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REVIEW ARTICLE

Efficacy of Complementary and Alternative Medicine Therapies in Relieving Cancer Pain: A Systematic Review

Aditya Bardia, Debra L. Barton, Larry J. Prokop, Brent A. Bauer, and Timothy J. Moynihan

From the Departments of Internal Medicine, Medical Oncology, and Medical Library, Mayo Clinic College of Medicine, Rochester, MN.

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Address reprint requests to Timothy J. Moynihan, MD, Department of Medical Oncology, 200 First St SW, Rochester, MN 55905; e-mail: moynihan.timothy@mayo.edu.

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ABSTRACT

Purpose
Despite widespread popular use of complementary and alternative medicine (CAM) therapies, a rigorous evidence base about their efficacy for cancer-related pain is lacking. This is a systematic review of randomized controlled trials (RCTs) evaluating CAM therapies for cancer-related pain.

Methods
RCTs using CAM interventions for cancer-related pain were abstracted using Medline, EMBASE, CINAHL, AMED, and Cochrane database.

Results
Eighteen trials were identified (eight poor, three intermediate, and seven high quality based on Jadad score), with a total of 1,499 patients. Median sample size was 53 patients, and median intervention duration was 45 days. All studies were from single institutions, four had sample size justification, and none reported any adverse effects. Seven trials reported significant benefit for the following CAM therapies: acupuncture (n = 1), support groups (n = 2), hypnosis (n = 1), relaxation/imagery (n = 2), and herbal supplement/HESA-A (n = 1, but study was of low quality without control data). Seven studies reported immediate postintervention or short-term benefit of the following CAM interventions: acupuncture (n = 2), music (n = 1), herbal supplement/Ai-Tong-Ping (n = 1), massage (n = 1), and healing touch (n = 2). Four studies reported no benefit of CAM interventions (music, n = 2; massage, n = 2) in reducing cancer pain compared with a control arm.

Conclusion
There is paucity of multi-institutional RCTs evaluating CAM interventions for cancer pain with adequate power, duration, and sham control. Hypnosis, imagery, support groups, acupuncture, and healing touch seem promising, particularly in the short term, but none can be recommended because of a paucity of rigorous trials. Future research should focus on methodologically strong RCTs to determine potential efficacy of these CAM interventions.

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INTRODUCTION

Pain is a major symptom in patients with cancer, affecting more than 75% of hospitalized patients.[1-3] Management of pain is crucial to improve the quality of life of patients with cancer and is widely recognized as a quality measure for optimal care by the Joint Commission on Accreditation of Healthcare Organizations. Unfortunately, cancer pain is frequently under-recognized and undertreated, and hence the call for pain to be recorded as the fifth vital sign.[4,5] The National Cancer Institute cites a number of major barriers for adequate control, including inadequate pain management skills among health care professionals; poor assessment of pain; reluctance of patients to report pain; concerns about regulation, addiction, and adverse effects of controlled substances; poor adherence; and inadequate reimbursement.[6,7]

Complementary and alternative medicine (CAM) therapies are used widely especially among cancer patients.[8-10] They have been used both as an alternative to conventional medicine (alternative medicine) and complementary to conventional medicine (complementary medicine). It has been suggested that they should be used in conjunction with conventional therapies in an integrative fashion (integrative medicine) and integrated with oncology clinics.[11,12] It is also known that patients frequently do not discuss CAM therapies with physicians[9,13] and that many oncologists have limited knowledge of CAM.[14] Thus, wider dissemination of evidence-based applications for CAM interventions has been suggested.[14]

CAM therapies, although used widely by patients, have been the subject of debate.[15] Critics note that some therapies are no more effective than placebo,[16] and many therapies have been associated with adverse effects and negative interactions.[9,17-21] Thus, it has been suggested that these therapies, like conventional medicine, should be used in an evidence-based fashion.

Although there have been many trials of CAM therapies for cancer pain and a few expert reviews, there is a lack of rigorous systematic review. Furthermore, studies have found that there is considerable variation in the search for CAM studies, making systematic reviews prone to bias.[22] Finally, the American Cancer Society and the National Comprehensive Cancer Network cancer pain practice guidelines recommend nonpharmacologic modalities if pain scores remain at 4 or above on a 10-point scale after re-evaluation and modification of pharmacologic management.[23,24] Although the recommendations list various nonpharmacologic therapies (including CAM therapies), they do not provide evidence-based recommendations regarding the clinical application of specific CAM therapies.

The aim of this article was to provide a rigorous systematic review to evaluate the efficacy of various CAM therapies for cancer pain. The CAM therapies were defined and evaluated based on National Center for Complementary and Alternative Medicine classification (Table 1). The trials were appraised based on their quality and sample size. Finally, directions for future research were also provided.

