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Insomnia and its Treatment in Women with Breast Cancer

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Abstract

Insomnia is a common complaint in breast cancer patients and has been shown to have a host of psychological and medical correlates and consequences. Typically insomnia is treated pharmacologically, however more recent findings from randomized controlled clinical trials support the use of cognitive behavioral therapies. The aim of this article is to review the empirically supported breast cancer literature on insomnia, briefly present and explain the insomnia treatment options available, and extrapolate research guidelines for future directions in this growing field. Behavioral therapeutic approaches for insomnia seem particularly suitable to use in the breast cancer populations because they have lower risk of interacting with the cancer treatment, do not burden the patients with additional pharmacological treatments, and can target the treatment towards ameliorating specific symptoms, like fatigue, that are characteristic in this population. However, there is a need for replication of efficacy studies of cognitive behavioral treatments for insomnia in breast cancer, as well as studies investigating vulnerability, risk and protective factors that might ultimately lead to insomnia prevention programs for use in this population.

Keywords

Insomnia; breast cancer; sleep; cognitive behavioral treatment for insomnia; fatigue

Introduction

Estimates of the prevalence of insomnia in cancer populations range from 23% to 61%, and are higher than that found in non-cancer patients.¹In 2001, Savard and Morin² underlined the severity of insomnia and its psychological and general health consequences in cancer populations, indicating the scarce attention that insomnia had received in these populations in terms of diagnosis and treatment. Since 2001, there have been some studies investigating sleep problems in cancer, but much more research needs to be done to achieve a clearer picture of the phenomenology of insomnia in cancer populations. The 2005 NIH State-of-the-Science conference on insomnia emphasized, among other needs, the necessity to explore the relationship between characteristics of insomnia and other psychiatric and medical comorbid disorders.³ Additionally, the NIH panel encouraged randomized controlled trials that would validate treatment options in different populations suffering from insomnia.

Most of the studies on sleep problems in cancer have been conducted in women with breast cancer (see Vena et al., 2004⁴ and Clark et al., 2004⁵) for a general overview of sleep in patients with different types of cancer). The population of women with breast cancer is prone

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to insomnia for various reasons including a possible disruption of sleep due to increased frequency and severity of hot flashes associated with the breast cancer treatment, and possible increased depression, anxiety and fatigue levels following the breast cancer diagnosis.⁶ The literature on insomnia in breast cancer reports severe levels of insomnia and debilitating physical and psychological correlates of poor sleep as well as reports of very promising treatment options. This article is a review of the current knowledge on the development and characteristics of insomnia in women with breast cancer and a summary of the efficacious treatment options.

Insomnia

Insomnia is characterized by complaints of difficulty initiating or maintaining sleep, or non-restorative sleep which last for at least one month and which cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.⁷ Insomnia is a heterogeneous disorder that has been classified by the International Classification of Sleep Disorders into subtypes with different characteristics.⁸ Until recently, most researchers and clinicians categorized insomnia into primary and secondary insomnias. Primary insomnias included any insomnia which has no other cause, such as psychophysiological insomnia (i.e., heightened arousal and learned sleep-preventing associations), physiological insomnia (i.e., in which the subjective reports of disturbed sleep is corroborated by objective polysomnography) and idiopathic insomnia (i.e., childhood onset chronic inability to obtain adequate sleep). Secondary insomnias, which the recent NIH State of the Science of insomnia panel suggested be called comorbid insomnias³, include insomnia associated with mental disorders, medical disorders, medications (both prescription and over-the-counter), alcohol or drug dependency, environmental factors, sleep induced respiratory impairment, movement disorders, disorders of the sleep wake schedule, and /or parasomnias (e.g., somnambulism, REM sleep behavior disorder).

Both primary and comorbid insomnia are characterized by reduced sleep duration and intensity. The underlying symptoms can be initial or sleep onset insomnia (i.e., difficulty falling asleep), middle or sleep maintenance insomnia (i.e., difficulty staying asleep), terminal or late insomnia (i.e., early morning awakening), and/or non-restorative sleep. Each of these can be transient, transient recurring, or chronic. In addition, many patients suffer from a combination of insomnia types. In general, most practitioners tend to see and treat patients with chronic insomnia as it can have the most serious consequences.

Insomnia is a very common sleep disorder,⁹ reported that 20% of the adult population and 1/3 of the elderly population reports complains of insomnia symptoms. Other estimates of insomnia prevalence in the general adult population have ranged from 9% to 17%.¹⁰⁻¹⁴

Chronic insomnia, which is defined by the minimum duration of the insomnia episode (duration ranges from 30 days or six months depending on the study³) has a host of debilitating consequences that include tiredness, negative mood, the inability to enjoy family and social relationships, difficulty concentrating, memory problems, decreased quality of life, increased absenteeism, decreased job performance, increased severity of pain and poor health, and increased risk of falls.¹⁵ Chronic insomnia has also been associated with greater functional impairment, loss of productivity,¹⁵ excess health care utilization,¹¹ and high psychiatric comorbidity, particularly depression and anxiety¹⁰ as well as increased suicide risk.^{16,17} In addition, insomnia is very often associated with medical disorders including irritable bowel syndrome,¹⁸ fibromyalgia,¹⁹ asthma²⁰ and gastroesophageal reflux disease.²¹

Not much is known about how to prevent insomnia, however there is some evidence that leading an active life style and having a satisfying social life are correlates of healthy sleep, and might represent protective factors against insomnia.²² Factors that make people more

vulnerable to insomnia, particularly complaints of initiating and maintaining sleep, include previous complaints of insomnia (odds ratio 3.5), female gender (odds ratio, 1.5), advancing age (odds ratio, 1.3), snoring (odds ratio, 1.3), and multiple concomitant health problems (odds ratios, 1.1 to 1.7).²³ Women with breast cancer have at least two of these main vulnerability factors for insomnia, i.e., being female and having cancer and its related health disturbances. In addition, many, although not all, women with breast cancer are older, which may put them at even greater risk of developing insomnia. While most of the literature on aging and sleep shows that the prevalence of insomnia increases with age, (e.g., Foley et al. 1995)²⁴, a study by Davidson et al.²⁵ showed that in cancer patients this relationship might be inverted with younger patients having more insomnia.

