

Disturbed Sleep And Prevalence Of Clinical Insomnia Among Italian Breast Cancer Women: A Pilot Study.

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ABSTRACT

Breast cancer patients frequently reported sleep problems. Limited evidences were found for the effects of radiation therapy, chemotherapy and hormone therapy on sleep quality; also the prevalence of sleep disorders remains unclear. The aims of this study were to measure the prevalence of clinical insomnia among patients with breast cancer and to describe the characteristics of poor sleep; to determine whether patients with clinical insomnia and those without differ in physiological, cognitive, and behavioural habits, and in relation to taking psychoactive drugs and natural remedies to treat sleep problems. **Methods:** 141 consecutive patients with breast cancer, women, (mean age = 61.81 ± 11.64) were required to complete: Insomnia Severity Index (ISI), Sleep Disturbance Questionnaire, Hospital Anxiety and Depression Scale and three measures of cancer severity, curability perception, and quality of life. ISI score >14 was categorised as clinical insomnia. **Results:** In a fully adjusted logistic regression model clinical insomnia was independently associated with the effort to sleep, mental overactivity, use of psychoactive drugs to control sleep problems, when adjusted for age, lymphoedema, joints pain, tamoxifene, hormone therapy, psychological disease as measured by HADS. **Conclusion:** patients with clinical insomnia had cognitive preoccupations about sleep and used less frequently psychoactive drugs to treat sleep problems. Despite the limited time for a routine clinical care, the clinicians must posed more attention to recognized and treated sleep problems. Future research must be developed to study the effectiveness of interventions designed to develop and improve habits and behaviours for a better sleep efficiency in patients with poor sleep.

Keywords: breast cancer, clinical insomnia, psychoactive drug, sleep disorders.

INTRODUCTION

Cancer patients frequently reported abnormal sleep-wake cycle [1-4]. The reasons for trouble in sleeping are been traced back to physical changes caused by cancer surgery, side effects of the radiation therapy, chemotherapy, hormonal therapy, long-term use of certain drugs, as well as psychological diseases, as anxiety and depression, about having cancer [5-7].

In 2001, Savard and Morin [8] have reported that insomnia was a really diffuse and neglected problem in cancer. More than 10 years later, Otte and colleagues [9] reviewed 254 English-language articles about sleep disorders stating that “the prevalence of particular types of sleep disorders in cancer remains unclear”. Sleep disorders are more prevalent in patients with cancer than in people without cancer [10 Davis MP, Goforth HW]. Among women with metastatic breast cancer, 63% reported one or more types of sleep disturbance [10], associated with depressive symptoms and pain. In most of the studies on sleep characteristics in patients with breast cancer there were no objective measure evaluating sleep and also accurate sleep disorders definition was lacking.

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), sleep-wake disorders encompass 10 conditions manifested by disturbed sleep and causing distress as well as impairment in daytime functioning. The core features of each disorder relate to the patient's dissatisfaction regarding the quality, timing, and amount of sleep with resulting daytime distress and impairment. Persistent insomnia is defined as problems initiating and/or maintaining sleep at least three nights/week accompanied by daytime distress or impairment. The inability to concentrate and to recover information from memory, as well as by the tendency to be irritable, depressed, and anxious, increase risk for mental health and physical problems, and decreased quality of life [11-13].

At this regard, the principal aims of this pilot study were to measure in a sample of breast cancer patients out of surgery, radiation therapy and/or chemotherapy, treated or no-treated with hormonal therapy: (1) the prevalence of clinical insomnia and sleep disturbances; (2) the use of pharmacological and natural remedies to treat sleep problems, the co-presence of anxiety and depression, joint pain, and hot flashes; (3) the study variables associated with clinical insomnia.

MATERIALS AND METHODS

One hundred forty-one patients with breast cancer, mean age 61.81 years (standard deviation, SD = 11.64), were consecutively enrolled in this single center, cross-sectional study, during their scheduled visit at the Day Hospital of the Department of Oncology, IDI in Rome. A clinician gave information about the study, and obtained study consent from patients. After the visit, a researcher gave patients the questionnaires and they individually completed them. If necessary, help was provided by clinical staff. Inclusion criteria were: postmenopausal breast cancer patients, aged more than 18 yrs, radiation therapy and chemotherapy terminate, written informed consent.