Table 1. NCCAM Classification of CAM Interventions and Their Brief Description

NCCAM Classification and Type of CAM	Brief Description
Alternative medical systems	
Homeopathy	Using highly diluted substances based on the principle of like is cured by like
Acupuncture	Stimulating specific discrete anatomic points known as acupuncture points by puncturing the skin generally with a needle
Reflexology	Manual technique in which the reflexologist applies pressure to various reflex areas on the patient's feet and hands
Mind-body medicine	
Hypnosis	Therapist suggests that a patient experience changes in sensation, thought, and behavior that may not be accessible normally to the conscious mind
Imagery	Uses the imaginative capacity of the mind to affect one's physical, emotional, or spiritual state
Relaxation techniques	Although there are many relaxation techniques, the most popular is progressive muscle relaxation; in progressive muscle relaxation, the patient is taught to systematically tense and relax approximately 30 different muscle groups and have controlled deep breathing
Support groups	Groups to help patients cope better with diseases including symptoms and behavioral and emotional aspects
Creative outlets, such as music	Music therapy includes an active intervention overseen by a music therapist and is different from passive listening to music
Biologic-based therapies	
Dietary supplements, herbal	A product (other than tobacco) taken by mouth that contains a dietary ingredient intended to supplement the diet, including herbs (herbal supplement)
Dietary supplements, nonherbal	Dietary supplements that do not contain herbs, such as minerals and vitamins
Manipulative and body-based methods	
Massage, aromatherapy	Massage involves stroking and kneading the body in a systematic fashion; aromatherapy involves the use of oils, extracts or essences) from flowers and herbs
Magnet/laser therapy	Use of magnets and lasers for therapeutic potential
Energy therapies	
Healing touch	Therapeutic touch involves the laying-on of hands by a therapist to enhance the patient's recovery by correcting energy imbalances
Reiki	Channeling of energy through a Reiki practitioner to heal receiver's spirit and physical body; the energy healing usually involves therapeutic touch

Abbreviations: NCCAM, National Center for Complementary and Alternative Medicine; CAM, complementary and alternative medicine.

METHODS

Literature Search

Two independent reviewers, including a librarian, conducted a systematic literature search using databases (MEDLINE, EMBASE and CINAHL, AMED, and the Cochrane Library), all from time of inception up to August 2005. The librarian's search was first broken into three concepts (cancer, pain, and alternative medicine), and separate searches for each concept were performed. Next, each database's official subject heading was used for those concepts, if they had any, and then the three sets were combined together with the Boolean "AND" operator to create a set of citations containing all of the concepts. Finally, a text word search was done in the title and abstract for each concept and combined with the subject heading searches (cancer or neoplasm$ [$ indicates truncation], pain, and major individual CAM therapies), and then the search was limited to clinical trials or review articles.

A similar search was done by another investigator (A.B.) independently using PubMed with the search term "cancer pain" and the limits of "clinical trials" and "complementary medicine." Both reviewers also visually scanned the results to manually remove any citations that were obviously irrelevant and also scanned reference lists of the identified articles to identify any additional articles.

Inclusion and Exclusion Criteria

A study protocol was developed to define the inclusion and exclusion criteria. We included all randomized clinical trials (RCTs) that had a CAM intervention for cancer-related pain in humans. A standard definition of CAM as defined by the National Center for Complementary and Alternative Medicine was used (http://nccam.nih.gov/health/whatiscam/). We did not include nonrandomized prospective trials, case reports, or case series. We also did not include articles related to procedural or postsurgical pain in cancer patients for analysis because they do not represent cancer pain per se.

Data Abstraction

The articles that met the inclusion criteria were reviewed by two independent investigators (A.B. and D.L.B.), and relevant data were extracted. The quality of the articles was appraised using the Jadad scale.[25,26] This scale gives one point each based on whether trials were randomized or double blinded and whether they included a description of dropouts. An additional point is given based on whether the method to generate the sequence of random assignment and method of double blinding was appropriate or inappropriate. A score of 4 or 5 is considered high quality, 3 is considered intermediate quality, and 2 or less is considered low quality.

For some CAM therapies (such as support groups, imagery, massage, and healing touch), true blinding of the participant might not be possible, and we then used the modified Jadad scale.[27,28] A study was considered to be double blinded if the control intervention was indistinguishable from the

actual intervention from the participant's viewpoint (1 point for yes and 0 points for no), and blinding was regarded as appropriate if it was stated that the person doing the assessments could not identify the intervention being assessed (1 point for yes and 0 points for no).

RESULTS

At total of 101 references were identified through database searches, of which 85 articles were excluded that did not meet our inclusion criteria (12 were not CAM, 20 were not cancer pain related, and 53 were not RCTs), yielding 16 relevant articles. Two additional articles were found by scanning reference lists,[29,30] bringing the total number of relevant articles to 18.[29-46]

A total of 1,499 study participants were identified from the 18 trials. Nine studies were based in the United States, two were in Europe, three were in Canada, two were in China, one was in Australia, and one was in Iran. Regarding the quality of studies, eight studies were of poor quality, three were of intermediate quality, and seven were of high quality (Table 2). The average sample size among all the studies combined was less than 100 patients, with a median of 53 patients (range, nine to 460 patients). The median duration of the intervention was 45 days (range, 30 minutes to 365 days).