Insomnia in breast cancer patients: Objective measurement studies

There have been very few objective studies of sleep in breast cancer patients and the results have been contradictory. Silberfarb et al.²⁶ compared polysomnographically recorded sleep of 32 cancer patients (15 with breast cancer) with age- and sex-matched healthy volunteers and 32 otherwise healthy insomnia patients and found that the breast cancer patients had sleep architecture similar to the normal sleepers. Conversely, polysomnographic studies in women with breast cancer who had completed chemotherapy showed that they had lighter sleep (i.e., increased stages 1 and 2), less deep sleep (i.e., decreased stages 3 and 4), less REM sleep, and lower sleep efficiency compared to normative data.²⁷

There is also evidence of objective sleep being disrupted by hot flashes in women with breast cancer. Carpenter et al.²⁸ found that 67% of participants in their study who were survivors of breast cancer experienced nighttime hot flashes compared to only 37% of healthy women matched, among other variables, on age and menopausal status. Savard et al.,²⁹ reported that nights with hot flashes were associated with more percentage wake time, lower percentage stage two, and less efficient sleep compared to nights with no hot flashes. Therefore hot-flashes may be one of the causes of complaints of poor sleep in women with breast cancer. Hence, recording and measuring hot flashes in future studies investigating sleep in women with breast cancer is desirable whenever possible.

Insomnia in breast cancer patients: Subjective measurement studies

Studies that examined subjective sleep reports in cancer patients found that cancer patients have significant complaints of difficulty sleeping³⁰ and that the severity of the complaints is comparable to the insomnia complaints in other medical conditions.³¹ In particular, it has been reported that women with breast cancer have severe complaints of poor sleep, insomnia, and fatigue.^{25,32} Savard et al.³² studied insomnia prevalence in 300 non-metastatic breast cancer women and found that 19% met diagnostic criteria for an insomnia syndrome with 95% of the cases being chronic insomnia. They also found that in 33% of the cases the onset of insomnia followed the breast cancer diagnosis, and that 58% of the patients reported that cancer either caused or aggravated their sleep problems. Ancoli-Israel et al.³³ also found that women with breast cancer complained of poor sleep after they were diagnosed but before they began their chemotherapy. Carpenter et al.²⁸ compared breast cancer survivors' sleep and fatigue levels to age, race and menopausal status matched healthy women and found that 73% of breast cancer survivors and 67% of healthy women had poor sleep quality and high sleep disturbance. Women with breast cancer also experienced shorter sleep duration and higher rates of nighttime flashes (67%) compared to healthy women (37%). These researchers found no group differences between women with breast cancer and healthy women in levels of fatigue and depression. However, other studies report that fatigue is one of the primary complaints in cancer patients (see Ancoli-Israel, et al. for a more complete review)³⁴. Koopman et al.³⁵ looked at sleep disturbances in women with metastatic breast cancer. The results showed that 63% reported sleep disturbance, and that 37% reported using sleeping pills in the previous 30 days.

This study also found interesting relationships between types of insomnia and correlates of breast cancer experience; all types of insomnia correlated with increased depression. In addition, problems falling asleep (i.e., initial insomnia) were associated with greater pain. Problems with awakenings during the night (i.e., middle insomnia) were related to less education, and finally, problems with early awakenings (i.e., terminal insomnia) were associated with less social support. Although insomnia in the context of metastatic cancer may be different than that of early stage cancer, these results still help in the overall understanding of sleep in breast cancer.

The relationship between insomnia and other psychiatric disorders such as depression and anxiety in the breast cancer population still needs to be established. However, there are studies that show a decrease in depression^{36, 37} and anxiety³⁶ in women with breast cancer, following successful treatment of insomnia with cognitive behavioral therapy for insomnia.

In summary many women with breast cancer have complaints of poor sleep with prevalence estimates that range from approximately 20% to 70% depending on the study. Most but not all breast cancer patients report having had poor sleep prior to the breast cancer diagnosis, but also report that the breast cancer experience has worsened their sleep problems.

Fatigue in breast cancer patients

Studies have shown that fatigue is one of the most frequent and most disturbing complaints of cancer patients^{38,39} with over 75% of patients undergoing chemotherapy or radiation therapy having complaints of fatigue (e.g., feeling tired and weak).^{40,41} Furthermore, research has shown that these complaints may persist months after completion of treatment.^{42,43} Fatigue is known to reduce quality of life^{38,44,45} and is often the reason for oncology patients to discontinue their cancer treatment.⁴⁰

The true relationship between sleep and fatigue in cancer patients has not been established,³⁰ however, there is evidence that fatigue and poor sleep are related. Akerstedt et al.⁴⁶ studied the relationship between mental fatigue, life style factors, and disturbed sleep in healthy participants and found that disturbed sleep was the most important predictor of fatigue, apparently stronger than previously well-established predictors such as workload, female gender, and lack of exercise.

