

Yoga for the Treatment of Insomnia Among Cancer Patients— Evidence, Mechanisms of Action, and Clinical Recommendations

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Abstract

Up to 90 % of cancer patients report symptoms of insomnia during and after treatment. Symptoms of insomnia include excessive daytime sleepiness, difficulty falling asleep, difficulty staying asleep, and waking up too early. Insomnia symptoms are among the most prevalent, distressing, and persistent cancer- and cancer treatment-related toxicities reported by patients and can be severe enough to increase cancer morbidity and mortality. Despite the ubiquity of insomnia symptoms, they are underscreened, underdiagnosed, and undertreated in cancer patients. When insomnia symptoms are identified, providers are hesitant to prescribe pharmaceuticals, and patients are reluctant to take them due to polypharmacy concerns. In addition, sleep medications do not cure insomnia. Yoga is a well-tolerated mode of exercise with promising evidence for its efficacy in improving insomnia symptoms among cancer patients. This article reviews existing clinical research on the effectiveness of yoga for treating insomnia among cancer patients. The article also provides clinical recommendations for prescribing yoga for the treatment of insomnia in this population.

Keywords

Yoga, sleep, insomnia, cancer, exercise

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Up to 90 % of cancer patients report symptoms of insomnia during and post-treatment, such as excessive daytime napping, difficulty falling asleep, difficulty staying asleep, and waking up too early.^{1–10} A diagnosis of insomnia is made when one or more of these symptoms (e.g. difficulty falling asleep or difficulty staying asleep) is present in a severe and persistent form (e.g. occurring for 3 or more days per week for 1 month or longer).¹¹ Insomnia and its symptoms are among the most prevalent and distressing problems reported by cancer patients.^{1–10,12,13} They increase the risk for fatigue and depression, impair treatment adherence, diminish physiologic function, and worsen quality of life (QOL).^{1–10,12,13} When insomnia symptoms are severe and become chronic, they may increase morbidity and play an indirect part in affecting mortality.^{1–10,12,13} Despite the ubiquity of insomnia symptoms, they are underscreened, underdiagnosed, and undertreated in cancer patients.^{1–10,12,14}

Treatment options for insomnia and its symptoms include exercise, pharmaceuticals, and psychobehavioral interventions.^{1–10,13} Unfortunately, pharmaceuticals do not cure insomnia and can lead to toxicities, negative interactions with cancer therapeutics (e.g. polypharmacy toxicities), dependency, and rebound impairment after discontinuing their use.^{1–10,13}

Traditional exercise is recommended in insomnia treatment guidelines, but not widely implemented in survivorship care plans.^{1–10,13} In most circumstances, if oncology professionals do suggest exercise to their patients, they only provide general, nonspecific recommendations, encouraging patients to be more physically active, instead of delivering individualized exercise prescriptions. Psychobehavioral interventions, such as cognitive behavioral therapy for insomnia (CBT-I), are considered the gold standard in terms of efficacy, but they can be demanding in terms of time and effort. These difficulties can result in low adherence among patients undergoing active treatment.^{1–10,13} Yoga is a well-tolerated exercise intervention with promising scientific evidence demonstrating its efficacy for improving insomnia symptoms among cancer patients.

Yoga

Yoga is an increasingly popular mind–body practice that is also characterized as a mindfulness mode of physical exercise.^{15–18} There are many different styles and types of yoga. They are based on Eastern traditions from India (e.g. Classical, Advaita Vedanta, Tantra) and Tibet (e.g. Tibetan).^{15,19,20} The word ‘yoga’ is derived from its Sanskrit root, ‘yuj,’ which literally means ‘to yoke’ or join together. In this case, yoga refers to

joining the mind and the body.^{15,19,20} The earliest forms of yoga were firmly rooted in physical and mindful (breathing and meditative) practices. These practices led to what is known as classical yoga, which forms the basis for most of the yoga currently taught today.¹⁹ Hatha yoga, the foundation of all yoga styles and the most popular form, includes both Gentle Hatha and Restorative yoga, and is growing in acceptance for therapeutic use in traditional Western medicine.^{13,15–18,21–24} Gentle Hatha yoga focuses on physical postures and is part of many styles of yoga, including Iyengar, Anusara, and others.^{15–18,21} Restorative yoga focuses on full relaxation and is part of the Iyengar style.^{25,26} The combination of Gentle Hatha and Restorative yoga may provide an effective approach for improving insomnia as it incorporates a holistic sequence of meditative, breathing, and physical alignment exercises, requiring both the active and passive engagement of skeletal muscles.^{15,16,21,22,25,26} Existing scientific evidence suggests that yoga is effective for improving insomnia symptoms in cancer patients.^{13,20,27–36}