Instruments

- The Insomnia Severity Index (ISI) [14,15] is a brief self-report screening measure of the patient's perception of insomnia, and it is used as an outcome measure in treatment research. The questionnaire measures symptoms and consequences of insomnia in the last 2 weeks. The items' content corresponds in part to the diagnostic criteria of the insomnia in DSM-5. The ISI is composed of seven items that evaluate (a) the severity of sleep-onset (initial), (b) sleep maintenance (middle), (c) early morning awakening (terminal) problems, (d) satisfaction with current sleep pattern, (e) interference with

daily functioning, (f) noticeability of impairment attributed to the sleep problem, and (g) level of distress caused by the sleep problem. Each of these items is rated on a 0-4 scale and the total score ranges from 0 to 28. Patients that reported ISI score >14 are probable cases affected by clinical insomnia. In our study, the internal consistency of the scale was $\alpha = 0.86$.

- The Sleep Disturbance Questionnaire (SDQ) [16,17] is a 12-item scale designed to evaluate subjective experiences of usual sleep habits and sleep disturbance. The items are grouped into four factors: restlessness/agitation, inadequate sleep pattern, mental overactivity, effort to sleep. Each item is answered on a 5-point scale (“never true”, “seldom true”, “sometimes true”, “often true”, “very often true”). Subjects are asked to rate items in relation to typical nights when they do not sleep well, and to specify if each problem was happened at least three nights per week for at least 3 months. In our study, the internal consistency of the scale was $\alpha = 0.87$.
- The Hospital Anxiety and Depression Scale (HADS) [18] was used to measure anxiety and depression status. HADS total score ≥ 11 has been considered positive for psychological disease. In this study, the internal consistency of the scale was $\alpha = 0.91$.
- Cancer curability, cancer severity, and quality of life (qol) were assessed with three 10-point visual analogue scales (VASSs) that ranges from 1 (low) to 10 (high) to assess the degree of patient perception of cancer curability and severity, and qol [19].

We also collected information about patients use of pharmacological and natural remedies used for sleeping, using 4 items. (1) During the last 30 days how many times have you used some kind of pharmacological remedies in order to sleep better? (2) During the last 30 days how many times have you used some kind of natural remedies in order to sleep better? Possible responses were: never, less than two times a week, several times a week, almost everyday, everyday. For each of the two items patients were requested to write the name of the remedies used.

In addition to these measures we collected data regarding joint pain, lymphoedema, and deficit in memory. demographic and clinical data were also collected.

The Committee of Ethics of the hospital approved the study protocol.

For analysis purpose, patients were subdivided into three groups with respect to age (<55;55-65;>65), into two categories for years of education (≤ 8 years of school versus >8 years of school). Data about curability, severity, and qol were dichotomised (score ≤ 5 versus >5). Data about joint pain and lymphoedema were also dichotomised (absent versus present), as data about pharmacological and natural remedies used, due to their heterogeneity. From the sample distributions a median split on the four SDQ factors were taken to create two groups (low versus high characteristic).

The internal consistency of the scales was estimated with a Cronbach alpha coefficient by the item-total correlations.

Multivariate odds ratios (ORs), and associated 95% confidence intervals (CIs) for potential variables associated with ISI-defined case of clinical insomnia (ISI score >14) were estimated using logistic regression models. Age, joints pain, lymphoedema, hormone therapy, tamoxifene and psychological disease, as measured by HADS, were treated as confounding variables.

All statistical analyses have been performed using STATA, version 11.0 (StataCorp, College Station, Tex).

RESULTS

Among 141 patients, 22 (15.61%) reported an ISI score >14 and were classified as probable cases of clinical insomnia. Of them, 19 (13.48%) had moderate insomnia, with ISI score between 15 and 21, and 3 (2.13%) had severe insomnia, with ISI score ranging 22-28.

Fifty-three patients (37.59%) had sub-threshold insomnia, with ISI score between 8 and 14. Sixty-six patients (46.81%) did not report any insomnia. In Table 1 are reported demographic and clinical characteristics of the sample in study, separately by clinical insomnia.

As shown in Table 2 there were different types of sleep problems, those related to the onset (N=57, 40.43%), to the maintenance (N=64, 45.39%), and to falling asleep (N=45, 31.91%).

Forty-eight (34.04%) patients reported HADS total score ≥ 11 .

Forty-three patients (30.50%) had lymphoedema, 119 (84.40) were in hormone therapy at the time of the study. 97 (68.79%) reported joint pain and 38 (26.95) deficit in memory. 26 (18.4%) perceived their disease as difficult to treat (score >5), and 50 (35.5%) as severe (score >5) despite 105 (74.5%) were satisfied of their qol (score >5).