In women with breast cancer, studies on fatigue have reported evidence of increased fatigue at each stage of treatment, i.e., before, during, and after chemotherapy. Ancoli-Israel et al.³³ found that women diagnosed with breast cancer had increased fatigue, disturbed sleep, and increased daily dysfunction before the start of chemotherapy. Fatigue continued to increase and circadian sleep/wake rhythms became desynchronized during chemotherapy.⁴⁷ Finally, Broeckel et al.⁴⁸ examined fatigue in women with breast cancer after a year of completion of treatment with chemotherapy and found that, compared to women with no history of breast cancer, patients reported more severe fatigue and worse quality of life due to fatigue. Particularly interesting for clinical treatment and cancer fatigue prevention program developments are the findings by Berger⁴⁹ who found an inverse correlation between fatigue and physical activity during most cycles of adjuvant chemotherapy treatment, with women most fatigued being the least active. Other studies also have found evidence that exercise might be related to less fatigue in breast cancer patients,^{50,51} and that women who are less active and have more nighttime awakenings have increased cancer related fatigue.⁵²

In summary fatigue and insomnia in women with breast cancer represent significant complaints with debilitating consequences for circadian sleep/wake rhythmicity, and daytime functioning. Augmenting activity levels might represent a good strategy to combat fatigue in breast cancer patients.

Treatment of insomnia in breast cancer patients

The severity and frequency of insomnia in the breast cancer population warrants a close look at what efficacious treatments available for insomnia and particular attention to which treatments are more adaptable to the specific needs of the breast cancer population.

Efficacy of pharmacotherapy—Although pharmacotherapy is the most prescribed therapy for cancer patients with insomnia,^{53,54,25} to our knowledge, there have been no studies examining the effect of pharmacotherapy on insomnia in patients with breast cancer. The medications most often used to treat insomnia in the general population are the benzodiazepines, benzodiazepine receptor agonists (BzRAs), anti-depressants, anti-histamines, and most recently, a melatonin receptor agonist. A meta-analysis of randomized controlled trials of benzodiazepine efficacy versus placebo for insomnia in otherwise healthy individuals, showed that benzodiazepines were superior to placebo in shortening sleep latency (mean of 14.3 minutes, and 95% confidence intervals of 10.6 and 18.0).⁵⁵ Studies on BzRAs show that they are also efficacious in improving various aspects of sleep including self-reported sleep latency, total sleep time, and wake time after sleep onset.⁵⁶ The NIH State-of-the-Science conference on insomnia³, concluded that the BzRAs are efficacious in the short-term management of insomnia and the frequency and severity of adverse effects associated with them are much lower than those seen with the benzodiazepines or with other sedating drugs. They also concluded that all antidepressants have potentially significant adverse effects raising concerns about the risk-benefit ratio, that barbiturates and antipsychotics have significant risks and thus their use in the treatment of chronic insomnia cannot be recommended, and that there is no systematic evidence for efficacy of the antihistamines (H1 receptor antagonists) yet there is significant concern about risks associated with these drugs.

In conclusion, insomnia in the cancer population is usually treated with hypnotic drugs. The literature on these drugs shows that benzodiazepines and BzRAs are generally effective in reducing sleep latency, augmenting total sleep time and/or improving sleep continuity. However, there are drawbacks to the use of some hypnotic drugs, particularly the longer acting hypnotics, which include the palliative and non-curative nature of the treatment in chronic insomnia cases, and various side effects as well as psychological and sometimes physiological dependence. Also, most long-term studies last only six months to one year so little is known about the continued efficacy and longer-term side effects when they are used for years. As described below, in cancer patients, these disadvantages are often complicated by other factors.

Efficacy of behavioral treatments—In the last seven years a growing literature on effectiveness of behavioral treatments for insomnia fostered a shift in what sleep medicine experts consider the gold-standard treatment for chronic insomnia. Several studies have shown that behavior therapies and cognitive behavioral therapies (CBT) in particular are as effective and more long lasting than pharmacotherapies for treating insomnia. Cognitive behavioral therapy for insomnia (CBT-I) combines behavioral therapies with cognitive restructuring and educational sleep hygiene. Cognitive behavioral therapy's efficacy in treating insomnia and improving sleep has been shown on both subjective and objective measures of sleep⁵⁷ and it is considered a safe and effective treatment for insomnia.⁵⁸

In 1999, Edinger and Wohlgemuth,⁵⁹ reviewed the literature on the management of persistent primary insomnia and reported the inadequacies of hypnotics in treating this disorder. They talked favorably about the promising behavioral and cognitive behavioral, patient specific approaches to insomnia treatment. More recently, randomized controlled trials have shown some clear advantages of cognitive behavioral techniques in comparison to pharmacotherapies. A randomized controlled trial on young and middle aged adults with chronic sleep onset insomnia found CBT-I more effective than pharmacotherapy in decreasing sleep latency and

increasing sleep efficiency, and in promoting the largest number of normal sleepers at the end of treatment.⁶⁰ This study found no advantages of combined CBT-I and pharmacotherapy treatments versus CBT-I alone. Another randomized controlled study on older adults suffering from chronic, primary insomnia found that initially CBT-I and pharmacotherapy were similarly efficacious in bettering sleep and that there was a trend for the combined CBT-I and pharmacotherapy approach to decrease wake time after sleep onset to a greater degree than each treatment modality separately. However, at one-year and two-year follow-up, only the CBT-I group still showed continued improvements in sleep.⁶¹ An earlier study by McClusky et al.⁶² comparing pharmacotherapy to behavioral therapy for sleep onset insomnia found that pharmacotherapy was efficacious immediately in reducing sleep latency, while behavioral therapies started having effects by the second week but then maintained their effects at follow-up to a larger degree than the pharmacological treatment. Finally, a meta-analysis by Smith et al.⁶³ comparing pharmacotherapy and cognitive behavior therapies (e.g., sleep restriction, stimulus control, cognitive restructuring) for chronic insomnia showed that both treatment approaches ameliorate sleep, but that cognitive behavior therapies result in greater reduction of sleep latency compared to pharmacotherapy. The average number of CBT sessions for the studies included in this meta-analysis was 4.9 over an average period of time of 5.3 weeks. The average length of the pharmacotherapy was 2.0 weeks.