All studies were from single institutions, and only four studies had sample size justification. Two trials were listed as RCTs but did not present any data about comparison with a control group.[31,32] No trial reported any significant adverse effect of CAM therapy. There were 11 different pain scales used among the 18 trials, with the Visual Analog Scale being the most common. Because of the heterogeneity of trials as well as CAM interventions, no attempt to do a meta-analysis was made.

The individual CAM therapy trials and their limitations are listed in Table 3. Of the 18 trials, two trials tested more than one CAM intervention in separate arms (hypnosis plus support groups, and massage plus healing touch).[30,43] Seven trials reported significant benefits of CAM interventions in reducing cancer pain, seven claimed short-term (shorter than 1 month) or immediate postintervention benefit, and four claimed no benefit (Table 3).

Of three acupuncture trials, one good-quality trial involving 90 patients reported efficacy in reducing cancer-related pain after two treatments spaced 1 month apart.[33] This study evaluated auricular acupuncture where needles were implanted at pain or placebo points. Investigators also included a third arm where seeds were implanted at placebo points in an effort to test the requirement for needles. This study reported that reduction in pain was associated with a decline in the average electrical signal detected at ear points.[33] The other two acupuncture studies were of poor quality with small sample size and incompletely reported statistical data.[32,34]

Of the five trials on various mind–body interventions, two good/intermediate-quality trials found support groups to be efficacious in decreasing cancer pain.[30,35] The type of cognitive therapy was group supportive psychotherapy in the form of weekly meetings for 1.5 hours with 7 to 10 women. In one study, the support groups were divided into hypnosis and no hypnosis arms.[30] Self-hypnosis provided a further reduction in pain sensation. Subsequently, a large study involving 253 patients was designed primarily to evaluate whether support groups increase the survival among cancer patients.[35] Although it found no difference in survival among the two groups, it did find that the group receiving supportive psychotherapy had significantly lower pain intensity compared with a control group. A trial evaluating hypnosis among 67 patients undergoing bone marrow transplantation compared hypnosis with other cognitive behavioral therapies and reported hypnosis to be more effective in decreasing oral mucositis pain than other cognitive-behavioral interventions and psychotherapeutic support.[36] Finally, two trials assessing relaxation and

Table 2. Quality of the Randomized Control Trials Conducted for Relieving Cancer Pain Based on Jadad Score

Reference	Randomization and Score	Appropriate Random Assignment and Score	Double Blinding and Score	Appropriate Blinding and Score	Withdrawal/Dropout and Score	Total Jadad Score
Alimi et al[33]	Y, 1	Y, 1	Y, 1	Y, 1	Y, 1	5
Dang and Jiebin[34]	Y, 1	NC, 0	NC, 0	NC, 0	NC, 0	1
Xia et al[32]	Y, 1	NC, 0	NC, 0	NC, 0	NC, 0	1
Goodwin et al[35]	Y, 1	Y, 1	NC, 0*	Y, 1*	Y, 1	4
Spiegel and Bloom[30]	Y, 1	Y, 1	N, 0*	N, 0*	Y, 1	3
Syrjala et al[36]	Y, 1	NC, 0	Y, 1*	Y, 1*	Y, 1	4
Sloman et al[38]	Y, 1	NC, 0	NC, 0*	NC, 0*	Y, 1	2
Syrjala et al[37]	Y, 1	NC, 0	Y, 1*	Y, 1*	Y, 1	4
Curtis[29]	Y, 1	NC, 0	N, 1*	N, 0*	NC, 0	2
Beck[40]	Y, 1	Y, 1	N, 0*	N, 0*	NC, 0	2
Zimmerman et al[39]	Y, 1	NC, 0	N, 0*	N, 0*	NC, 0	1
Ahmadi et al[31]	Y, 1	NC, 0	Y, 1	NC, 0	NC, 0	2
Wu et al[41]	Y, 1	NC, 0	Y, 1	NC, 0	NC, 0	2
Weinrich and Weinrich[42]	Y, 1	NC, 0	Y, 1*	Y, 1*	Y, 1	4
Wilkie et al[44]	Y, 1	NC, 0	N, 0*	Y, 1*	Y, 1	3
Soden et al[45]	Y, 1	NC, 0	Y, 1*	Y, 1*	Y, 1	4
Post-White et al[43]	Y, 1	Y, 1	N, 0*	N, 0*	Y, 1	3
Olson et al[46]	Y, 1	Y, 1	Y, 1*	N, 0*	Y, 1	4

Abbreviations: Y, yes; N, no; NC, not clear.
*Modified Jadad score.