Biological Mechanisms

The pathophysiology of insomnia, as well as its relationship with cancer and cancer treatments, is largely unexplained.^{14,37,38} Research suggests that insomnia symptoms may arise through multiple pathophysiologic pathways, including dysregulated hypothalamic-pituitary-adrenal (HPA) axis function stemming from abnormal sleep/wake homeostasis; hyperarousal; disruptive cognitive and behavioral factors; and impaired circadian, physical (i.e. cardiopulmonary and muscular), and immune function. Cancer and its treatments directly and negatively influence these same physiologic processes and, therefore, can directly affect the development of insomnia. Cancer and its treatments also lead to a reduction in physical activity and exercise, resulting in physical deconditioning that, in turn, leads to diminished function in these same systems, further impairing sleep. Yoga is a form of exercise capable of positively influencing each of these systems and of improving circadian, physical, and immune function. While not exhaustive, we provide examples of plausible mechanistic pathways through which yoga may ameliorate the insomnia symptoms experienced by cancer patients.

Yoga and the Circadian Clock System

Yoga may regulate circadian function by acting as an exogenous behavioral nonphotosensitizer for the circadian clock system. The circadian clock system consists of a central component: the suprachiasmatic nucleus (SCN) of the hypothalamus, also known as the body's 'master clock,' as well as peripheral components involving multiple organ- and tissue-specific 'clocks.' These peripheral clocks are synchronized through humoral and neural connections throughout the body that, in turn, affect behavioral and physiologic output rhythms (i.e. diurnal fluctuations in sleep, physical activity, heart rate, strength, and cytokines).^{39–41} The master clock, however, has its own intrinsic rhythm that is entrained or synchronized to a 24-hour cycle by exogenous photo- and nonphotosensitizers. While the strongest photosensitizer is light, one of the strongest nonphotosensitizers is exercise (e.g. yoga).⁴¹ Our prior research suggests that yoga favorably alters circadian activity rhythms as a behavioral nonphotosensitizer and can, thereby, address cancer-related insomnia.³¹

Yoga, the Immune System, and Inflammatory Responses

Yoga may regulate immune function in the same way as other modes of exercise: by dampening the chronically upregulated pro-inflammatory responses exhibited in cancer patients as a result of their disease and its

treatments. This dampening, in turn, may normalize overall inflammatory responses and improve insomnia. Exercise reduces low-grade inflammation by triggering the immediate, but transient, release of interleukin (IL)-6.⁴² IL-6 is released from skeletal muscle in proportion to exercise intensity and duration, the proportion of muscle mass used during an exercise bout, and training status.⁴² In this environment, IL-6 functions as an anti-inflammatory molecule by triggering the release of tumor-necrosis factor receptor-1 (TNFR1), IL-10, and IL-1 α that, consequently, inhibits the production of tumor-necrosis factor alpha (TNF α), IL-8, IL-1 α , and IFN γ and regulates overall inflammatory responses.⁴² Research suggests that yoga may improve inflammatory immune responses in cancer patients.^{43–45}

Yoga and Physical Function in the Cardiopulmonary and Muscular Systems

Yoga may improve physical function (i.e. cardiopulmonary and muscular function) in the same way as other modes of exercise: by eliciting a physiologic conditioning response. This physical conditioning response may improve the reduced physical function exhibited by cancer patients as a result of their disease and its treatment, consequently improving insomnia. It is well documented that traditional modes of exercise, performed frequently at high enough intensities for a sufficient duration, improve cardiopulmonary and muscular function as part of a desirable physical conditioning response.^{46,47} In addition, regular exercise that improves physical function (cardiopulmonary and muscular) results in medium to large improvements in total sleep time, slow wave or 'deep' sleep, nighttime wakefulness, sleep onset latency, and insufficient sleep.^{48–51} Research suggests that participation in yoga improves cardiopulmonary and muscular function in healthy individuals and in those with other diseases.^{52–57}

Yoga for the Treatment of Insomnia

Studies demonstrate that yoga may help to improve depression, anxiety, fatigue, and sleep difficulties in both a disease-free population and those with cancer.^{58–60} We review below the existing scientific literature on the use of yoga for the treatment of insomnia within an oncologic population.

