intervention results showed that baseline-dependent variable mean scores revealed no significant differences between the groups.
The methodological quality of this trial is reasonably satisfactory, given that an appropriate method of randomisation was applied and drop-outs were reported.
White carried out two RCTs to study the effects of MT on anxiety and cardiac autonomic balance [22, 23]. In one study 40 myocardial infarction patients were randomly assigned to either receive one session of music therapy (4 pre-selected Adagios) or standard care [22]. Outcome measures included the STAI, heart and respiratory rates. Statistically significant reductions in all of the outcome measures were found for the intervention group (STAI: $F=29.72$, $p<0.001$; heart rate: $F=0.21$, $p=0.653$; respiratory rate: $F=4.14$, $p=0.049$). Thus, it was found that the MT intervention helped to reduce the autonomic nervous system indicators of heart and respiratory rate as well as elevate anxiety in patients suffering from acute MI.
The quality of the study design was fairly poor, as the study was not single-blinded and the number of drop-outs and method of randomisation were not described.
Forty-five acute MI patients in a later study were randomised into one of the following groups: 1) music intervention (pre-selected classical music), 2) attention control or 3) standard care [23]. STAI, heart and respiratory rate, and systolic blood pressure were measured at baseline and after the intervention. Outcome measures were taken at baseline, immediately after and one hour after the intervention. Between-group analyses of the results indicate that immediately after the intervention reduction in heart rate ($F=3.46$, $p=0.04$), respiratory rate ($F=4.62$, $p=0.02$) and STAI scores ($F[4, 84]=10.09$, $p<0.001$).
Again, this study also lacked of methodological rigour, as no assessor-blinding, number of drop-outs or method of randomisation were reported.
Finally, in two RCTs Zimmerman et al investigated the effects of MT on patient anxiety, pain and sleep in CCUs [33, 34]. In one of the trials 75 suspected MI patients were randomly assigned to participate in one session of one of the three interventions: 1) MT (Halpern relaxation tape, classical music or Country Western music), 2) patients listening to a 'synthetic silence' tape, which contained recordings of ocean waves or 3) 30 minutes of scheduled rest [33]. Outcome measures including STAI, heart rate, blood pressure and skin temperature were taken at baseline, after 10, 20 and 30 minutes. There were no statistically significant differences between groups for any of the outcome measures taken. This trial was of poor methodological quality.
In the other study 96 coronary bypass patients who had undergone coronary artery bypass grafting were included [34]. Patients were either receiving 1) MT (Country Western Instrumental by Country Pops, Fresh Aire by Mannheim Steamroller, Winter into Spring by George Winston or Prelude and Comfort Zone by Steve Halpern), 2) a 30-minute video cassette playing soft instrumental music combined with visual images or 3) scheduled rest. The Verbal Rating Scale (VRS) for pain scores, the McGill Pain Questionnaire and the Richards-Campbell Sleep Questionnaire were the outcome measures that were obtained. The results of this study showed that for the evaluative component of pain,

as measured by the VRS there were no statistical significant differences between groups. However, on the MPQ pain intensity score after session 2 the evaluative component pain showed a significant group effect ($F[2, 93]=4.74$, $p<0.05$) for postoperative day 2 though not for day 3. Post-hoc Tukey tests revealed that participants in the MT group had significantly lower pain scores than the resting group. There was a significant difference among groups for the total RSQ measuring sleep ($F[2, 92]= 3.18$, $p<0.05$). Again, this trial showed to be of poor methodological quality.

The overall results from all 12 included trials can be summarised as follows: 4 RCTs showed significant effects of MT on STAI scores [22, 23, 30, 31], two trials demonstrated significant reductions in heart rate [23, 29], two RCTs showed a significant decrease of respiratory rate [23, 27], one RCT demonstrated significant drops of dialostic blood pressure [27] and two studies showed a significant drop in systolic blood pressure [23, 27], one RCT demonstrated significant changes for skin temperature [29], and two RCTs showed significant effects for subject's mood ratings [25, 27].

Discussion

A music therapy intervention is aimed at addressing the physical and emotional needs of patients as an adjunct to pharmacological pain and symptom management. Music therapy is known to have healing and relaxing effects. Although these effects appear to be mediated by release of neurotransmitters and hormones, the specific hormonal systems involved have not yet been fully investigated. The mechanism of action of MT might be a relaxation response, which can be induced by soothing music and has been suggested to alter the autonomic, immune, endocrine and neuropeptide systems [23, 30].

This systematic review implies that MT can have desirable effects in patients suffering from various cardiac symptoms. Some of the included studies indicate an improvement of physiological outcome variables, such as blood pressure and respiratory rate after MT intervention; others show an improvement for psychological outcome measures, such as mood and anxiety.

Several limitations complicate the interpretation of these results. The type of music employed in these studies differed greatly. In most of the trials the patients were supplied with preselected music. Music, however, is often of very personal taste and thus, the same music may have different effects in different people. The presence of a music therapist may increase the impact of MT yet none of the studies mentioned the employment of a music therapist [37]. Moreover, some of the criteria used to define improvement are of debatable relevance. It is not generally accepted, for example, that the STAI is a measure of improvement in cardiac patients. The same may be said about some of the other outcome measures. In most of the studies the duration of the effect is unknown. Thus, the longevity of any observed effect seems uncertain.

The low Jadad score for most of the studies reflects the overall poor quality of research on MT. Only one study employed single blinding [26] but fails to describe the method of blinding. Only two studies describe the method of randomisation [25, 31]. A further problem is that only few studies exist for any single cardiac condition or outcome measure. The conditions vary from acute MI to coronary bypass rehabilitation, angina pectoris and patients undergoing invasive procedures. Obviously, different conditions could yield different physiological and psychological outcomes. What is needed to advance our knowledge is an adequately powered clinical trial of a homogeneous group of patients exposed to uniform (but individualised) MT measuring valid clinical rather than surrogate endpoints.

The question arises whether MT is cost-effective. On the basis of the data provided by the primary studies, a formal cost analysis is not possible. However, supplying an audio-tape is low-cost and does not demand much professional time. It therefore seems likely that a cost-benefit-analysis would reach positive conclusions provided that effectiveness of MT can be established.

Despite these limitations some preliminary implications seem to emerge from the data. MT does seem to have potential for coronary patients in that it can have positive effects on a range of clinically relevant endpoints. Moreover, it is not associated with significant risks and is inexpensive. The fact that none of the included trials have reported adverse effects is somewhat assuring. Loud music may cause hearing impairment [38], but adequately applied MT seems to be a safe treatment. Thus, one might be tempted to advocate its inclusion in routine cardiovascular care. The present reviewers, however, believe that this may be premature and suggest further research to define the optimal type of MT, dosage, length of therapy, duration of effect and type of condition.

In conclusion, the trial data on MT for cardiac patients is encouraging. Due to a range of limitations they are, however, not convincing. Positive recommendations seem warranted only after its benefits have been demonstrated beyond reasonable doubt. □

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