NON-PHARMACOLOGICAL MANAGEMENT OF INSOMNIA IN CANCER PATIENTS

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Abstract

Introduction: *Insomnia is a common sleep disorder in cancer patients, characterized by a reduction in the quality or quantity of sleep. It can lead to fatigue, mood disturbances, and may contribute to immunosuppression, affecting both disease progression and quality of life.*

Materials and Methods: *In an attempt to answer the question: "Does non-pharmacological treatment of insomnia improve the quality of life in cancer patients?", we conducted a systematic search in the international databases PubMed and ScienceDirect, following the PRISMA guidelines. The search keywords were "insomnia," "sleep disorders," "cancer," and "quality of life."*

Results: *The systematic review included eight randomized trials that evaluated the effect of non-pharmacological therapies on insomnia and quality of life in oncology patients. Cognitive-behavioral therapy (CBT) is the first-line treatment with proven efficacy. Variants of CBT delivered through online platforms were found to be non-inferior in studies involving small patient groups. Another alternative treatment is acupuncture, which, while not as effective as CBT, improves sleep quality and enhances quality of life. Physical exercise, dance, nutrition programs, and psychological counseling also improve sleep and enhance quality of life compared to the usual hospital approaches.*

Conclusions: *Non-pharmacological treatment of insomnia improves the quality of life in cancer patients.*

Keywords: *insomnia, sleep disorders, cancer, quality of life, non-pharmacological treatment*

Rezumat

Introducere: *Insomnia este o tulburare a somnului frecventă la pacienții oncologici, ce implică scăderea calitativă sau cantitativă a somnului. Aceasta poate cauza oboseală, tulburări de dispoziție și poate contribui la imunosupresie, afectând evoluția bolii și calitatea vieții.*

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***Materiale și metode**: Încercând să răspundem la întrebarea: "Îmbunătățește tratamentul non-farmacologic al insomniei calitatea vieții la pacienții diagnosticați cu cancer?" am efectuat o căutare sistematică în bazele de date internaționale PubMed și ScienceDirect, respectând ghidul PRISMA. Cuvintele după care s-a efectuat căutarea au fost "insomnia","sleep disorders", "cancer "și "quality of life".*

***Rezultate:** în revizia sistematică de literatură au fost incluse 8 studii randomizate, care au evaluat efectul terapiilor nonfarmacologice la pacienții cu afecțiuni oncologice în tratarea insomniei și creșterea calității vieții. Terapia cognitiv-comportamentală este tratamentul de primă intenție, cu eficacitate dovedită. Variantele de terapie cognitiv-comportamentală cu ședințe desfășurate prin platforme online s-au dovedit non-inferioare în studii pe loturi mici de pacienți. O altă variantă de tratament alternativ este acupunctura, aceasta deși nu este la fel de eficientă ca terapia cognitiv-comportamentală, îmbunătățește și ea calitatea somnului și crește calitatea vieții. Exercițiile fizice, dansul, programele de nutriție și consiliere psihologică îmbunătățesc somnul și cresc calitatea vieții în comparație cu abordarea uzuală din spitale.*

***Concluzii:** Tratamentul non-farmacologic al insomniei crește calitatea vieții la pacienții diagnosticați cu cancer.*

***Cuvinte cheie:** insomnia, tulburări de somn, cancer, calitatea vieții, tratament non-farmacologic.*

Introduction

Insomnia is common among cancer patients. This sleep disorder involves a decrease in the quality or quantity of sleep, characterized by difficulty in falling asleep, frequent awakenings, or early morning awakening with the inability to return to sleep, occurring at least three nights a week for at least three months. It causes significant impairments or affects normal daytime functioning[1]. Insomnia can lead to fatigue, mood disturbances, and may contribute to immunosuppression, impacting disease progression and quality of life[2]. In patients with advanced cancer, insomnia can be exacerbated by various factors such as pain, depression, and anxiety. Moreover, insomnia can cause daytime fatigue, which in turn can lead to brief periods of sleep that further

contribute to insomnia, creating a vicious cycle[2,3].