Qualitative Yoga Studies/Yoga Program Evaluations

There have been a number of studies that obtained their data through program evaluations or through qualitative measures.^{61–64} Studies of this nature are useful in showing patient-reported benefits, but often carry less scientific weight because of their lack of randomization and validated outcome measures. One of the first examinations of yoga in cancer patients was performed by Joseph et al. in 1983.⁶² Cancer patients undergoing radiation therapy were offered yoga, meditation, or support therapy. Those in all three groups, reported improvements in sleep, treatment tolerance, mood, appetite, and QOL. A similar study was published in 2004, in which cancer patients were invited to participate in the Stanford Cancer Supportive Care Program (SCSCP).⁶³ The SCSCP consisted of 11 activities, including fatigue management, nutrition, massage, and Restorative yoga. Of the 380 participants who participated in Restorative yoga and evaluated their experience, 96 % felt it reduced their stress, 74 % felt an increase in energy, and 65 % reported more restful sleep. In 2008, Duncan et al. described how yoga can be used to treat symptoms and QOL in cancer patients.⁶¹ Using pre/post analyses, yoga participants reported significant gains in overall well-being and reductions in the severity of their most bothersome symptoms. In a 2010 study of a yoga program of 17 breast cancer patients, yoga participants reported improvements

in QOL and psychosocial functioning.⁶⁴ Furthermore, yoga participants in two of these publications attributed improvements in strength, physical function, and physical fitness to their yoga program. While these results are extremely promising, they must be interpreted with caution due to their use of convenience samples and the lack of validated outcome measures for assessing sleep quality. Additionally, these programs did not use standardized versions of yoga, making it difficult to replicate the various interventions that were used.

Clinical Trials

A total of 11 clinical trials of yoga for insomnia and sleep difficulties in cancer patients were identified.^{20,25,28,30,34,36,65–69} Some of the trials used cancer patients on active therapy, while others used cancer patients who had already completed their primary therapy but still reported symptoms and side effects. These trials were very diverse, with the number of yoga classes ranging from one to five per week. Class duration also varied from 50 minutes to 120 minutes per session. There was also a very wide range regarding the duration of the intervention, with some studies lasting only 4 weeks and others lasting as long as 26 weeks. Perhaps most varied were the different types of yoga postures and poses used within these studies. Despite the use of different types of yoga, these studies showed that yoga was safe, feasible, and acceptable within cancer patient populations, reinforcing the findings from the previous section.

The first clinical trial of yoga in cancer patients for sleep difficulties was performed by Cohen et al. (2004) who found that yoga participants had better subjective sleep quality, faster sleep latency, longer sleep duration, and less use of sleep medications than wait-list controls.²⁰ The yoga study by Bower et al. (2012) was the first to blind the participants to the study hypothesis and use a time and attention control in a yoga study for insomnia.⁶⁵ Overall, eight of the randomized controlled trials (RCTs) compared yoga to a waitlist control,^{20,25,28,34,36,66,68,69} one to a support therapy control condition,³⁰ one to a stretching control condition,⁶⁷ and one to a health education control condition.⁶⁵ The sample size in these trials also greatly varied, from 16 to 410. The largest study, by Mustian et al., was the only phase III and multicenter trial of yoga for sleep difficulties in cancer patients.⁶⁸ In addition, that study was one of the only studies to use both validated patient-reported outcome measures and objective measures, via actigraphy, of sleep. The trial compared a standardized yoga intervention (YOCAS[®]: 4 weeks, two times a week, 75 minutes/session; Gentle Hatha and Restorative yoga) to a usual care waitlist control condition among 410 cancer patients from 12 community oncology practices throughout the US. Yoga participants had statistically significant improvements in wake after sleep onset, sleep efficiency, self-reported sleep measures, and sleep medication usage compared with the controls.⁶⁸ Overall, the results are encouraging, with seven trials reporting significant sleep-related benefits for yoga^{20,25,28,30,36,68,69} and four trials reporting null findings.^{34,65–67} However, there are a number of matters that should be considered when interpreting these results.

Empirical Limitations of Existing Research

There has only been one large phase III RCT on the effects of yoga on insomnia that suggests that yoga is effective to treat insomnia symptoms. Therefore, the existing literature on yoga needs to be interpreted with caution.

