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Hypnotic Use for Sleep Disturbances in Breast Cancer: A Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author LTA designed the study, managed the literature search, and wrote the first draft of the manuscript. Author IG and author JR designed the study and revised the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Aims: Sleep disturbances are common in patients with breast cancer. The aim of this systematic review was to present the literature on pharmacological interventions against sleep disturbances and use of hypnotics in patients with breast cancer. We wanted to study patients both in the perioperative period as well as when they were receiving oncological (medical) treatment.
Study Design: Systematic review.
Methodology: According to the PRISMA guidelines, a literature search was performed on May 10th 2012 in Pubmed and Embase. Primary outcomes were pharmacological interventions against sleep disturbances. No restriction on publication status was made. Only articles in English were included. Case reports and studies with less than ten patients were excluded.
Results: Five studies met the inclusion criteria and were included in the review. One study investigated pharmacological intervention in the perioperative period and showed that treatment with triazolam significantly improved sleep three consecutive nights after surgery. Two studies investigated patients undergoing endocrine oncological treatment. The studies showed that zolpidem combined with an SSRI/SNRI improved sleep in patients having hot flashes, and that hypnotics were prescribed significantly more often in patients undergoing endocrine treatment compared with healthy patients not receiving endocrine treatment. Two studies investigated patients receiving

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chemotherapy. The studies showed that hypnotics were prescribed to almost every second patient. Prior users of hypnotics and patients with a psychiatric diagnosis were more likely to take hypnotics during chemotherapy.

Conclusion: Sleep disturbances occur frequently in patients with breast cancer indicated by the high prevalence of hypnotic use. It therefore is of concern that only few clinical trials exist on pharmacological intervention against sleep disturbances in the different treatment time periods. At present, there is insufficient evidence to recommend one single pharmacological intervention in this patient group.

Keywords: Breast cancer; sleep disturbances; hypnotics.

1. INTRODUCTION

Improved surgical and oncological treatment is leading to increasing survival rates in patients with breast cancer, leading to an increased focus on the physiological factors and stress associated with a life-threatening disease [1,2]. Sleep disturbances have been reported in 51-63% of patients with breast cancer [3–6]. Furthermore, 18-39% of the patients with breast cancer meet the criteria for having insomnia syndrome [5,6] (a heterogonous syndrome involving difficulties initiating and maintaining sleep and with impairment of daytime functioning) [7]. In the general population 1/3 has sleep disturbances and the prevalence of insomnia syndrome is about 6% [8]. Despite the high prevalence of sleep disturbances in patients with breast cancer, and in other cancers as well, there are no international guidelines in the treatment of sleep disturbances in this group of patients. In addition, it has not been systematically investigated, whether pharmacological interventions might have a positive or negative impact on quality of life and morbidity in this patient group. Sleep disturbances have an impact on quality of life (QOL) [9,10] and may be associated with the development of clinical depression, depressive symptoms and anxiety [11]. In some studies, it has been suggested that sleep disturbances can lead to decreased pain threshold [12], excessive fatigue and disturbed immune function [13,14]. Sleep disturbances in patients with breast cancer are usually treated pharmacologically with hypnotics [15–17]. However, the effects of pharmacological interventions against sleep disturbances in patients with breast cancer have not been extensively investigated.

This systematic review provides an overview of the studies regarding use of pharmacological intervention on sleep disturbances in patients with breast cancer, both in the immediate postoperative period as well as later when the patients are in adjuvant treatment with endocrine treatment and/or chemotherapy.

2. METHODS

The literature search was performed according to the PRISMA guidelines [18]. A librarian, specialized in search of medical literature, and the principal author performed the search. The population was limited to patients with breast cancer. Primary outcomes were pharmacological interventions on sleep disturbances. According to the Anatomical Therapeutic Chemical (ATC) classification system the main group of hypnotics is N05C. Pharmacological interventions based on melatonin were not included. No restriction on publication status was made. Only articles in English were included. Case reports and studies with less than ten patients were excluded from the review.