Adverse effects of cancer treatment and psychological dysfunctions related to cancer can also lead to sleep disturbances, while pre-existing sleep disorders at the time of diagnosis are another predictive factor for insomnia[4]. Diagnosis is made through patient history, which includes sleep history (sleep habits, sleep environment, circadian factors), questions about somatic and mental health, the use of sleep questionnaires and diaries, physical examination, and additional methods if deemed necessary (blood tests, electrocardiogram, electroencephalogram, polysomnography)[5].

Treatment is multimodal, including both pharmacological and non-pharmacological therapies. It is essential to identify and treat factors contributing to insomnia, such as pain, depression, anxiety, delirium, nausea, as well as the side effects of certain medications or withdrawal syndromes (corticosteroids, opioids, anticonvulsants, caffeine, hormones, herbal medicines, barbiturates, benzodiazepines, alcohol, tricyclic antidepressants)[2,6]. The "National Comprehensive Cancer Network" Palliative Care Guidelines recommend cognitive-behavioral therapy for Insomnia (CBT-I) as the first-line treatment, with the addition of pharmacological therapy (antipsychotics, sedatives/hypnotics, antidepressants, alpha-adrenergic receptor blockers, or melatonin receptor agonists) only for refractory sleep disorders[6].

CBT-I targets behavioral, cognitive, and psychological factors, aiming to modify distorted behaviors and beliefs about sleep. It can be delivered as individual or group therapy, face-to-face, or in digital formats, either guided or unguided[7]. An alternative therapy studied in the literature is acupuncture, which improves sleep quality and increases sleep duration. Existing data suggest that its effects are due to the regulation of neurotransmitters in the central nervous system (amines, amino acids, and peptides), modulation of certain cytokines (TNF-α, IL-6, and IL-1β), and regulation of hormones associated with the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis[8].

Other therapies found in complementary and alternative medicine include herbal therapy, nutrition, yoga, tai chi, and mind-body practices[9]. Studies have shown that insomnia can be both a risk factor and a consequence of cancer. Some data on the molecular mechanisms associated with insufficient sleep in cancer patients suggest that it may play a role in carcinogenesis and cancer progression[10].

Considering the role of insomnia in the progression of cancer, the multitude of factors that can influence sleep, the direct relationship between sleep disorders and other symptoms such as depression, pain, and anxiety, and the large number of pharmacological treatments necessary for cancer patients that can also cause or exacerbate sleep disturbances, we aim to conduct a systematic review to synthesize the available literature on the association between non-pharmacological treatment of insomnia and improved quality of life in these patients.

Materials and Methods

Research Question

In an attempt to answer the question: “Does non-pharmacological treatment of insomnia improve the quality of life in cancer patients?”, we conducted a systematic search in the international databases PubMed and ScienceDirect, following the PRISMA

guidelines[11]. The keywords used for the search were "insomnia," "sleep disorders," "cancer," and "quality of life."

Inclusion and Exclusion Criteria

The inclusion criteria were: quality and quantity of sleep measured with specific or non-specific validated questionnaires that included sleep-related subitems, histopathologically confirmed cancer diagnosis, quality of life measured with validated instruments, non-pharmacological therapeutic intervention, and the following study characteristics: randomized trials, open access, published in English, and published in the last five years (2019–2023).

Exclusion criteria included non-open access articles, studies that did not include cancer patients or did not refer to non-pharmacological therapeutic interventions, studies that did not use validated sleep or quality of life measurement tools, and case studies or non-randomized studies, which were excluded to minimize systematic bias. Additionally, articles published in languages other than English and those published before 2019 were excluded.

Selection Process Flowchart

Potentially relevant articles were identified (n=8,878), duplicates were removed (n=453), and articles not published in English were excluded (n=10: French n=8 and Spanish n=2). The remaining articles were evaluated based on titles and abstracts, and book chapters, literature reviews, and case studies were excluded (n=5,640).