Several of the smaller phase I and II yoga studies need to be interpreted cautiously. Many were small (ranging in total sample size from 20 to 88)

and did not use validated measures of insomnia. None of these studies were powered *a priori* to test the effects of yoga on insomnia as a primary outcome. Many of these treatment studies did not screen for baseline level of sleep difficulty as a criterion for study entry. Furthermore, the studies did not blind participants, with the exception of the Bower study.²⁷ Importantly, yoga interventions were highly variable in content, type, intensity, and duration, making it difficult to determine the actual dose of yoga needed to effect improvements in insomnia symptoms. In many of the published studies, details regarding the format and components of the yoga interventions were not provided, making repeatability and standardization for dissemination difficult. Details on participant attendance, compliance, and attrition, as well as rates and types of adverse events, were also lacking. Details of the prescribed yoga dose versus the actual dose achieved (e.g. mode, frequency, intensity, duration) were limited, as was information on the sustainability of improvements in sleep quality impairment stemming from yoga. Lastly, only one study investigated the effects of yoga at several long-term follow-up time-points up to 6 months post-treatment.

The only phase III clinical trial conducted to date has addressed many of the limitations of the phase I and II clinical trials. This study was appropriately *a priori* designed and powered to test the effects of yoga on sleep quality as the primary outcome. It had a sample of 410 patients, screened for a predefined baseline level of sleep quality impairment, used validated patient report and objective measures of sleep, rigorously standardized the yoga intervention and checked for intervention quality, fidelity, and drift. The yoga prescription details were fully described as part of the published manuscript, as well as full reporting of unexpected and serious adverse events, attendance, compliance, and attrition. Furthermore, the authors described the achieved dose (in minutes) of yoga versus the prescribed dose.

While promising, this phase III RCT included only one specific type of yoga and was of only 4 weeks duration. This study, along with many of the pilot studies, include primarily Caucasian, well-educated, middle to upper-middle class women. There was little racial, economic, social, cultural, gender, or age diversity in sample populations, limiting external validity. Importantly, this limits the ability to determine which patient profile may be best suited for and have the best response to yoga therapy. Another major limitation is that none of the previously conducted studies compared yoga with a clinically approved therapy for insomnia. Yoga may improve insomnia or sleep quality impairment, but an important body of knowledge needs to be further developed in order to better tailor yoga prescriptions to improve insomnia, and meet the unique needs of individual cancer patients (e.g. the needs of a male patient versus a female patient; a nonwhite patient versus a white patient; and a breast cancer patient versus a colorectal cancer patient).

Clinical Recommendations

While yoga is increasingly popular throughout the world at gyms, via self-directed books and DVDs, and at cancer centers and community programs marketed toward cancer patients (e.g. 'Gentle Yoga for Cancer Patients,' 'Yoga for Breast Cancer Patients and Survivors,' and 'Healing Yoga'), there is little, if any, scientific evidence as to the efficacy of these programs in improving insomnia symptoms among cancer patients. Often, these yoga programs are not professionally regulated in terms of instructor qualifications and licensure, or adherence to best practice,

standard of care, or evidence-based therapeutic guidelines, resulting in significant variability in what is offered to cancer patients. For example, some yoga programs focus on gentle, low-intensity, meditative practices (e.g. Restorative, Integral, Svaroopaa), while others focus on vigorous practices (e.g. Power, Ashtanga), or a combination of both (e.g. Hatha, Iyengar, Kundalini).⁵³ Some programs modify the yoga environment by using heaters and humidifiers (e.g. Bikram) or props such as straps, blocks, ropes, and chairs (e.g. Iyengar).⁵³ These variations lead to classes that vary widely in structure and overall formats.

The small number of studies examining the safety and effectiveness of only limited styles and types of yoga for improving insomnia and sleep quality impairment among patients, coupled with the lack of regulation and wide variability of yoga offerings, substantially increases the chance that patients may spend a sizable amount of time, energy, and money participating in yoga programs that may not be safe, effective, or meet their specific needs. For example, yoga in a room heated to over 100 degrees may be contraindicated for some patients, and vigorous yoga may result in excessive muscle soreness and joint pain, increasing insomnia, or sleep quality impairment. These considerations need to be considered by oncology practitioners who may be recommending yoga to their patients so that they can ensure appropriate classes are taken.

