

Review

Integrating yoga into cancer pain management: A review of the research evidence

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ABSTRACT

Cancer-related pain is one of the most prevalent health care concerns among cancer patients. Opioids, the commonly recommended pharmacologic intervention for managing pain, remain inadequate and often associated with adverse effects and addiction. Patients, therefore, turn to non-pharmacological therapies, i.e., complementary and alternative medicine (CAM). The use of yoga, as a mind-body medicine of CAM, is becoming increasingly popular to cope with pain. This article reviews published clinical evidence supporting the use of yoga intervention in pain management. An electronic database, PubMed, was used to search published research on the efficacy of yoga on pain management in cancer patients. Our search identified 12 clinical trials on the subject; 6 single-armed trials, 1 non-randomized controlled trial, and 5 randomized controlled trials. A total of 531 patients (314 in yoga group, and 217 in control group) were recruited for these studies. Despite some methodological deficiencies, 11 studies reported improvement in cancer pain symptoms suggesting that yoga could be integrated in conventional cancer interventions for the management of pain.

KEYWORDS: yoga, meditation, pranayama, pain, cancer, complementary and alternative medicine

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INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with a "wide range of injury and sometimes the disease itself. Acute or chronic pain, ranging from mild to severe, is experienced by all, at least once in their life time. Pain is a significant health problem in the United States of America that costs society at least \$560-635 billion annually" in health care expenses, lost productivity and hours of work lost [1].

With improved strategies for cancer treatment it is estimated that more than 26 million cancer patients will be surviving in the next 40 years posing a great challenge to the health care system [2-7]. According to the American Cancer Society's report, in addition to other problems, 75% to 90% of >1.6 million new cancer cases diagnosed each year experience pain, at least some time during their illness [8, 9], thus making cancer-related pain one of the most prevalent health issues in cancer patients [10-13]. Reasons for cancer pain are varied [2]. Starting from knowing the diagnosis of cancer, direct tumor involvement (i.e., metastasis to bone and organs), adverse effects of treatment (chemotherapy, radiation, and surgery), and diagnostic procedures (biopsies, radiological diagnostic scans) cause stress, depression and pain [14-21].

Cancer pain is classified into 3 major types: visceral, somatic, and neuropathic. Visceral pain is throbbing in nature and caused by tumor's pressure on organs, the stretching of viscera, and cancer metastasis. Somatic pain is dull and achy that is usually caused due to tumor metastasis to bone. Neuropathic pain, on the other hand, is more severe of the three,

resulting from the tumor's pressure on the spinal cord and/or nerves. Damage to the nervous system by treatment (chemotherapy and radiation) may also cause neuropathic pain [22, 23]. Fatigue and depression, among other cancer related problems, also contribute to cancer pain [16, 24]. Thus, cancer pain is a multidimensional symptom that, despite advances in its pharmacological management, remains undertreated [24-27].

Opioids, the commonly recommended pharmacologic therapy for managing pain remain inadequate and their chronic use is often associated with adverse effects such as endocrinopathies, osteoporosis, neurological and cardiopulmonary effects, cell cycle alterations, abuse, and addiction [2]. Many patients, therefore, turn to non-pharmacological therapies, CAM.

The definition of CAM has changed over time. Initially, the National Center for Complementary and Alternative Medicine (NCCAM), included a wide range of therapies as CAM, that were not considered to be part of conventional medicine - the medicine as practiced by holders of M.D. or medicine practiced in the West, i.e., (i) alternative whole medical systems (Ayurveda, Chinese traditional medicine, homeopathy, and naturopathy); (ii) mind-body interventions; (iii) biologically based therapies; (iv) manipulative and body-based methods; and (v) energy therapies [28]. In January of 2015 the NCCAM incarnated with a new name, NCCIH (National Center for Complementary and Integrative Health). NCCIH has dropped the alternative whole medical systems from its definition of CAM as they are based on complete systems of theory and practices, they are commonly used as one of the major medical practices in countries like India and China, and only a few patients in USA (3-6%) use them as an alternative to conventional medicine. The focus, therefore, is now changed from the alternative medicine to CAM and integrative medicine. The term integrative medicine refers to combining of "treatments from conventional medicine and CAM for which there is some high quality evidence of safety and effectiveness" [29].