Next, articles without open access (n=2,113), those published before 2019 (n=295), and non-randomized studies (n=220) were excluded. The remaining articles were fully reviewed, and those that did not use validated tools for measuring sleep quality, quantity, or quality of life, those that did not refer to non-pharmacological therapeutic interventions, or those that did not include cancer patients were excluded (n=139). A total of 8 studies were included in the literature review (Figure 1).

Systematic Bias

Randomized studies were included in the literature review in an attempt to reduce systematic bias; however, not all studies had a control arm, with some comparing two interventions. Four studies included patients with different cancer types, three studies included only breast cancer patients, and one study included only pancreatic cancer patients, though at different stages and with different prognoses. Additionally, some studies did not include in their final analysis patients who withdrew from the study or were lost to follow-up.

Results

Only 8 studies were included in the systematic literature review, despite a comprehensive search in two databases, highlighting that there are few studies analyzing the link between insomnia and

quality of life in cancer patients. There was heterogeneity among the subjects, with different cancer locations, varying disease stages, and some subjects undergoing treatment (most frequently chemotherapy, but also radiotherapy or surgical treatment) or immediately post-treatment. Most of the extracted data referred to women diagnosed with breast cancer.

For each study, the first author's name, year of publication, measurement tools used, study design, non-pharmacological intervention, measurement frequency, and study outcomes were extracted, and these data are summarized in Table 1. Table 2 presents data on the number of patients enrolled in the study, the primary cancer location (Figure 2), and stage (Figure 3), as well as participant characteristics: education level (Figure 4), gender (Figure 5), and marital status or presence of a partner (Figure 6).

Insomnia in the selected studies was measured using specific tools: the **Insomnia Severity Index (ISI)**, consisting of 7 questions evaluating sleep disturbances over the last two weeks, with a 5-point scale (0-4). The higher the score, the more severe the insomnia. A score above 14 was established as the optimal cut-off for diagnosing insomnia. The **Pittsburgh Sleep Quality Index (PSQI)**, consisting of 19 questions, refers to sleep quality and disturbances over the last month. A higher score indicates lower sleep quality, with a score above 5 indicating a sleep disorder[15,20]. Studies that used general questionnaires, but which included sleep-related questions (PAN26, QoL-C30), were also included.

Quality of life was measured using **FACT-B (Functional Assessment of Cancer Therapy-Breast Cancer)**, which includes 37 questions across 5 subscales (physical, social/family, emotional, functional, and concerns related to breast cancer). The **EORTC QLQ-C30** contains 30 questions distributed across 5 functional scales (physical function, role performance, emotional function, cognitive function, and social function), 5 symptom scales (fatigue, pain, nausea/vomiting, sleep problems, appetite loss, constipation, and diarrhea), and general health status[16]. Another tool used was the **Patient-Reported Outcomes Measurement Information System (PROMIS)**, which measures pain, fatigue, physical function, emotional stress, and social roles. This system collects information on symptoms, function, emotions, and perceptions directly from patients, without additional interpretation[15,21].

In patients with breast cancer, gynecological cancers, or hematologic cancers, sleep characteristics (excluding insufficient sleep duration) were associated with quality of life in the physical component, with patients suffering from sleep disorders having lower HRQoL-PCS scores. The psychological component was similar between patients with sleep disorders and those without[12].

Another study that included women with breast cancer demonstrated a significant improvement in quality of life in the arm of patients who received short-term cognitive-behavioral therapy for insomnia (CBT-I), compared to the arm that only received nutritional education and chemotherapy side effect management. In the CBT-I group, ISI scores decreased, while FACT-B scores increased[17]. A study conducted in breast cancer patients undergoing chemotherapy analyzed the effects of dance therapy on sleep disorders and quality of life. The intervention consisted of 6 instructed dance sessions at the hospital and 16 weeks of dancing at home, compared to usual care.

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Following the intervention, fewer sleep disturbances and improved quality of life were reported in the intervention group compared to the control group. However, the study also reported a decrease in quality of life in both arms compared to baseline[19].

In pancreatic cancer patients who underwent a 6-month physical exercise training program, there was a reduction in sleep disturbances and an improvement in quality of life at 3 months (measured with EORTC-C30), but these effects were not maintained at 6 months[16].