There are also randomized controlled trials of CBT-I versus placebo and comparisons of different modalities of CBT-I. A randomized controlled trial of CBT-I versus relaxation therapy and a placebo (i.e., quasi-desensitization treatment) in adults with sleep maintenance insomnia showed that CBT-I was more efficacious in improving measures of sleep fragmentation than either the relaxation training or the placebo.⁶⁴ A randomized controlled trial of different modalities of CBT-I (i.e., individual therapy, group therapy, and telephone consultations) applied to the treatment of primary sleep onset and sleep maintenance insomnia showed that all modalities were efficacious in treating insomnia, that improvements in sleep were maintained at six months follow-up, and most interestingly that there were no significant differences between modalities.⁶⁵ Cervena et al.⁵⁷ found that CBT-I for insomnia was associated with improved sleep architecture, specifically an increased amount of stage 2, REM and slow wave, and reduced beta and sigma activity.

In summary, cognitive behavioral treatments are at least as effective, and maybe more effective than pharmacological treatment for insomnia. There is some evidence that pharmacotherapy is faster acting in acute stages of insomnia, and that cognitive behavioral treatments have better long-term outcomes. The better long term effects of cognitive behavioral therapy compared to pharmacotherapy may be due to the fact that with this therapy the individual has learned coping skills to tackle acute insomnia as well as to prevent or mitigate in severity future insomnia episodes. The NIH State-of-the-Science conference on insomnia also concluded that CBT-I is as effective as prescription medications for brief treatment of chronic insomnia and there are indications that beneficial effects of CBT-I, in contrast to those produced by medications, may last well beyond termination of treatment.³

Other promising behavioral approaches to aid sleep in breast and other types of cancer patients have been reported in the literature. Berger et al.^{66,67} studied the feasibility and the effects of an individualized sleep promotion plan composed of sleep hygiene, relaxation therapy, stimulus control and sleep restriction on women undergoing chemotherapy for breast cancer. The authors reported that the intervention was feasible with adherence rates improving over time. In addition, most of the sleep measures remained consistent with normal values with the exception of nighttime awakenings which were higher than desired (>30min. per night). Cannici et al.⁶⁸ reported a reduction in sleep onset latency in cancer patients with insomnia after muscle relaxation training, and results were sustained at three month follow-up.

Allison et al.⁶⁹ used a psycho-educational intervention that emphasized skills building (i.e., problem solving techniques, relaxation, cognitive coping, goal setting, communication, social support and lifestyle factors) in head and neck cancer patients and found that the intervention was feasible and was related to increased self reported sleep quality. Simeit et al.¹ compared the subjective sleep of cancer patients with insomnia after either progressive muscle relaxation or autogenic training in addition to a standard rehabilitation program. Both interventions reduced sleep disturbance compared to a standard rehabilitation program, with no significant differences between the two interventions. Finally, Coleman et al.⁷⁰ reported an increase in total nighttime sleep minutes after an individualized exercise program in patients treated with aggressive chemotherapy for multiple myeloma.

Interventions based on eastern medicine and holistic practices have also recently been studied as possible treatments for poor sleep in cancer patients, with promising results. Carlson et al.⁷¹ reported that mindfulness-based stress reduction techniques may help improve sleep in breast and prostate cancer. Tibetan yoga practices have been reported to increase self-perceived quality of sleep in lymphoma patients.⁷² Gentle touch healing may also have a positive effect on sleep in cancer patients.⁷³

Integrating CBT-I in breast cancer patients—There are several published CBT-I manuals. Two of these manuals can be used in group or individual therapy settings^{74,75} and the second is geared specifically for individual settings.⁷⁶ Briefly, the components of these CBT-I treatment manuals are cognitive (e.g., maladaptive thoughts restructuring), behavioral (e.g., sleep restriction, stimulus control), and educational (e.g., sleep hygiene). Both manuals spell out the agenda components for each session.

In research settings however, there seems to be flexibility in terms of what components to apply and emphasize depending on the type of population being treated. With breast cancer patients, Quesnel et al.,³⁷ and Savard et al.³⁶ in addition to the core components of the CBT-I, used strategies to encourage coping with fatigue by encouraging physical activity, and by educating participants on fatigue and the differentiation between fatigue and somnolence.

The theoretical framework on which the manuals are based is Spielman's three factor model of insomnia,⁷⁷ which postulates that three factors are necessary for the development of chronic insomnia. The three factors are *predisposing* factors that make the person prone or vulnerable towards insomnia, *precipitating* factors that trigger the insomnia, and *perpetuating* factors that maintain the insomnia. The model postulates that predisposing, precipitating, and perpetuating factors may have different weights or importance at different times in the course of the insomnia. The cognitive behavioral technique for combating insomnia is to target the perpetuating factors. Perpetuating factors of insomnia are thought to be maladaptive thoughts (e.g., I have to sleep for at least eight hours or I will not function during the day), and maladaptive behaviors (e.g., staying in bed when one cannot fall asleep). Behavioral perpetuating factors are often maladaptive coping attempts to counteract the effects of the insomnia (e.g., napping for sleepiness).

The predisposing factor most often hypothesized for insomnia is arousability or hyperarousal. Arousability is a relatively stable tendency to be easily aroused,⁷⁸ and can be expressed through physiological, cognitive and/or emotional hyperarousal.⁷⁴ According to Morin,⁷⁴ arousability is a central mediating feature of insomnia. He suggests that people with insomnia are generally in a state of greater arousal both during the day and during the night compared to people without insomnia.

The precipitating factors of insomnia have been reported in the literature as events having mostly negative valence, and being related to experiences with family, health, or work-school events.⁷⁹

An example of an application of Spielman's model to an insomnia patient with breast cancer can be seen in Table 1.