The use of CAM has significantly increased during the last decade [30-33]. About 38% of US adults used CAM to manage physical conditions (e.g., chronic pain, arthritis, cancer, heart diseases and high blood pressure) and psychological and emotional health concerns (post-traumatic stress disorder, anxiety, and depression), at the out-of-pocket expense of \$33.9 billion [30, 32]. Recognizing the rising use of CAM, NCCIH has increased its budget from \$50 million in 1999 to \$124 million annually in 2015 (NCCIH).

Yoga belongs to the mind-body intervention group of CAM, a large and diverse group of procedures (meditation, massage, relaxation techniques, breathing exercises, pranayama, qi gong etc.), that affect the mind's ability to positively influence physiological, psychological and emotional functions. Evidence for mind-body interventions that affect pain have been reported in a number of studies and reviews [34-44]. Research evidence suggests that among CAM therapies the use of yoga intervention (yoga postures, meditation, pranayama and relaxation), is increasing in popularity among health care providers, general public, and cancer patients [30, 45-59]. Except for a few undesirable experiences in elderly patients with chronic musculoskeletal disease [60], yoga intervention is a safe practice [61]. Despite a number of studies and reviews on yoga's efficacy on health [37, 46, 47, 62-68], yoga remains a "relatively underused health care resources" according to Sulenes et al. [30]. It is, therefore, important that oncologists, researchers, and the patients are aware of the evidence supporting the use of this relatively safe modality. The focus of this article is to review the published clinical research on the use of yoga in the pain management in cancer patients.

METHODS

A search of English language literature published through August 8, 2016 on yoga for cancer pain was conducted using the National Library of Medicine electronic data base, PubMed. An advanced search using Boolean operators (i.e., "AND", "OR", "NOT") was performed using the medical subject heading (MESH) terms and the key words yoga, breathing meditation, pranayama, exercises. mindfulness, mindfulness-based stress reduction (MBSR), cancer, and pain. Additional secondary references were obtained from the reviews and other publications. The primary results obtained were further analyzed by using filters, i.e., reviews, clinical trials, and randomized controlled trials. Initially the abstracts were independently examined by two persons and then selected for further evaluation.

RESULTS

Electronic database search resulted in 157 articles. Of the 157 articles 134 (47 reviews and 87 others) were excluded from further analysis. Upon dual examination of the titles and abstracts of the remaining 23 clinical trials, 11 were excluded as they failed to meet the desired criterion of all three components – pain and cancer and yoga [69-72] or they were not directly related to pain but studied the effect of yoga on inflammatory gene expression and sleep-related salivary α -amylase [73, 74] or they were protocol development and others [75-79] (Figure 1).

Of the 12 clinical trials that met inclusion criteria for further evaluation, 6 were single-arm studies [51, 56, 80-83] without a control group and 6 were controlled studies (1 non-RCT and 5 RCTs). A total of 531 participants (314 in yoga groups and 217 in control groups) volunteered for these trials that were conducted in 6 countries (Australia 1, Canada 1, Japan 1, Sweden 1, Turkey 2, and USA 6).

Single-armed trial of yoga in cancer pain management

A total of 106 patients participated in single-armed trials (104 women and 4 men); 100 had breast cancer and 2 each had colon, stomach, and bladder cancers. Only 94 of 106 patients recruited were able to complete the intervention. Even though the sample size was small, intervention duration was short and a control group was lacking for comparison; all the studies reported improvement in the pain symptoms and other quality of life (QOL) measures (Table 1).

Non-randomized controlled and randomized controlled trials of yoga in cancer-related pain

Details of these trials are summarized in table 2.

Study #1 [59]

Twenty breast cancer patients were divided into two groups (10 in the yoga group and 10 in an exercise group), but not randomized.

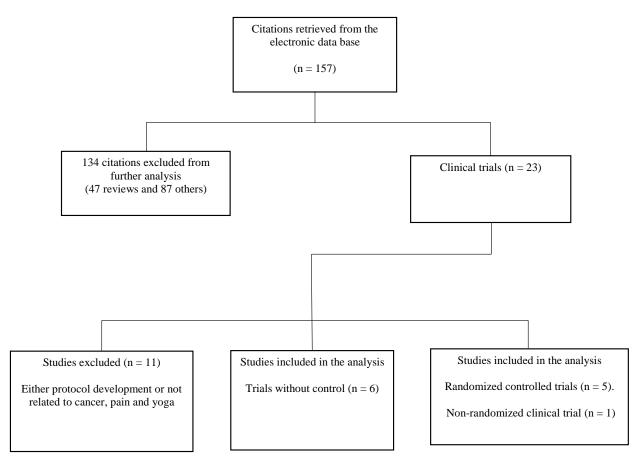


Figure 1. Flow diagram of PubMed search.