Table 3. Summary of the Various Randomized Control Trials Conducted for Relieving Cancer Pain

Reference	Sample Size (No. of patients)*	Treatment Groups	Treatment Duration	Pain Scale	Results	Limitation
Alimi et al[33]	90	Group 1: acupuncture; group 2: sham control; group 3: control	≥ 1 month	VAS	The treatment group had a significant decrease ($P < .001$) in pain intensity after 2 months (36% decrease) compared with the placebo group (2% decrease)	Single acupuncturist
Dang and Jiebin[34]	48	Group 1: acupuncture; group 2: sham control; group 3: control	2 months	WHO grade 1 to 3	Although acupuncture had short-term decrease in pain ($P < .05$), there was no long-term significant difference in pain improvement among the three groups	Low methodologic quality, low sample size
Xia et al[32]	76	Group 1: body acupuncture; group 2: conventional cancer treatment	15 days	Verbal assessment	Chest pain relieved in intervention group compared with conventional treatment (*P* not mentioned)	Low methodologic quality, short duration, statistical analysis and comparison not clear
Curtis[29]	9	Group 1: music; group 2: background noise; group 3: no noise	2 days	Graphic rating scale, 0-10 cm	No significant difference in pain improvement among the three groups	Low methodologic quality, small sample size, short duration of study
Beck[40]	15 (×2)	Group 1: music; group 2: sound	3 days and then cross over	MPQ	Although the mean percentage of change in pain for music was twice that for sound, there were no statistically significant differences among the groups	Low methodologic quality, small sample size, short duration of study, lack of washout period, minimal patient control
Zimmerman et al[39]	40	Group 1: music; group 2: sound	30 minutes	MPQ and VAS	Significant decrease in various pain scales in treatment group ($P < .05$)	Low methodologic quality, small sample size, very short duration of study
Goodwin et al[35]	253	Group 1: psychological support; group 2: no such adjunct therapy	Weekly for 1 year	VAS	Less worsening of pain intensity in supportive-expressive therapy group than in control group ($P = .04$)	Absence of adequate sham control
Spiegel and Bloom[30]	58	Group 1: weekly group supportive psychotherapy (support group was further randomly assigned to no hypnosis and self-hypnosis arms); group 2: standard treatment	10 months	VAS	Patients in group therapy experienced a statistically significant reduction in pain sensation and pain suffering (both $P < .01$) over 10 months of follow-up but no difference in frequency and duration of pain episodes; self-hypnosis provided a further reduction in pain sensation ($P < .05$)	Single therapist, absence of adequate sham control
Syrjala et al[36]	67	Group 1: hypnosis; group 2: therapist support; group 3: cognitive-behavioral therapy, excluding imagery; group 4: no treat, control	30 minutes twice weekly for 5 weeks	VAS	Group receiving hypnosis had significant reduction in pain compared with other groups ($P = .01$)	Small size/inadequate power, complex cognitive-behavioral coping skills training
Sloman et al[38]	67	Group 1: progressive muscle relaxation and guided imagery sessions (either taped relaxation or live nurse); group 2: no sessions, control	Twice weekly for 3 weeks	SF-MPQ, VAS	Significant reduction in pain sensation ($P = .02$), present pain intensity ($P = .001$), overall pain severity ($P = .001$), and nonopioid PRN analgesia ($P = .001$) but not in pain affect and morphine analgesia; both methods of relaxation and imagery were equally effective	Low methodologic quality, no significant reduction in pain affect or morphine analgesia, probably because of the reluctance of nurses to lower morphine doses, even though the doctors had prescribed adjustable doses
Syrjala et al[37]	94	Group 1: relaxation/imagery; group 2: therapist support; group 3: cognitive therapy package; group 4: no treatment, control	30 minutes twice weekly for 5 weeks	VAS	Significantly less pain in relaxation/imagery and the cognitive therapy groups than in the other two groups ($P < .01$); however, no greater pain relief was obtained by adding cognitive-behavioral skills to relaxation/imagery	Small size/inadequate power, complex cognitive-behavioral coping skills training
Ahmadi et al[31]	24	Group 1: HESA-A; group 2: placebo	6 months	Narcotic use	Patients receiving HESA-A had lower requirements of opioids compared with placebo group (*P* not mentioned) after 2, 3, and 6 months	Low methodologic quality, small sample size, and comparison not clear
Wu et al[41]	60	Group 1: Ai-Tong-Ping capsule; group 2: control, diclofenac	7 days	Various pain variables	Patients receiving Ai-Tong-Ping had significantly lower pain degree, fewer pain episodes, shorter initiation time of analgesic action, and longer analgesic duration but no difference in total effective rate compared with controls	Low methodologic quality, small sample size, and short duration of study

(continued on following page)

Table 3. Summary of the Various Randomized Control Trials Conducted for Relieving Cancer Pain (continued)