Despite their limitations, these phase I–III studies collectively support the benefits of yoga, demonstrating that:

- cancer patients can safely participate in yoga during and after cancer treatments;
- yoga interventions are feasible in a variety of cancer centers and community-based yoga studios;
- participating patients find yoga programs enjoyable and beneficial;
- participation in low- to moderate-intensity yoga that incorporates Gentle Hatha and Restorative postures, breathing and meditation exercises ranging from one to five sessions/week for 50–120 minutes per session over a period of 4 to 26 weeks may lead to improvements in insomnia and sleep quality impairment; and
- participation in standardized yoga programs designed explicitly for cancer patients experiencing insomnia will reduce the symptoms of insomnia they experience.

Oncology practitioners can provide important information to help cancer patients understand how they can safely begin and/or continue a yoga program during and after treatments.⁷⁰ Patients can benefit from being aware of potential contraindications (e.g. orthopedic, cardiopulmonary, and oncologic) that might affect their exercise safety and tolerance.⁷¹ Contraindications do not necessarily mean that a cancer patient cannot participate in yoga at all; in fact, this is rarely the case. In most instances, contraindications simply mean that specified modifications must be made so that the individual can safely and effectively participate and achieve physical and mental health benefits. The American College of Sports Medicine Exercise Guidelines for Cancer Patients and Survivors—the only guidelines currently based on scientific evidence—provide an excellent resource regarding recommendations for screening and evaluation of cancer patients prior to participation in yoga (available at: http://journals.lww.com/acsm-msse/Fulltext/2010/07000/American_College_of_Sports_Medicine_Roundtable_on.23.aspx).

Referral resources can help patients connect with the most-qualified and competent yoga instructors in their community, including those who have special training and experience in working with cancer patients, or individuals with other chronic medical conditions. Patients may also benefit from understanding that the styles and types of yoga that have been scientifically tested in a randomized clinical trial and shown to be safe and effective for improving sleep among cancer patients include a low- to-moderately intense program, consisting primarily of Gentle Hatha and Restorative postures, combined with breathing and meditation exercises.

When screening patients for insomnia symptoms and making clinical recommendations about the use of yoga for managing insomnia, research suggests yoga is effective for individuals who reported mild-to-moderate sleep quality impairment, as well as clinical insomnia, who continue to report insomnia symptoms after trying pharmaceutical treatments, who demonstrate more than 1 hour of wakefulness in the middle-of-the night, who have poor sleep efficiency (60 % or lower), or who have some combination of these characteristics. Patients with these characteristics were shown to derive the greatest benefits from participation in yoga—specifically in improved sleep and reduced medication use.

Summary

While a large, multicenter phase III trial and five additional smaller RCTs have shown that yoga improves sleep in cancer patients, the variability across studies and the inherent limitations in the literature limit the extent to which yoga can be considered effective for treating insomnia or sleep quality impairment among cancer patients. Further research is needed to determine whether yoga is equal to, or superior to, existing gold standard treatment for insomnia and sleep quality impairment, such as CBT-I. Future clinical trials need to employ reliable and validated patient-reported outcomes of insomnia and sleep quality impairment, along with objective measures of insomnia and sleep quality impairment, such as actigraphy and polysomnography. There is also a lack of studies that include long-term, follow-up assessments (e.g. 3, 6, 9, and 12 months post intervention) to determine the duration and magnitude of any sleep benefits derived from yoga. In addition, researchers should make an effort to standardize their yoga program so that it can be replicated and reproduced for patients.

Another goal of future research should be to determine which components of yoga (e.g. postures, breathing, or meditation) are most effective in treating sleep disorders by using only separate components. In addition, mechanistic studies are needed to elucidate the biopsychosocial pathways through which yoga exerts a positive influence on sleep and other toxicities related to cancer and its treatments, such as fatigue, functional decline, cognitive impairment, and deregulated immune function, among others. Furthermore, in the US and other Western nations, yoga is most popular among white females, typically of higher socioeconomic status. Future research is needed to investigate ways to increase yoga participation among racially, economically, socially, and culturally diverse patients, as well as older and male cancer patients. Trials are also needed to compare the efficacy of yoga to other modes of exercise, such as walking and resistance training, for improving sleep. Research shows that the effects of behavioral interventions, such as yoga, may be enhanced by enlisting

a care partner to participate with them. Moreover, care partners often tend to higher levels of psychologic distress, such as anxiety and depression. Trials are needed that extend yoga to these care partners (e.g. sister, brother, mother, father, child, spouse, or friend) who provide

unpaid care and support to the patient at significant expense to their own health throughout the cancer experience. The benefits this type of study may be twofold, both enhancing the intervention for the patient and reducing distress for the care partner. ■

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