Table 1. Single-armed clinical trials.

Results Comments	Though not The study demonstrated significant, pain, beneficial effects of anxiety and depression decreased post intervention. Shoulder lacking power, and flexibility yoga procedures not improved well defined significantly.	Significant The study established improvement in the definite efficacy of functional reach, flexibility and QOL. Significant reduction in pain.	
Measures	Pain (using Dallas Pain questionnaire), shoulder flexibility, and anxiety and depression (using Hospital Anxiety and Depression Scale).	Primary: Balance and flexibility. Secondary: Selfreported Patient Specific Functional Scale, Functional Assessment of Cancer Therapy-Breast and Pain inventory.	Participants were
Interventions	Hourly yoga session for 12 weeks. Pre- and post- intervention assessment.	An individualized need-based Iyengar yoga program (1.5 hourly twice per week) for 8 weeks. Also an abbreviated version was suggested for home practice for 2 weeks.	A colors
Number of patients	17 (14 completed the study)	10	10
Cancer type	Stage I-III post- operative breast cancer patients	Stage I-III breast cancer patients with aromatase inhibitor- associated arthralgia.	A colorio
Reference	Sudarshan et al., [80] (a prospective study)	Galantino et al., [81]	
Study #	1	2	

Table 1 continued..

Duration of intervention was short and not well defined. The study concluded that, "yoga might be considered as positively facilitating cancer treatment".	Yoga procedures were not well defined, number of participants was small, and the duration of intervention was short. In contrast to other studies this study included males and varied cancer types.	Low statistical power and short duration of intervention. The study was followed with a randomized controlled trial.
All the measures improved significantly after 8 sessions of yoga intervention.	Significant improvement in all the measures	Levels of pain decreased. Levels of invigoration, acceptance, and relaxation were higher.
Stress, anxiety, emotional levels, level of energy, pain, sleep, social adaptation, physical skills and satisfaction levels were determined preand post-intervention.	Anxiety and depression (using the Japanese version of Anxiety and Depression Scale, HADS). Sense of meaning measures (FACIT-SP scale). Psychological appreciation, intensity of pain and physical symptoms (constipation, nausea, and sleep disorders).	Daily measures of pain, fatigue, distress, invigoration, acceptance, and relaxation during two pre-intervention weeks and the final two weeks of the intervention.
Eight sessions of classical yoga twice a week.	The cyclic meditation program (meditation and breathing); 30-60 minutes per session, for 2 weeks. Patients were recommended to perform the procedure at home once per day.	Eight weekly group sessions of Yoga Awareness Program included gentle yoga postures, breathing exercises, meditation didactic presentations, and group interchange.
20	28 (4 males, 24 females). Breast (n = 21), colon (n = 2), stomach (n = 2), and bladder (n = 2),	21 women volunteered for the study, but 3 withdrew just before and 4 shortly after beginning the intervention for various reasons. Thirteen women completed the intervention and pre- and postassessment measures
Breast cancer (Patients were 30-50 years of age)	Breast, colon, stomach and bladder	Metastatic breast cancer
Ulger and Yagli, [51]	Ando et al., [83]	Carson et al., [56] (A pilot/ feasibility study)
4	2	9

Table 2. Randomized and non-randomized controlled trials.