Reference	Sample Size (No. of patients)*	Treatment Groups	Treatment Duration	Pain Scale	Results	Limitation
Weinrich and Weinrich[42]	28	Group 1: massage for 10 minutes; group 2: visitor, placebo	2 hours	VAS	In men, immediate pain relief, from 4.2 to 2.9 ($P = .01$), but effect subsided in 1 hour; no benefit in females	Small sample, noncomparability of groups at baseline, low intensity of pain in groups, and use of multiple student therapists
Wilkie et al[44]	29	Group 1: massage; group 2: placebo	Twice weekly for 4 months	PAT, 0 to 10	No significant difference among the massage group compared with the control group in pain intensity reduction (42% *v* 25%, respectively; $P > .05$), long-term relief of pain, and lower intramuscular morphine equivalent doses required	Low sample size, high attrition rate, absence of research nurses at some participating units, and stoppage of the trial before planned sample size
Soden et al[45]	42	Group 1: aromatherapy (lavender); Group 2: massage; group 3: no treatment	30 minutes weekly for 1 month	VAS, Modified Tursky Pain Scale	No significant difference in pain reduction among groups	Low sample size, high attrition rate
Post-White et al[43]	230 (×2)	Group 1: massage therapy; group 2: healing therapy; group 3: rest	1 month and then cross over	BPI, VAS	Significant reduction in immediate pain after healing therapy and massage therapy compared with rest (both $P < .01$) but no significant difference in pain index or pain outcome function among the groups after 1 month	High attrition rate, lack of blinding, variability in data collection, and lack of a sham control
Olson et al[46]	24	Group 1: standard opioid plus Reiki; group 2: standard opioid	7 days	VAS	Significant decrease in pain from days 1 to 4 among those receiving Reiki compared with other group ($P = .002$), but there was no significant difference in opioid use reduction	Small size, high attrition rate in control arm, short duration of study, limited life expectancy of participants, and lack of a sham control

Abbreviations: VAS, Visual Analog Scale; MPQ, McGill Pain Questionnaire; SF-MPQ, Short Form-McGill Pain Questionnaire; PRN, pro re nata/as needed; PAT, Patient Assessment Tool; BPI, Brief Pain Index.
*Studies that had a cross-over design can be thought to have twice the sample size of number of patients enrolled and a sign of "(× 2)" is thus added.

imagery concluded that these therapies significantly reduced cancer pain (various scores) compared with a control group,[37,38] and one trial reported that no greater pain relief was obtained by adding cognitive-behavioral skills to relaxation/imagery.[38]

All three trials investigating music were of poor quality with small sample sizes (all < 50 patients, and one had a sample size of nine patients) and short duration (< 1 week).[29,39,40] Two concluded that music was no more effective than a placebo sound. The third trial concluded that listening to music along with positive suggestion was more effective in reducing pain than suggestion alone. However, the only measured effect was at 30 minutes after intervention.[39]

One trial each suggested that HESA-A (an herbal mixture)[31] and Ai-Tong-Ping capsules (an herbal supplement)[41] reduced cancer pain, but both trials were of low quality, and one did not report statistical comparison with control.[31] Moreover, the exact composition, justification of dose, and information about quality of herbal supplement was not provided. Finally, pain outcome was loosely defined. Thus, it was difficult to draw any meaningful information from these two trials.

All four of the trials evaluating massage therapy measured pain before and after intervention,[42-45] and three studies measured intervention effects after 4 weeks as well.[42-44] Two of the trials did report statistically significant reductions in pain measures immediately after massage,[42,43] with one trial finding significant reductions only in men.[42] One study added lavender aromatherapy to massage and found no difference in effect on pain.[45] None of the trials found statistically significant intervention effects over 4 weeks.[42-44] The majority of these trials had samples sizes of less than 20 patients per group,[42,44,45] except for one trial involving 230 patients in a cross-over trial.[43]

There were two trials assessing efficacy of healing touch/Reiki.[43,46] One of the trials evaluating massage also assessed healing touch as an intervention for pain.[43] This study included before and after measures as well as an analysis of change from baseline to 4 weeks. In this study, healing touch did provide pain reduction compared with before treatment but did not reduce pain over the 4 weeks of the intervention.[43] Similarly, another trial found that Reiki plus opioids statistically significantly reduced pain immediately after treatment compared with before treatment, but the control arm was opioid plus rest.[46] Therefore, the effect of the intervention could have been related to distraction versus thinking about whether the pain medication was working and, thus, was not an adequate control group. Furthermore, in the study evaluating Reiki, investigators had to prematurely end the trial because patients were not willing to be randomly assigned to the control arm.[46]

DISCUSSION

This systematic review provides a striking observation about the paucity of well-designed, multi-institutional trials evaluating CAM interventions for cancer-related pain. Most trials were of short duration, had small numbers without sample size justification, and did not report the adverse effects of CAM intervention. It has been stated that the quality of CAM trials is correlated with their sample sizes.[47] Moreover, many trials lacked an appropriate sham control arm, and for

those that included a control group, some trials did not report statistical data of comparison.