We searched Pubmed and Embase on May 10th 2012 supplemented by manual reference list searches. Keywords used were (breast cancer OR breast neoplasms) AND (sleep disturbances OR sleep disorders OR sleep disorder OR sleeping disorders OR sleep disturbance OR insomnia OR Sleep Initiation and Maintenance Disorders OR sleep) AND (sleeping aids OR sleeping aid OR Hypnotics and Sedatives OR hypnotics OR sedatives OR psychotropic drugs OR psychotropic drug OR psychotropic). The keyword "drug" was replaced with "agent" in Embase.

3. RESULTS

42 articles were identified in the Pubmed database and 34 studies in Embase. One article was included through manual search of the reference lists. Seven duplicates were removed and 70 articles were screened. Based on titles and abstracts, 31 studies did not meet all the inclusion criteria, and were excluded. Based on language, one study was excluded. Based on study design, one study was excluded. 37 articles were assessed for eligibility and 32 studies did not meet all the inclusion criteria and were excluded. Thus, five studies were included in this systematic review (Fig. 1). Information was extracted from each included study regarding population, treatment during study, intervention, and primary and secondary outcome measures (Table 1). One study investigated sleep disturbances in patients in the immediate postoperative period, two studies investigated sleep disturbances in patients in treatment with chemotherapy, one study investigated patients undergoing endocrine therapy, and one study investigated patients in endocrine therapy or in chemotherapy, though with the vast majority in endocrine therapy. Due to this heterogeneity between the included studies, these were analysed and discussed in three different groups.

3.1 Perioperative Period

The effect and safety of the benzodiazepine triazolam on sleep after surgery for breast cancer was investigated in a randomized double-blind placebo controlled study (RCT) [19]. The primary outcome was daily sleep measurements (difficulty falling asleep, morning restfulness and sleep quality) on 100 mm visual analogue scales (VAS) and estimates on time required to fall asleep and nightly awakenings. The secondary outcome was adverse reactions reported by the patients or reviewed in the charts. There was no clinical testing of psychomotor–type adverse reactions and withdrawal effects were not evaluated. The study included 100 patients undergoing surgery for breast cancer, had no history of clinical sleep disorders and who had received triazolam 0.125 mg the evening prior to surgery. They were randomly assigned to receive triazolam 0.125 mg (n = 49) or placebo (n = 51). Depending on the patients' alertness the evening on the day of surgery, they received the first dose of study medication on the same evening or the evening after surgery. They received study medication for three consecutive evenings. The patients who received triazolam had significantly less difficulty falling asleep ($p = 0.002$), had fewer nightly awakenings ($p = 0.004$), were more rested in the mornings ($p = 0.008$) and the overall sleep quality was better ($p = 0.001$). The above listed significant differences in sleep parameters were most evident on the first night after surgery. There was no significant difference between the two groups on estimates of the time required to fall asleep ($p= 0.14$). A dose-response relationship existed when there was an increase in triazolam dose to 0.25 mg ($p < 0.05$) with a significant improvement in all sleep measurements (difficulty falling asleep, nightly awakenings, morning restfulness, sleep quality and time to fall asleep). Adverse reactions were seen in both groups. Drowsiness was the most reported adverse reaction, 35% in the triazolam group and 39% in the placebo group with no significant differences in adverse reactions

between the two groups. Patients who received placebo reported insomnia more frequently as an adverse reaction ($p < 0.05$).