Study #	Reference	Cancer type	Study type	Number of patients	Intervention	Measures	Results	Comments
1	Yagli and Ulger, [59]	Breast cancer elderly patients (65-70 years old).	Non-RCT	20 (10/10)	One hour session/week for 8 weeks (asanas, 15 min, breathing exercises, 15 min, meditation, 30 min) based on patients' need and ability. Control: Exercise	QOL were assessed using Turkish version of the Nottingham Health Profile. Emotional levels were determined using the Turkish version of the Beck Depression Inventory. Severity of pain, fatigue, and sleep quality were measured using the visual analog scale.	All QOL scores were better after yoga and exercise. Except for energy levels, pain, emotional reaction, social isolation, and sleep quality were significantly improved after the intervention. Exercise also improved these parameters.	The control group was not randomized, sample size was small and the duration of intervention was short. Both the yoga and exercise improved QOL in the elderly breast cancer patients.
6	Peppone <i>et al.</i> , [84]	Breast cancer patients with musculoskeletal symptoms, receiving tamoxifen (n = 72) and aromatase inhibitor (n = 95).	RCT	167 (84/83)	Seventy five minutes each, twice a week over 4 weeks (total of 8 sessions) of YOCASC program (University of Rochester Yoga for Cancer Survivors Program) consisting of: breathing exercises (slow, controlled diaphragmatic, and movement coordinated breath), gentle Hatha yoga postures (standing, transitional, and supine poses), and mindfulness exercises (meditation, visualization, and affirmation activities).	Fatigue, pain, and physical well-being using the Functional Assessment of Chronic Illness Therapy and Fatigue Subscale (FACIT-F) and the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF).	Yoga significantly improved physical sub-scores and reduced pain and muscle aches.	This study was reasonably well designed, and included a large number of patients.

Table 2 continued..

An 8-week yoga intervention was effective but the benefit didn't last on cessation of the intervention. Sample size small. Intervention well defined.	The weakness in the study was that only 18 of 32 participants completed the study. Also, according to the authors, interviews could have biased the answers and influenced the responses.
Significant decrease in induration and improvement in QOL. No change in extracellular fluid, sensation, pain, and fatigue.	Only 18 (breast cancer,
Primary outcome measures: arm volume of lymphedema measured by circumference and extracellular fluid measured by bioimpedance spectroscopy. Secondary measures: tissue induration by tonometry, levels of sensation, pain, and fatigue by visual analog scale, and QOL by Lymphoedema Quality of Life Tool.	Psychological measures (perceived stress and well- being)
The Intervention (breathing exercises, physical postures, and meditation) consisted of 90-minutes weekly teacher-led class and 40-minute daily DVD delivered sessions for 8 weeks. Control: usual self-care. The group was offered yoga after the completion of the final measurement.	Eight 2-hour sessions of a modified Kabat-Zinn program and 6-days a week at home using instruction tapes. Control: Standard care. Assessment was performed through telephone interviews: pre-, post-intervention and follow up after 3 months.
28 (15/13)	Total 71 participants (70 women and one man). Interventio n group (32 women). Control group (male n = 1; women n = 38).
RCT	RCT
Breast cancer Stage I patients with breast cancer related Iymphoedema.	Varying cancers, but mainly breast cancer patients participated
Louden et al., [85] (A pilot RCT)	Kvillemo and Branstrom, [86]
κ	4

Table 2 continued..

This was a well- organized study with a significant number of subjects (n = 84). Also there was a significant improvement in psychological, physical status, and QOL.	Yoga was found beneficial in breast cancer. However deficiencies such as limited number of participants and lack of power were noted.
Depression, anxiety, and fear of recurrence were significantly lowered and energy and physical functioning improved in the yoga group.	Yoga significantly improved hot flash frequency and severity, joint pain, fatigue, sleep disturbance, symptom-related bother, and vigor. Although there were trends in improvement in negative mood and relaxation, the change was not significant. At 3-month follow-up all these outcomes were maintained and additional significance gained in negative mood.
Psychological status (depression, anxiety, perceived stress, fear of recurrence, optimism, social support) and psychological and physical subscales of QOL (SF-36)	Hot flash frequency and severity, joint pain, fatigue, negative mood, sleep disturbance, night sweats, symptoms-related bother, relaxation, vigor, and acceptance. Assessments were done pre-, post intervention and 3 months after the intervention by maintaining daily diaries.
Six-week modified Kabat-Zinn program (meditation, visualization, and yoga postures). The subjects were requested to formally meditate and perform yoga exercises for a minimum of 15-45 min/day, 6-days/week, and maintain a written record.	Eight weekly 120-minutes group sessions of Yoga of Awareness tailored for hot flashes, fatigue, and mood disturbance (breathing 10 min, meditation 25 min, study of pertinent topics 20 min, and group discussion 25 min).
84 (41/43)	37 (17/20)
RCT	RCT
Breast cancer (stages 0-III)	Early-stage (IA-IIB) breast cancer patients experiencing hot flashes.
Lengacher et al., [87]	Carson et al., [88] (A pilot study)
v	9

Both yoga and exercise improved the QOL scores. However, whereas the improvement in emotional reaction, social isolation, sleep, and physical activity was significant (p < 0.05), the improvement in pain and energy levels were not statistically significant (p > 0.05). The investigators concluded that "yoga helped in diminishing depression, pain, fatigue, and increased the QOL in elderly breast cancer patients", and, therefore, yoga might be considered as a positively facilitating cancer treatment.