Further problems with trials included the lack of description of the qualifications of the person or people delivering the intervention. In one of the trials evaluating massage therapy, senior nursing students delivered the 10-minute intervention after a 1-hour training that included all elements of study design and implementation.[42] Other studies neglected to include any qualifications at all on the interventionists. In addition, trials rarely provided justification for dose or duration of interventions. The lack of rigor of CAM trials has been supported by other systematic reviews and meta-analyses.[27,48]

This review suggests that, at best, promising data exist for the ability of some CAM therapies to positively impact cancer pain. The most promising therapy seems to be related to mind–body medicine. Four studies suggested that these therapies, particularly hypnosis, imagery, and relaxation, might have some efficacy in decreasing cancer pain. Authors have speculated that such therapies may contribute to pain relief by distraction.[49,50] It is to be noted that patients with cancer often have cognitive impairment caused by the malignancy itself or by the adverse effects of opioids, chemotherapy, or radiation.[51] Therefore, cognitive interventions, particularly imagery, could be difficult for these patients. Two studies suggested that support groups seem to reduce cancer pain, including long-term pain. However, although the beneficial effect of support groups is speculated to be a result of increased expression of emotions and support, it could also be a result of increased awareness and thus more frequent visits to doctors and better drug compliance. Finally, acupuncture and healing touch seem to be other promising therapies. However, none of these therapies can be recommended as effective, and they need testing in more rigorous trials that would include an adequate control group, adequate power, and appropriate statistical analyses.

Of note, one study evaluating support groups found the benefit greater in distressed women than those who were not distressed, possibly because of a floor effect (ie, the response options on the questionnaires focused on distress and were not sufficiently broad enough to detect worsening when baseline distress was low).[35] The concept of a floor effect might be applicable to therapies for pain as well as symptoms in general, and it is possible that effect sizes of therapies might be more discernible among patients with higher pain ratings.

There could be multiple reasons for the paucity of rigorous trials in relationship to CAM therapies. Foremost, CAM is a relatively young "science, and there is a great deal of variability in the level of scientific discipline that has developed in various CAM modalities."[52] For example, there are a significant number of relatively well-designed protocols evaluating acupuncture, where significant effort has been expended to try and create credible controls, blinding, and sham interventions. However, practitioners of many other CAM therapies have not developed a significant scientific framework for evaluating their discipline. Furthermore, some CAM proponents consider it to be an art, with emphasis on patients' needs, and have questioned the applicability of strict scientific measures to assess the validity of CAM therapies.[53,54] However, others have suggested that CAM therapies should have similar standards of scientific rigor as conventional medical treatments to judge their true merit.[55] Second, funding for CAM research is usually poor because pharmaceutical companies are not routinely interested in CAM, and these therapies can usually not be patented.[56] Third, although some institutions now offer CAM therapies, in most places, CAM practitioners are not fully integrated within the oncology community, making it difficult to accrue sizeable number of patients and conduct multi-institutional research.[57,58] Fourth, because these therapies are not considered drugs, there is absence of strict regulation by the US Food and Drug Administration.[59,60] This could contribute to the presence of less rigorous CAM trials, and it has been observed that CAM therapies often progress to phase III trials without data from phase II trials.[48,61]

This review has a few limitations. First, the study was a systematic review, and thus, there is a potential that some published studies were missed and that only positive trials were identified because of publication bias. However, the current methodology was comprehensive, involved a librarian with extensive literature search experience to ensure that trials were not missed, and had independent reviewers to minimize observer bias and enhance reproducibility. Second, most of the trials were of low quality with missing data, making it difficult to extract reliable and accurate information. Although issues such as random assignment procedures may have been rigorously and correctly instituted, sometimes, because of word limitations, a research article may not contain sufficient information to adequately evaluate the quality of a trial. Finally, this review did not evaluate studies of therapies for mood, stress, or depression that did not have pain as a primary or secondary outcome. Because pain is a subjective symptom, it could be indirectly affected by therapies that benefit these symptoms. However, the aim of this study was to evaluate the currently published literature on CAM therapies for cancer pain only. Including other symptoms in this systematic review would have made it difficult to focus and derive meaningful results.

Future RCTs assessing efficacy of CAM therapies for cancer pain should be well designed with adequate sample size, have sufficient duration, have good sham controls groups, involve multiple institutions, and adequately monitor and report adverse effects. Research should be standardized with clear definitions of procedures, area of intervention on body (if any), duration of intervention, standardized instrument for pain assessment, and a standard outcome. Such well-designed trials are particularly needed for CAM therapies that seem promising such as acupuncture, hypnosis, imagery, support groups, and healing touch. Larger well-designed studies of adequate duration assessing the effect of massage and music on cancer pain might also be fruitful. Other untested CAM therapies, such as yoga, tai chi, or qi gong, could be explored as pilot trials, if supported by anecdotal experience. Finally, there is also a need to understand the scientific mechanism by which these therapies are beneficial. This would optimize the likelihood of success.

There is a paucity of well-designed, multi-institutional RCTs evaluating CAM interventions for cancer pain that have adequate power, duration, and sham control. CAM modalities such as hypnosis, imagery, support groups, acupuncture, and healing touch seem promising, particularly in the short term, but none can be fully recommended because of the paucity of rigorous trials. Future research should focus on methodologically strong RCTs to determine the potential efficacy of these CAM interventions.