It is reasonable to assume that in many women with breast cancer the precipitating event is the diagnosis of breast cancer, which is a life threatening and life disrupting trauma. Kryger reported that women with breast cancer are prone to insomnia and sleep disturbances for various reasons.⁶ As mentioned above, the treatment for breast cancer may increase the frequency and severity of hot flashes which are known to disrupt sleep. Furthermore, being diagnosed with breast cancer and having to face treatment may create or increase symptoms of anxiety and/or depression that also disrupt sleep. It should also be taken into consideration that the insomnia could be a pre-breast cancer condition, in which case the cancer diagnoses will most likely aggravate the insomnia severity. Once the insomnia is triggered, many factors including comorbid conditions such as depression and anxiety may work as perpetuating factors. It is important to note that medical and psychiatric illnesses, such as cancer or depression, may play a role in both predisposing, precipitating and perpetuating the insomnia.

It is important to realize that, while knowing the predisposing and precipitating factors of insomnia is important for educational and theoretical background, the primary focus of the CBT-I intervention are the factors that can be changed, i.e., the perpetuating factors. Hence, the target of the therapy will not change whether a breast cancer patient developed insomnia before the breast cancer diagnosis or as a result of the breast cancer.

Efficacy of CBT for insomnia in breast cancer patients—The studies that have looked at cognitive behavioral treatments for insomnia in the breast cancer population are very few but promising. Quesnel et al.,³⁷ analyzed the effects of treating insomnia with group CBT in breast cancer patients and found significant improvements in sleep efficiency, total sleep time, mood and cognitive aspects of quality of life. Savard et al.³⁶ recently studied the effects of CBT on women with breast cancer and secondary chronic insomnia in a randomized wait-list control study and found that CBT was effective in ameliorating subjective sleep indices as well as decreasing levels of depression and anxiety and increasing quality of life. Therapeutic effects were maintained at follow-up. While the subjective reports in this study are very promising, the objective polysomnographic effects of CBT were unclear. The authors also investigated the relationship between insomnia secondary to breast cancer and the immune system in the same sample of women.⁸⁰ The preliminary but promising results showed that after successful treatment of insomnia with CBT the participants had increased cytokine (interferon gamma) secretion activity at post-treatment, and increased immune variables at follow up suggesting that insomnia and immune regulation are related and that amelioration of insomnia symptoms might booster the immune system.

Summary and conclusions of treatment of insomnia in breast cancer patients—Insomnia is a common complaint in breast cancer patients. Insomnia has been shown to have a host of psychological and medical correlates and consequences. Typically insomnia is treated with hypnotic drugs, however more recent findings from randomized controlled clinical trials support of CBT-I therapies to treat insomnia. In the breast cancer population, CBT-I has been shown to be both efficacious and suitable in two studies implemented by the same research group. These studies used a tailored approach to treating insomnia, addressing the specific needs of breast cancer patients, e.g., targeting fatigue by promoting activity levels. Although these findings are very promising and incorporate a highly desirable tailored approach, replication studies by other research groups as well as generalizability, effectiveness, and

feasibility studies are needed before CBT-I can be established as an empirically validated treatment for insomnia in the breast cancer population. In addition, in order to render available a wider spectrum of empirically supported insomnia treatment options to the breast cancer patient, randomized controlled trials of different behavioral treatments used to aid sleep, including holistic approaches (e.g., mindfulness based stress reduction, yoga, gentle healing) should be implemented.

Discussion and Future directions

This review of the literature on insomnia in breast cancer highlights the breadth and diversity of research findings, the promising treatment options, and the need for further investigation of the phenomenology of sleeplessness in the breast cancer population. Not much is known for example on the relationship between subtypes of insomnia and the breast cancer experience, or relationships between stages of cancer, types of cancer treatments or regimens, and characteristics of sleep in breast cancer. Furthermore, we know very little about etiological processes, vulnerability, risk, and protective factors of insomnia in breast cancer.

Sleep disturbance is common in this population, but there are many women with breast cancer that do not develop insomnia, and among those who do there are differences in severity and chronicity of the disorder. This variability in the development and evolution of insomnia in breast cancer inspires important questions: Why do some women with breast cancer develop insomnia and others do not? Why does insomnia become more severe and chronic in some breast cancer patients and not in others? Why does insomnia sometimes resolve itself with the completion of the breast cancer treatment and other times remains a problem for months or years after the treatment? Also, is there a particular type of breast cancer patient who might benefit more from a pharmacological approach to insomnia treatment versus a behavioral treatment approach? Examination of drop-out rates in behavioral therapy groups versus pharmacological groups, and the analysis of the psychological, medical, and SES characteristics between drop-out participants and complaint participants might inspire hypothesis for future studies aiming at finding the ideal treatment for the specific patient.

It is likely that the different subtypes of insomnia (e.g., primary, comorbid) and difference symptoms (initial, middle, and late) result from different etiological pathways that interact differentially with physiological, psychological, and social correlates of the breast cancer experience. To understand these processes more studies are needed to investigate the bio-psycho-social characteristics of women with breast cancer who suffer from insomnia in comparison to those without insomnia. There is a strong need for longitudinal retrospective and prospective research on psychological, medical, and social characteristics of women with breast cancer who do not develop insomnia or whose insomnia does not become chronic. Future studies need to take into account models that include vulnerability, risk and protective factors surrounding insomnia in women with breast cancer in the pursuit of a better understanding of the developmental trajectories of insomnia in breast cancer patients. Protective factors against insomnia have not been clearly identified in the literature, however a cross-sectional survey of 13,057 people conducted by Ohayon et al.,²² across the United Kingdom, Germany, and Italy revealed that being active and having a satisfying social life are related to sleeping well and are probable protective factors against insomnia. Do these factors apply to the breast cancer population? Can we use them in developing insomnia prevention programs in women with breast cancer? More research is needed to confirm or disconfirm vulnerability and protective factors for insomnia in the breast cancer population. In addition, studies that look at the relationships between insomnia and its correlates and other psychiatric disorders often expressed in the breast cancer population (e.g., depression, anxiety) are necessary to understand the relationships between different factors contributing to discomfort in this population. Greater clarity on the intricacies of the etiological phenomenology (e.g., risk, vulnerability,

and protective factor) and expression of insomnia (e.g., subtypes, and severity) as well as the relationship between insomnia and other psychiatric disorders in breast cancer patients will guide the development of effective treatments targeted to the specific needs of a specific individual, making treatment delivery enhanced, quicker, less expensive, and more efficient.