Study #2 [84]

One hundred and sixty-seven breast cancer patients who were receiving tamoxifen (n=72) and aromatase inhibitor (n=95) volunteered for the study. They were randomized to a yoga group (n=84) or a standard care wait-listed control group (n=83). Yoga significantly reduced (p<0.05) the musculoskeletal symptoms (general pain, muscle ache, and total physical discomfort) compared to pretreatment and the control group. The limitation of the study was, as noted by the investigators, that the questionnaire used for the evaluation was not specifically designed to measure musculoskeletal symptoms. Another gap in the study was that it didn't specify the number of participants completing the study.

Study #3 [85]

Twenty-eight breast cancer patients with lymphoedema were randomized to yoga intervention (n=15) and wait-listed control group (n=13). Compared to the control group, 8-week yoga intervention significantly (p<0.05) reduced the tissue induration and enhanced QOL symptoms, but there was no difference in the degree of sensation, pain, and fatigue between the groups. Also the beneficial effects of yoga in tissue induration and QOL didn't last after the cessation of intervention.

Study #4 [86]

Seventy-one women and one man were randomized to a yoga group (n = 32) or a wait-listed controlled group (n = 39, one man and 38 women). Most of the participants in yoga group reported increase in calm, sleep quality, energy, and decrease in physical pain. A few patients had no effect. Patients reported both the negative and positive views of a specific meditation and yoga exercise. However, the weakness of the study was that only 12 of 32 participants in yoga group were available for final analysis.

Study #5 [87]

Eighty-four stage 0-III breast cancer survivors were randomized to a mindfulness-based stress reduction (MBSR) program (n = 41) or to a usual care control group (n = 43). Compared to the control group, the MBSR group had significant improvement in depression, anxiety, fear of recurrence, energy, physical functioning, and QOL including pain. The strength of this study was that almost all (40 of 41) MBSR participants completed the study, and 85% attended at least 75% of the classes.

Study #6 [88]

Thirty-seven adult women with an early-stage (IA-IIB) breast cancer volunteered for this pilot study. The participants were randomized to a yoga group (n = 17) or wait-listed control group (n = 20). The aim of the study was to test whether yoga intervention, compared to control, changed hot flashes total score. In the intervention group, 16 of 17 patients received yoga and only 12 were available for post treatment (8 week) assessment and 4 for 3-month assessment. In the control group, 17 and 14 participants completed 8-week and 3-month assessment, respectively. Relative to the control group, significant post intervention improvements were noted in the frequency and severity of hot flashes, joint pain, fatigue, sleep disturbance, and vigor in the yoga group. Most importantly, the treatment gains were maintained at 3-month follow up. Whereas the study provided support for the beneficial effects of yoga, small sample size limited the statistical power.

DISCUSSION

Improved life expectancy among patients with cancer has significantly increased the number of cancer survivors experiencing pain [89].

Since cancer pain is a multidimensional experience – physiologic, sensory, effective, cognitive, and behavioral [62, 90], the management of cancer pain requires integration of interdisciplinary and multimodal intervention strategies [43, 91, 92]. This review focuses on the published clinical research evidence on the use and effect of yoga intervention in the management of pain in cancer patients.

A total of 12 clinical trials was identified by search, 6 were without a control group (Table 1) and

5 randomized controlled trials and 1 non-randomized controlled trial (Table 2). All but 1 study [59] reported that yoga improved pain symptoms in cancer patients. Since all the participants in intervention groups were women with breast cancer, there is no information if the intervention will produce similar results in other types of cancers.