Specialty guidelines recommend cognitive-behavioral therapy as the first-line treatment, with proven efficacy in improving sleep. This was compared with an alternative version of CBT-I (StepCBT-I), where patients with an ISI score between 8 and 15 received online CBT-I, reading weekly information published on a website and watching a video, while those with an ISI score above 15 received 6 weekly CBT-I sessions.

The ISI score was then reevaluated, and patients with a score below 8 did not receive further treatment. Patients with a higher score or who used hypnotic medication more than one night per week received 3 additional individual CBT-I sessions. In both study arms, patients reported lower insomnia rates, which were maintained during follow-up, and improved quality of life, which remained significantly elevated over the next 12 months[18]. Another non-pharmacological therapy used in insomnia treatment is **acupuncture**, which involves stimulating specific points on the body with needles. Acupuncture was compared head-to-head with CBT-I in a study that included cancer patients with an ISI score above 7. Both treatment methods showed reductions in ISI scores and improvements in sleep during treatment and at 20 weeks of follow-up. While acupuncture was more effective in increasing total sleep time, CBT-I was more effective in reducing insomnia severity (improving sleep quality, reducing sleep onset latency, and decreasing wakefulness after sleep onset), and quality of life improved in both groups. CBT-I proved more effective for educated white males without baseline pain[15].

Another study compared an active acupuncture regimen with a simulated acupuncture regimen, using points located 1-2 cm away from the actual acupuncture points, which are not effective in treating insomnia. Participants received 15 treatment sessions. Both groups showed improved sleep quality, with fewer awakenings after sleep onset and an improvement in quality of life[13].

In patients with gynecological tumors undergoing chemotherapy, standard treatment was compared with a psychological nursing approach, which involved establishing a good nurse-patient relationship, building trust,

psychological counseling, relaxation therapy, and guiding family or social support to show a positive attitude. Both groups showed a decrease in PSQI scores, with lower scores in the intervention group compared to the control group, which were associated with improved quality of life (higher FACT-B scores in the intervention group)[14].

Discussion

Pharmacological treatment for insomnia can be associated with adverse effects, such as cognitive impairment and accidental falls. In cancer patients, who represent a vulnerable population, they may present with multiple symptoms requiring complex treatments, with an increased risk of drug interactions. Moreover, these patients may also have renal or hepatic insufficiency, and adverse reactions may be more frequent in those over 65 years of age[22]. Non-pharmacological therapy can be a valid and effective alternative for these patients.

In the studies reviewed, most of the data referred to cognitive-behavioral therapy (CBT-I), which has proven efficacy and is recommended as a first-line treatment in the NCCN guidelines[6]. However, this can be difficult to access for patients who do not live in large cities or have mobility issues. In this context, StepCBT-I, a hybrid form of therapy combining face-to-face sessions with online sessions based on the ISI score, becomes a viable alternative.

This approach demonstrated non-inferiority to CBT-I in a study conducted on 177 patients, both in treating insomnia and improving quality of life[18]. Given the small sample size, further studies with larger patient cohorts are necessary to confirm if the reduction in insomnia-related symptoms and the improvement in quality of life can be sustained.

Another alternative is acupuncture, which, although not superior to CBT-I in treating insomnia, did reduce sleep disturbances, improve sleep quality, and was just as effective as CBT-I in reducing fatigue, depression, and improving quality of life. Acupuncture was more effective than CBT-I in reducing pain[15]. When compared to sham acupuncture, although it did not demonstrate superiority in reducing ISI scores, it improved total sleep time, sleep efficiency, anxiety, depression, and quality of life[13].

Psychological nursing programs, which included building a strong nurse-patient relationship, patient trust enhancement, targeted psychological counseling by the nurse, psychological relaxation, and family and social support, as well as physical exercises and dance, improved sleep quality and quality of life compared to the usual hospital approach[12,14,16,19].