Practice Points

1. Women with breast cancer have complaints of insomnia and fatigue. There are both objective and subjective studies that report sleep disruption in this population.
2. Treatments for insomnia primarily include hypnotic drugs and behavioral treatments, mainly cognitive behavioral therapy for insomnia (CBT-I). The use of CBT-I versus pharmacological treatment for insomnia in breast cancer patients is both desirable and promising.
3. In the general population CBT-I treatments are at least as, if not more, effective compared to pharmacotherapies in reducing insomnia, and they are longer lasting.
4. In women with breast cancer CBT-I can be adapted to tackle specific symptoms, like fatigue, that are common in this population and may be related to poor sleep.
5. Pharmacotherapies have added disadvantages in breast cancer patients including possible interactions with the cancer treatment drugs, and possible individual preferences toward non-pharmacological treatments given the pharmacological burden already endured by most cancer patients.
6. Cognitive behavioral therapy for insomnia (CBT-I) combines behavioral therapies with cognitive restructuring and educational sleep hygiene, targeting the perpetuating factors (e.g., maladaptive thoughts and/or maladaptive coping attempts) of Spielman's insomnia model.

Research Agenda

Future studies on insomnia in breast cancer should investigate:

1. The bio-psycho-social vulnerability, risk and protective factors for the development and maintenance of insomnia
2. The relationships between different insomnia subtypes and cancer stages and cancer treatment
3. The relationships between different insomnia subtypes and different insomnia treatment
4. The efficacy of different insomnia treatments for different breast cancer patients (e.g., stage and type of cancer treatment)
5. Prevention programs

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Abbreviations

CBT-I, Cognitive behavioral therapy for insomnia; BzRA, Benzodiazepine receptor agonist.

References

1. Simeit R, Deck R, Conta-Marx B. Sleep management training for cancer patients with insomnia. *Support.Care Cancer* 2004;12:176–183. [PubMed: 14760542]
- * 2. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;19:895–908. [PubMed: 11157043]
3. Sleep; NIH State of the Science Conference Statement on Insomnia. Manifestations and Management of Chronic Insomnia in Adults; June 13-15, 2005; 2005. p. 1049-1058.
4. Vena C, Parker K, Cunningham M, Clark J, McMillan S. Sleep-wake disturbances in people with cancer part I: an overview of sleep, sleep regulation, and effects of disease and treatment. *Oncology Nursing Forum* 2004;31:735–746. [PubMed: 15252429]
5. Clark J, Cunningham M, McMillan S, Vena C, Parker K. Sleep-wake disturbances in people with cancer part II: evaluating the evidence for clinical decision making. *Oncology Nursing Forum* 2004;31:747–771. [PubMed: 15252430]
6. Kryger, MH. *A women's guide to sleep disorders*. McGraw-Hill; New York: 2004.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision: DSM-IV-TR*. American Psychiatric Association; Washington, D.C.: 2000.
8. American Academy of Sleep Medicine. *The international classification of sleep disorders*. American Academy of Sleep Medicine; Westchester: 2005.
9. Hublin CG, Partinen MM. The extent and impact of insomnia as a public health problem. *Primary Care Companion to Journal of Clinical Psychiatry* 2002;4:8–12.
10. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: An opportunity for prevention? *Journal of the American Medical Association* 1989;262(11):1479–1484. [PubMed: 2769898]
11. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *American Journal of Psychiatry* 1997;154:1417–1423. [PubMed: 9326825]
12. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: Results of the 1991 National Sleep Foundation Survey. I. *Sleep* 1999;22:S347–S353. [PubMed: 10394606]
13. Ishigooka J, Suzuki M, Isawa S, Muraoka H, Murasaki M, Okawa M. Epidemiological study on sleep habits and insomnia of new outpatients visiting general hospitals in Japan. *Psychiatry Clin.Neurosci* 1999;53:515–522. [PubMed: 10498235]
14. Ohayon MM, Roth T. What are the contributing factors for insomnia in the general population? *J Psychosomatic.Res* 2001;51:745–755.
15. Roth T, Ancoli-Israel S. Daytime consequences and correlates of insomnia in the United States: Results of the 1991 National Sleep Foundation Survey. II. *Sleep* 1999;22:S354–S358. [PubMed: 10394607]
16. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. *American Journal of Psychiatry* 1990;147:1189–1194. [PubMed: 2104515]
17. Agargun MY, Kara H, Solmaz M. Subjective sleep quality and suicidality in patients with major depression. *Journal of Psychiatric Research* 1997;31:377–381. [PubMed: 9306295]
18. Elsenbruch S, Thompson JJ, Hamish MJ, Exton MS, Orr WC. Behavioral and physiological sleep characteristics in women with irritable bowel syndrome. *Am.J.Gastroenterol* 2002;97:2306–2314. [PubMed: 12358249]
19. Jennum P, Drewes AM, Andreasen A, Nielsen KD. Sleep and other symptoms in primary fibromyalgia and in healthy controls. *J Rheumatol* 1993;20:1756–1759. [PubMed: 8295190]
20. Vir R, Bhagat R, Shah A. Sleep disturbances in clinically stable young asthmatic adults. *Ann.Allergy Asthma Immunol* 1997;79:251–255. [PubMed: 9305233]
21. Raiha I, Impivaara O, Seppala M, Knuts LR, Sourander L. Determinants of symptoms suggestive of gastroesophageal reflux disease in the elderly. *Scand.J.Gastroenterol* 1993;28:1011–1014. [PubMed: 8284623]
22. Ohayon MM, Zulley J, Guilleminault C, Smirne S, Priest RG. How age and daytime activities are related to insomnia in the general population: consequences for older people. *Journal of the American Geriatrics Society* 2001;49:360–366. [PubMed: 11347777]