Yoga has been used for thousands of years by Hindus and Buddhists as a spiritual practice and for maintaining a balanced health. Because of its health-related beneficial effects, yoga is an integral part of Ayurveda, the oldest Indian indigenous medical system. In the West, interest in yoga as a therapeutic tool started only during the end of last century and is steadily increasing. A commonly used version of yoga in the West is Hatha Yoga called as yoga exercise that constitutes various stretching postures (asanas), and is sometimes combined with breathing exercises (pranayama) and meditation [93]. In fact, yoga has a wide range of techniques that gradually harmonize the body and mind. These techniques were arranged by Patanjali into eight progressive stages called Astanga yoga (eight disciplines of yoga) or Patanjali yoga sutras [94]. They are: (i) Yamas (five self-control codes – truthfulness, non-violence, honesty, self-control, and non-possessiveness); (ii) Niyamas (Five personal codes – cleanliness, contentment, austerity, self-study, and surrender to cosmic will); (iii) Asanas (postures about 84 in number popularly known as yoga exercises or Hatha yoga); (v) Pranayama (breath control); (vi) Dhaarna (concentration); (vii) Dhyana (meditation) and; (viii) Samadhi (super consciousness, self-realization, or enlightenment). Thus yoga is different from simple exercise; whereas exercise focusses on the stimulation of muscles, yoga, on the other hand, stimulates internal glands, thereby regulating hormonal flow and balancing physiological equilibrium of the body and enhances psychological, emotional and spiritual wellbeing. The therapeutic potential of yoga is, therefore, based on the principles of biochemistry, physiology, psychology, five sheaths of bodily existence, five pranas, bodily glands and other bodily elements [95]. According to Ayurveda human body is capable enough to fight diseases. Disturbance in the equilibrium of three humors (Tridosas) - Pitta (fire), Vata (air), and Kapha (phlegem or water) causes disease. Yoga, by helping reestablish the equilibrium in *Tridosas*, not only

helps cure diseases but also helps to prevent attack from new diseases and maintain a healthy state [96, 97]. The trend of yoga intervention in health care is rapidly increasing [47]. Even though the sample size remains small, "oncologists are currently recommending yoga to improve health-related outcomes in adult cancer" [98].

Although not well defined, a number of hypotheses have been proposed on the possible mechanisms of yoga in reducing pain. Three hypotheses are based on the observations that massage reduces pain and that yoga may act like self-massage. The first hypothesis, based on the Gate theory, assumes that yoga initiates pressure signals transmitting the stimulus to the brain much faster than the slow moving pain signals transmitted through the less myelinated nerve fibers. Second, like massage, yoga may enhance deep sleep leading to lowering of substance P, consequently reducing pain [45, 99]. Third, similar to massage, yoga may affect multiple biochemical and physiological pathways, thereby increasing body's natural anti-pain chemicals such as serotonin [45].

Other mechanisms may include yoga's effect on increasing anti-inflammatory glucocorticoid receptor genes, reducing pro-inflammatory transcription factor and cytokines, nuclear factor kappa B (NF-kB), and reducing the activity of cAMP response element binding protein (CREB). Yoga's effect on these signaling pathways may consequently reduce pain in the patients [73, 100-102]. Another possibility, yet to be investigated, is that yoga may increase threshold level of pain's feeling so that patients feel less pain after yoga intervention.

This review reveals a number of limitations. First, one of the most significant methodological problems was the heterogeneity of yoga techniques used in different studies, i.e., Iyengar yoga, varied modifications of Kabat-Zinn program, Hatha yoga or tailor made yoga versions of their own, thus, lacking a standardized approach. Second, intervention durations were short and different in each study. Third, most of the studies lacked a follow up program. Thus it is not clear as to how long the effect persisted after the intervention and how much? Fourth, except for a few studies, the sample size was small. Fifth, the assessment protocols differed from study to study and most of the effects were self-reported rather than objective measures. Since yoga

is a subjective intervention, the scale used for the evaluation of pharmacological compounds may not be applicable. Therefore, new guidelines are needed for the clinical assessment of mind-body interventions.

Further well designed rigorous research using RCTs, larger sample sizes, longer durations, and identification of specific outcomes is necessary to establish benefits of yoga in the management of cancer pain. Despite inherent problems yoga is a relatively safe non-pharmacological intervention that can be integrated with conventional therapies to treat pain in cancer patients.

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Not applicable.

INFORMAL CONSENT

Not applicable.

COMPLIANCE WITH ETHICAL STANDARDS

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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