Cancer patients represent a heterogeneous population, and most of the data found in the literature refer to women diagnosed with breast cancer, with fewer data available for other cancer locations (Figure 2). Most patients had early-stage cancers (Figure 3), with inclusion criteria often requiring a life expectancy greater than one year and no metastases. Thus, patients with advanced cancer were excluded, even though they are a group with multiple associated symptoms, such as pain, fatigue, constipation, nausea, and complex pharmacological treatments, who could benefit from non-pharmacological therapies.

Data regarding pancreatic cancer, which is characterized by aggressiveness and rapid metastasis, show that although quality of life improved after three months following the proposed exercise program, this improvement was not sustained at six months[16], possibly

due to disease progression. Another group of patients excluded from the studies were those with pre-existing sleep disorders, such as obstructive sleep apnea, who are at high risk of developing insomnia and could also benefit from non-pharmacological treatments in addition to their treatment for the underlying sleep disorder.

The outcomes of non-pharmacological sleep disorder treatments could also be influenced by the concomitant medication taken by patients, as most studies excluded patients receiving pharmacological treatment. One study that included participants (23.8%) on psychotropic medication (antidepressants) and hypnotics or sedatives showed a reduction in dosage and frequency of medication use[15]. Other factors that may influence treatment response and quality of life include marital status or the presence of a life partner (Figure 6), education level (Figure 4), and gender (Figure 5). For example, CBT-I was more effective for white males with a higher education level compared to those with lower education levels or female patients, regardless of education level. The study arm that received CBT-I included 80 patients, of which only 32 were male[15], emphasizing the need to analyze patient characteristics in larger cohorts.

One of the included studies, which investigated dance therapy in patients undergoing adjuvant chemotherapy, reported a decrease in quality of life in both arms of the study compared to baseline. However, the decrease was smaller in the intervention arm than in the control arm[19]. A possible cause could be that the baseline was established before the initiation of chemotherapy, with chemotherapy's adverse effects potentially explaining the decline in quality of life.

Cognitive-behavioral therapy is the first-line and preferred treatment when accessible, but other interventions have also demonstrated efficacy in improving sleep, reducing insomnia-associated symptoms, and enhancing quality of life. Thus, physical exercise, dance, acupuncture, lifestyle changes, and psychological support provided by the medical team are valid, easily implemented options.

These results are consistent with findings from previous reviews and meta-analyses. A meta-analysis published in 2023 that studied the effect of physical exercise on the quality of life of cancer patients demonstrated that high-intensity exercise (performed at least twice a week, for a minimum of 120 minutes per week, with an intensive component of at least 15 minutes) improves quality of life and provides physical, cognitive, and social benefits while reducing fatigue, pain, dyspnea, and insomnia[23]. Another literature review that evaluated insomnia in breast cancer patients highlighted the effect of insomnia on quality of

life and the efficacy of CBT-I in improving sleep quality, with effects maintained for up to 12 months[24].

The limitations of this literature review are the small number of identified studies, the exclusion of studies published in languages other than English, and the heterogeneity of the included patients, with different education levels, primary cancer sites, stages, treatment types, and prognoses. The tools used to measure insomnia and quality of life varied by study, and although the reviewed studies were randomized, comparisons were made with cognitive-behavioral therapy, which is the standard non-pharmacological treatment in only two studies. The rest compared usual hospital care with non-pharmacological therapies, such as acupuncture, physical exercise, dance, and various counseling and nutrition programs.

Conclusions

Non-pharmacological treatment of insomnia improves the quality of life in cancer patients. Although cognitive-behavioral therapy is the preferred therapeutic option, when it is not available, modified versions, such as online sessions, or other non-pharmacological interventions like acupuncture, physical exercise, and dance can be used. While these alternatives are not as effective as cognitive-behavioral therapy, they can still improve sleep quality and overall quality of life in this patient population.

Based on the evaluated data, it is recommended that the medical team treating oncology patients assess sleep quality and quantity to diagnose insomnia, provide psychological support and counseling to improve lifestyle, and recommend non-pharmacological therapy when deemed necessary. Additionally, we believe that further studies on larger patient cohorts are needed to evaluate these therapies head-to-head.

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