23. Klink ME, Quan SF, Kaltenborn WT, Lebowitz MD. Risk factors associated with complaints of insomnia in a general adult population. Influence of previous complaints of insomnia. *Archives of Internal Medicine* 1992;152(8):1634–1637. [PubMed: 1497397]
24. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* 1995;18:425–432. [PubMed: 7481413]
25. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. *Social Science and Medicine* 2002;54:1309–1321. [PubMed: 12058848]
26. Silberfarb PM, Hauri PJ, Oxman TE, Schnurr PP. Assessment of sleep in patients with lung cancer and breast cancer. *J Clin Oncol* 1993;11:997–1004. [PubMed: 8487063]
27. Fiorentino L, Mason W, Parker B, Johnson S, Amador X, Ancoli-Israel S. Sleep disruption in breast cancer patients post-chemotherapy. *Sleep* 2005;28:A294.
28. Carpenter JS, Elam JL, Ridner SH, Carney PH, Cherry GJ, Cucullu HL. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. *Oncology Nursing Forum* 2004;31:591–5598. [PubMed: 15146224]
29. Savard J, Davidson JR, Ivers H, et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. *J Pain Symptom Manage* 2004;27:513–522. [PubMed: 15165649]
- * 30. Ancoli-Israel, S. Sleep and Fatigue in Cancer Patients. In: Kryger, MH.; Roth, T.; Dement, WC., editors. *Principles and Practice of Sleep Medicine*. Saunders; Philadelphia: 2005. p. 1218-1224.
31. Fortner BV, Stepanski EJ, Wang SC, Kasprovicz S, Durrence HH. Sleep and quality of life in breast cancer patients. *Journal of Pain and Symptom Management* 2002;24:471–480. [PubMed: 12547047]
- * 32. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep* 2001;24:583–590. [PubMed: 11480655]
33. Ancoli-Israel S, Liu L, Marler M, et al. Fatigue, sleep and circadian rhythms prior to chemotherapy for breast cancer. *Support Care Cancer*. 2005 in press
- * 34. Ancoli-Israel S, Moore P, Jones V. The relationship between fatigue and sleep in cancer patients: A review. *European Journal of Cancer Care* 2001;10:245–255. [PubMed: 11806675]
35. Koopman C, Nouriani B, Erickson V, et al. Sleep disturbances in women with metastatic breast cancer. *The Breast Journal* 2002;8:362–370. [PubMed: 12390359]
- * 36. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: Sleep and psychological effects. *J Clin Oncol* 2005;23:6083–6096. [PubMed: 16135475]
- * 37. Quesnel C, Savard J, Simard S, Ivers H, Morin CM. Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. *J Consult Clin Psychol* 2003;71:189–200. [PubMed: 12602439]
- * 38. Richardson A. Fatigue in cancer patients: a review of the literature. *European Journal of Cancer Care* 1995;4:20–32. [PubMed: 7620651]
39. Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. *Cancer Practice* 1998;6:143–152. [PubMed: 9652245]
40. Wittingham ML, Nail LM, Burke MB, et al. Fatigue and the cancer experience; the state of the knowledge. *Oncology Nursing Forum* 1994;21:23–36. [PubMed: 8139999]
41. Smets EMA, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory in cancer patients receiving radiotherapy. *British Journal of Cancer* 1996;73:241–245. [PubMed: 8546913]
42. Dow KH, Ferrell BR, Leigh Seal. An evaluation of the quality of life among long-term survivors of breast cancer. *Breast Cancer Res Treat* 1996;39:261–273. [PubMed: 8877006]
43. Ferrell BR, Grant M, Funk B, Garcia N, Otis-Green S, Schaffner ML. Quality of life in breast cancer. *Cancer Practice* 1996;4:331–340. [PubMed: 9128486]
44. Visser MRM, Smets EMA. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998;6:101–108. [PubMed: 9540167]
45. Stromborg MF, Wright P. Ambulatory cancer patients' perception of the physical and psychosocial changes in their lives since the diagnosis of cancer. *Cancer Nursing* 1984;7:117–130. [PubMed: 6561062]

46. Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Mental fatigue, work and sleep. *Journal of Psychosomatic Research* 2004;57:427–433. [PubMed: 15581645]
47. Liu L, Marler M, Parker BA, et al. The relationship between fatigue and light exposure during chemotherapy. *Support.Care Cancer* 2005;13:1010–1017. [PubMed: 15864659]
48. Broeckel J, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology* 1998;16:1689–1696.
49. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncology Nursing Forum* 1998;25:51–62. [PubMed: 9460773]
50. Berger AM, Higginbotham P. Correlates of fatigue during and following adjuvant breast cancer chemotherapy: a pilot study. *Oncology Nursing Forum* 2000;27:1443–1448. [PubMed: 11058976]
51. Schwartz AL, Mori M, Gao R, Nail LM, King ME. Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Med Sci.Sports Exerc* 2000;33:718–723. [PubMed: 11323538]
52. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncology Nursing Forum* 1999;26:1663–1671. [PubMed: 10573683]
53. Derogatis LR, Feldstein M, Morrow G, et al. A survey of psychotropic drug prescriptions in an oncology population. *Cancer* 1979;44:1919–1929. [PubMed: 40688]
54. Stiefel FC, Kornblith AB, Holland JC. Changes in the prescription patterns of psychotropic drugs over a 10-year period. *Cancer* 1990;65:1048–1053. [PubMed: 1967546]
55. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *Canadian Medical Association Journal* 2000;162:225–233. [PubMed: 10674059]
56. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. *Human Psychopharmacology: Clinical and Experimental* 1998;13:191–198.
57. Cervena, k; Dauvilliers, Y.; Espa, F., et al. Effect of cognitive behavioural therapy for insomnia on sleep architecture and sleep EEG power spectra in psychophysiological insomnia. *J Sleep Res* 2004;13:385–393. [PubMed: 15560773]
58. Morin CM. Cognitive-behavioral approaches to the treatment of insomnia. *Journal of Clinical Psychiatry* 2004;65(Suppl 16):33–40. [PubMed: 15575803]
59. Edinger JD, Wohlgenuth WK. The significance and management of persistent primary insomnia: the past, present and future of behavioral insomnia therapies. *Sleep Med.Rev* 1999;3:101–118. [PubMed: 15310480]
60. Jacobs GD, Pace-Schott EF, Stickgold R, Otto MW. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Arch Intern Med* 2004;164:1888–1896. [PubMed: 15451764]
61. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late life insomnia. *Journal of the American Medical Association* 1999;281:991–999. [PubMed: 10086433]
62. McClusky HY, Milby JB, Switzer PK, Williams V, Wooten V. Efficacy of behavioral versus triazolam treatment in persistent sleep-onset insomnia. *American Journal of Psychiatry* 1991;148:121–126. [PubMed: 1888345]
- * 63. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *American Journal of Psychiatry* 2002;159:5–11. [PubMed: 11772681]
64. Edinger JD, Wohlgenuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *Journal of the American Medical Association* 2001;285:1856–1864. [PubMed: 11308399]
65. Bastien CH, Morin CM, Ouellet MC, Blais FC, Bouchard S. Cognitive-behavioral therapy for insomnia: comparison of individual therapy, group therapy, and telephone consultations. *J.Consult Clin.Psychol* 2004;72:653–659. [PubMed: 15301650]
66. Berger AM, VonEssen S, Khun BR, et al. Feasibility of a sleep intervention during adjuvant breast cancer chemotherapy. *Oncology Nursing Forum* 2002;29:1431–1441. [PubMed: 12432414]

- * 67. Berger AM, VonEssen S, Kuhn BR, et al. Adherence, sleep, and fatigue outcomes after adjuvant breast cancer chemotherapy: results of a feasibility intervention study. *Oncology Nursing Forum* 2003;30:513–522. [PubMed: 12719750]
68. Cannici J, Malcolm R, Peek LA. Treatment of insomnia in cancer patients using muscle relaxation training. *Journal of Behavior Therapy and Experimental Psychiatry* 1983;14:251–6. [PubMed: 6358270]
69. Allison PJ, Edgar L, Nicolau B, Archer J, Black M, Hier M. Results of a feasibility study for a psycho-educational intervention in head and neck cancer. *Psychooncology* 2004;13:482–485. [PubMed: 15227717]
70. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B. Feasibility of exercise during treatment for multiple myeloma. *Cancer Nurs* 2003;26:410–419. [PubMed: 14710804]
71. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. *Psychosomatic Medicine* 2003;65:571–581. [PubMed: 12883107]
72. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer* 2004;100:2253–2260. [PubMed: 15139072]
73. Weze C, Leathard HL, Grange J, Tiplady P, Stevens G. Evaluation of healing by gentle touch in 35 clients with cancer. *Eur.J.Oncol.Nurs* 2004;8:40–49. [PubMed: 15003743]
74. Morin, CM. *Insomnia: Psychological Assessment and Management*. Guilford Press; New York: 1993.
75. Morin, CM.; Epsie, CA. *Insomnia: A clinician's guide to assessment and treatment*. Kluwer Academic/Plenum Publishers; New York: 2003.
76. Perlis, ML.; Jungquist, C.; Smith, MT.; Posner, D. *Cognitive behavioral treatment of insomnia*. Springer; New York: 2005.
77. Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. *Psychiatric Clinics of North America* 1987;10(4):541–543. [PubMed: 3332317]
78. Coren S. Prediction of insomnia from arousability predisposition scores: scale development and cross-validation. *Behaviour Research and Therapy* 1988;26:415–420. [PubMed: 3190651]
79. Bastien CH, Vallières A, Morin CM. Precipitating Factors of Insomnia. *Behavioral Sleep Medicine* 2004;2:50–62. [PubMed: 15600224]
- * 80. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: Immunologic effects. *J.Clin.Oncol* 2005;23:6097–6106. [PubMed: 16135476]

Table 1
An example of Spielman's three factor model of insomnia in a patient with breast cancer

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- 1 Predisposing factors:
 - a. Arousability
 - b. Decreased homeostatic sleep drive
 - 2 Precipitating factors:
 - a. Acute stress related to breast cancer diagnosis
 - b. Breast cancer treatment side effects
 - c. Surgical pain
 - 3 Perpetuating factors:
 - a. Poor bed-sleep stimulus control
 - b. Poor sleep hygiene
 - c. Maladaptive thoughts, e.g., "I will not be able to sleep tonight, which will make me miserable throughout the whole day tomorrow"
 - d. Psychological conditioning
 - e. Depression
 - f. Anxiety
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