Among 37 that have used psychoactive drugs in the last 30 days, 34 (91.89%) used some benzodiazepine, 2 a Selective Serotonine Reuptake Inhibitor (SSRI), and 1 a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA), all drugs have some ipnogico effect.

Among 32 that have used natural remedies to contrast sleep problems, 15 (10.64%) consumed chamomile, 8 (5.67%) melatonin, 3 (2.13%) valerian, 3 (2.13%) herbal tea, and 3 (2.13%) back flowers. No significant association between clinical insomnia and joint pain was found. Furthermore, the women reporting joint pain did not use psychoactive drug more frequently (p-value 0.851).

As shown in Table 2, patients with clinical insomnia showed more dysfunctional habits as measured by SDQ domains (p-values, <0.001) compared to patients without clinical insomnia. In a fully adjusted logistic regression model clinical insomnia was independently associated with the effort to sleep (OR=9.83; 95%CI 2.42-39.91), mental overactivity (OR=5.24; 95%CI 1.20-22.82), the use of psychoactive drugs to control sleep problems (OR=0.12; 95%CI 0.03-0.60), partially with sleep pattern (OR=3.26; 95%CI 0.87-12.25) and not with natural remedies use (OR=1.45; 95%CI 0.77-5.43), when adjusted for age, lymphoedema, joints pain, tamoxifene, hormone therapy, psychological disease as measured by HADS.

DISCUSSION

In our sample, disruption of a normal sleep pattern is common in a substantial proportion of patients, women, with breast cancer surgery, radiation therapy, and chemotherapy (taxane or other) done, in hormone therapy treatment or not. More than 15% are probable cases of clinical insomnia as measured by ISI, considered the gold standard for insomnia among the self-reported instruments to measure sleep disturbances.

The comparison with published results is not easy. Difficult in comparability is due to the heterogeneity of the study samples, the lack of definition of sleep disorders, the use of different diagnostic instruments or measures, the difference in time points for assessing sleep disorders, the concurrent occurrence of other symptoms. The prevalence of sleep disturbances varied among different types of cancer. In a recent study on 2862 cancer outpatients [1] 30% reported sleep problems. Patients with lung cancer had the highest prevalence of general sleep

problem, while patients with breast cancer had a high prevalence of insomnia [20 Davidson et al.]. Among 300 women with breast cancer, 19% met the criteria for insomnia [8]. This estimated prevalence of insomnia is consistent with that of 18.6% reported in a recent study on 413 breast cancer patients treated with aromatase inhibitors [2].

We have found two cognitive variables independently associated with clinical insomnia, the SDQ-effort to sleep and SDQ-mental overactivity. There are different results for most of the covariates associated with clinical insomnia. In our sample, age, hormone therapy treatment, joint pain and lymphoedema did not result associated with insomnia, differently from other authors. Desai et al. [2] found that clinical insomnia was independently associated with severe joint pain, hot flashes, anxiety, depression, age >65 years, and time since breast cancer diagnosis 2-5 years. Espie [16] reported worries as the most frequently identified contributors to insomnia.

In our sample, more than 36% of patients used psychoactive drugs and/or natural remedies to relieve sleep disturbances. Only patients that didn't use psychoactive drugs, as remedies to sleep, were also patients with clinical insomnia. Differently, Desai et al. [2] noted that clinical insomnia was more common among patients that used medication for treating insomnia. Probably, these medications did not help patients. Our patients used psychoactive drug with hypnagogic effect, like benzodiazepine, that seems help them enough since they did not have clinically significant insomnia.

Using both ISI and SDQ in the future research on insomnia could help researchers to investigate the role of the sleep related cognitive characteristics, to confirm or not the association with specific pharmacological treatment.

In conclusion, our results reinforce the conviction that clinicians must put more attention in diagnosis and appropriate treatment of a common side effect as sleep problems. Disturbed sleep is modifiable, to cure sleep disturbances could mitigate patients' discomfort and it might help to provide optimal cancer care. The principal obstacle for the correct assessment of side effects in cancer patients is the lack of time in clinical routine care. In the future, the implementation of standardized form to record all symptoms that patients experienced, but that they didn't report, could improve the medical practice.

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AUTHOR'S DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST

The authors indicated no potential conflicts of interest.

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