REFERENCES

1. Brescia FJ, Portenoy RK, Ryan M, et al: Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol 10:149-155, 1992

2. Wells N: Pain intensity and pain interference in hospitalized patients with cancer. Oncol Nurs Forum 27:985-991, 2000

3. McMillan SC, Tittle M, Hagan S, et al: Management of pain and pain-related symptoms in hospitalized veterans with cancer. Cancer Nurs 23:327-336, 2000

4. Weiss SC, Emanuel LL, Fairclough DL, et al: Understanding the experience of pain in terminally ill patients. Lancet 357:1311-1315, 2001

5. Bernabei R, Gambassi G, Lapane K, et al: Management of pain in elderly patients with cancer: SAGE Study Group—Systematic Assessment of Geriatric Drug Use via Epidemiology. JAMA 279:1877-1882, 1998

6. National Cancer Institute: Pain. http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/healthprofessional

7. Jadad AR, Browman GP: The WHO analgesic ladder for cancer pain management: Stepping up the quality of its evaluation. JAMA 274:1870-1873, 1995

8. Ernst E, Cassileth BR: The prevalence of complementary/alternative medicine in cancer: A systematic review. Cancer 83:777-782, 1998

9. Eisenberg DM, Davis RB, Ettner SL, et al: Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. JAMA 280:1569-1575, 1998

10. Richardson MA, Sanders T, Palmer JL, et al: Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol 18:2505-2514, 2000

11. Johnstone PA, Polston GR, Niemtzow RC, et al: Integration of acupuncture into the oncology clinic. Palliat Med 16:235-239, 2002

12. Cohen MM: CAM practitioners and "regular" doctors: Is integration possible? Med J Aust 180: 645-646, 2004

13. Adler SR, Fosket JR. Disclosing complementary and alternative medicine use in the medical encounter: A qualitative study in women with breast cancer. J Fam Pract 48:453-458, 1999

14. Newell S, Sanson-Fisher RW: Australian oncologists' self-reported knowledge and attitudes about non-traditional therapies used by cancer patients. Med J Aust 172:110-113, 2000

15. Koretz RL, Rotblatt M: Complementary and alternative medicine in gastroenterology: The good, the bad, and the ugly. Clin Gastroenterol Hepatol 2:957-967, 2004

16. Shang A, Huwiler-Muntener K, Nartey L, et al: Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet 366: 726-732, 2005

17. Pinn G: Adverse effects associated with herbal medicine. Aust Fam Physician 30:1070-1075, 2001

18. Saper RB, Kales SN, Paquin J, et al: Heavy metal content of ayurvedic herbal medicine products. JAMA 292:2868-2873, 2004

19. Ko RJ: Adulterants in Asian patent medicines. N Engl J Med 339:847, 1998

20. Angell M, Kassirer JP: Alternative medicine: The risks of untested and unregulated remedies. N Engl J Med 339:839-841, 1998

21. Izzo AA, Ernst E: Interactions between herbal medicines and prescribed drugs: A systematic review. Drugs 61:2163-2175, 2001

22. Sood A, Sood R, Bauer BA, et al: Cochrane systematic reviews in acupuncture: Methodological diversity in database searching. J Altern Complement Med 11:719-722, 2005

23. American Cancer Society: Cancer pain: Treatment guidelines for patients. Version 1. http://www.cancer.org/downloads/CRI/NCCN_pain.pdf

24. American Cancer Society: Homepage. http://www.cancer.org/docroot/home/index.asp

25. Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 17:1-12, 1996

26. Clark HD, Wells GA, Huet C, et al: Assessing the quality of randomized trials: Reliability of the Jadad scale. Control Clin Trials 20:448-452, 1999

27. White AR, Ernst E: A systematic review of randomized controlled trials of acupuncture for neck pain. Rheumatology (Oxford) 38:143-147, 1999

28. Lee H, Schmidt K, Ernst E: Acupuncture for the relief of cancer-related pain: A systematic review. Eur J Pain 9:437-444, 2005

29. Curtis S: The effect of music on pain relief and relaxation of the terminally ill. J Music Ther 23:10-14, 1986

30. Spiegel D, Bloom JR: Group therapy and hypnosis reduce metastatic breast carcinoma pain. Psychosom Med 45:333-339, 1983

31. Ahmadi A, Mohagheghi MA, Fazeli MS, et al: HESA-A: New treatment for breast cancer and choroidal metastasis. Med Sci Monit 11:CR300-CR303, 2005

32. Xia YQ, Zhang D, Yang CX, et al: An approach to the effect on tumors of acupuncture in combination with radiotherapy or chemotherapy. J Tradit Chin Med 6:23-26, 1986

33. Alimi D, Rubino C, Leandri EP, et al: Analgesic effect of auricular acupuncture for cancer pain: A randomized, blinded, controlled trial. J Clin Oncol 21:4120-4126, 2003

34. Dang W, Jiebin Y: Clinical study on acupuncture treatment of stomach carcinoma pain. J Tradit Chin Med 18:31-38, 1998

35. Goodwin PJ, Leszcz M, Ennis M, et al: The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med 345:1719-1726, 2001

36. Syrjala KL, Cummings C, Donaldson GW: Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: A controlled clinical trial. Pain 48:137-146, 1992

37. Syrjala KL, Donaldson GW, Davis MW, et al: Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: A controlled clinical trial. Pain 63:189-198, 1995

38. Sloman R, Brown P, Aldana E, et al: The use of relaxation for the promotion of comfort and pain relief in persons with advanced cancer. Contemp Nurse 3:6-12, 1994

39. Zimmerman L, Pozehl B, Duncan K, et al: Effects of music in patients who had chronic cancer pain. West J Nurs Res 11:298-309, 1989

40. Beck SL: The therapeutic use of music for cancer-related pain. Oncol Nurs Forum 18:1327-1337, 1991

41. Wu MH, Zhong XP, Cheng HB: Clinical study on aitongping capsule in treating cancerous pain. Zhongguo Zhong XiYi Jie He Za Zhi 25218-221, 2005

42. Weinrich SP, Weinrich MC: The effect of massage on pain in cancer patients. Appl Nurs Res 3:140-145, 1990

43. Post-White J, Kinney ME, Savik K, et al: Therapeutic massage and healing touch improve symptoms in cancer. Integr Cancer Ther 2:332-344, 2003

44. Wilkie DJ, Kampbell J, Cutshall S, et al: Effects of massage on pain intensity, analgesics and quality of life in patients with cancer pain: A pilot study of a randomized clinical trial conducted within hospice care delivery. Hosp J 15:31-53, 2000

45. Soden K, Vincent K, Craske S, et al: A randomized controlled trial of aromatherapy massage in a hospice setting. Palliat Med 18:87-92, 2004

46. Olson K, Hanson J, Michaud M: A phase II trial of Reiki for the management of pain in advanced cancer patients. J Pain Symptom Manage 26:990-997, 2003

47. Bausell RB, Lee WL, Soeken KL, et al: Larger effect sizes were associated with higher quality ratings in complementary and alternative medicine randomized controlled trials. J Clin Epidemiol 57: 438-446, 2004

48. Vickers AJ, Kuo J, Cassileth BR: Unconventional anticancer agents: A systematic review of clinical trials. J Clin Oncol 24:136-140, 2006

49. Fernandez E, Turk DC: The utility of cognitive coping strategies for altering pain perception: A meta-analysis. Pain 38:123-135, 1989

50. Devine EC, Westlake SK: The effects of psychoeducational care provided to adults with cancer: Meta analysis of 116 studies. Oncol Nurs Forum 22:1369-1381, 1995

51. Fan HG, Houede-Tchen N, Yi QL, et al: Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. J Clin Oncol 23:8025-8032, 2005

52. Rosenthal DS, Dean-Clower E: Integrative medicine in hematology/oncology: Benefits, ethical considerations, and controversies. Hematology Am Soc Hematol Educ Program 491-497, 2005

53. Hufford DJ. Evaluating complementary and alternative medicine: The limits of science and scientists. J Law Med Ethics 31:198-212, 2003

54. Vanherweghem JL: Evidence-based medicine and art of healing: The dead end of incommensurate paradigms. Bull Mem Acad R Med Belg 160:459-465, 2005

55. O'Mathuna D: The best of both approaches: The role of science in complementary and alternative medicine. EMBO Rep 2:1054-1057, 2001

56. Seidman MD, Babu S: Alternative medications and other treatments for tinnitus: Facts from fiction. Otolaryngol Clin North Am 36:359-381, 2003

57. Frenkel MA, Borkan JM: An approach for integrating complementary-alternative medicine into primary care. Fam Pract 20:324-332, 2003

58. Eisenberg DM, Cohen MH, Hrbek A, et al: Credentialing complementary and alternative medical providers. Ann Intern Med 137:965-973, 2002

59. Dietary Supplement Health and Education Act. Pub L No. 103-417, Stat 4325 (codified at USC §301), 1994

60. Neuhouser ML: Dietary supplement use by American women: Challenges in assessing patterns of use, motives and costs. J Nutr 133:1992S-1996S, 2003

61. Pauling L: Vitamin C therapy of advanced cancer. N Engl J Med 302:694-695, 1980

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Author Contributions

Conception and design: Aditya Bardia, Debra L. Barton, Brent A. Bauer, Timothy J. Moynihan
Financial support: Debra L. Barton, Timothy J. Moynihan
Administrative support: Aditya Bardia, Debra L. Barton, Timothy J. Moynihan
Provision of study materials or patients: Aditya Bardia, Debra L. Barton, Larry J. Prokop, Timothy J. Moynihan
Collection and assembly of data: Aditya Bardia, Debra L. Barton
Data analysis and interpretation: Aditya Bardia, Debra L. Barton, Brent A. Bauer, Timothy J. Moynihan
Manuscript writing: Aditya Bardia
Final approval of manuscript: Aditya Bardia, Debra L. Barton, Larry J. Prokop, Brent A. Bauer, Timothy J. Moynihan