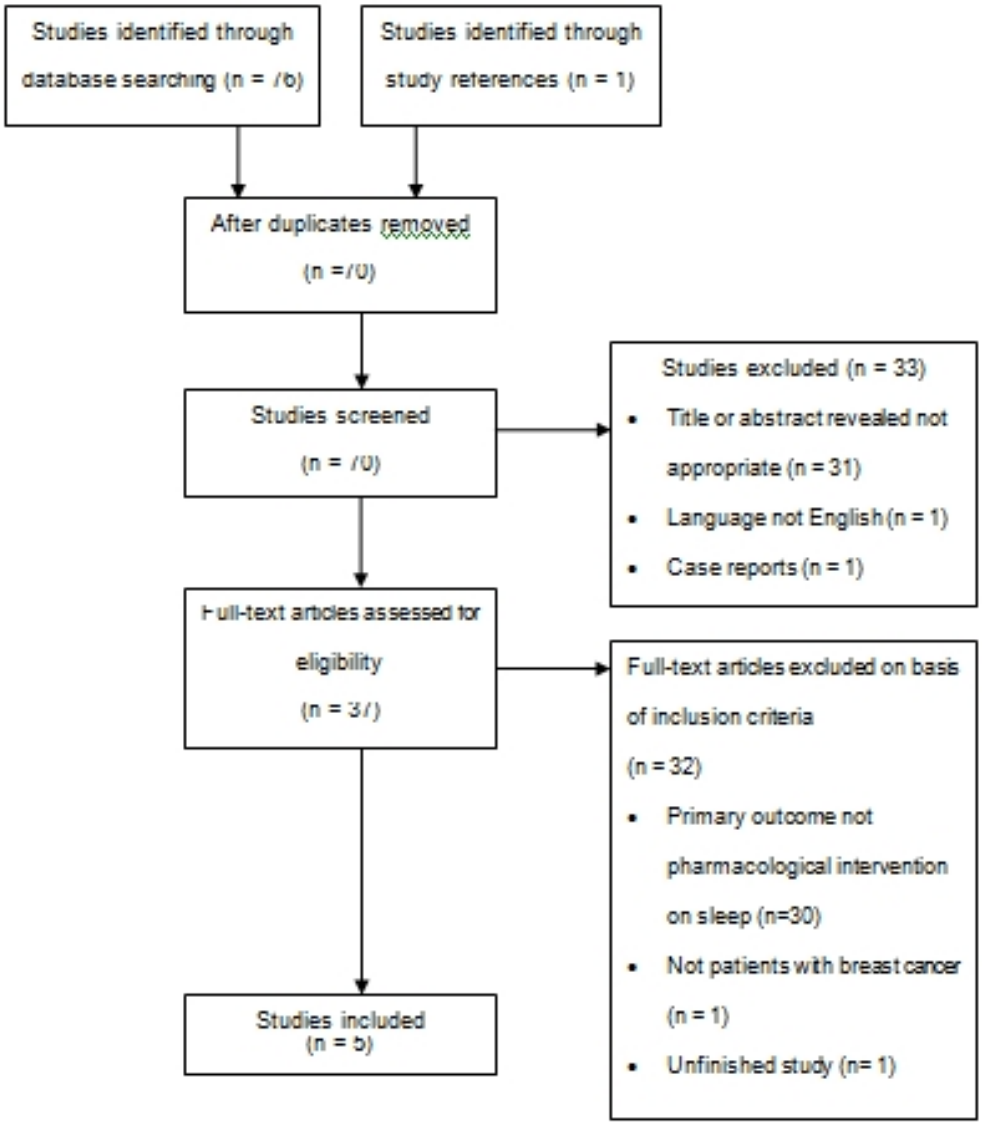

Fig 1. Flow chart

Table 1. Characteristics of the included studies

Treatment during study	No	Study design	Intervention	Primary outcome	Secondary outcome	Results
Perioperative period						
Jacobsen et al. [19]	100	Double-blinded placebo controlled	Triazolam 0.125-0.25 mg/day(n=49) or placebo (n=51)	Response in sleep measured with VAS	Adverse reactions	VAS ↑ Adverse reaction drowsiness: 35% in the triazolam group, 39% in the placebo group. No significant difference in adverse reactions between groups
Systematic Therapy						
Joffe et al. [20]	53	Double-blinded placebo controlled	Zolpidem 10 mg/day (n=25) or placebo (n=28)	Response in sleep monitored with actigraphy	QOL	WASO ↓ PSQI↓ QOL ↑
De Bock et al. [21]	1031	Cohort	NA	Use of psychotropic medication in index group compared to reference group	Prevalence of the prescriptions over time	IRR 2.59 95% CI 2.34-2.87 Half-year prevalence in use of hypnotic is increased
Chemotherapy						
Constantini et al. [22]	124	Retrospective	NA	Description of the prescribing patterns	The effect of menopausal status on use of hypnotics	32% were prescribed hypnotics. Prior users of hypnotics more likely to start using hypnotics. Users of hypnotics more likely to take psychiatric medications No association between menopausal status and use of hypnotics
Moore et al. [23]	219	Retrospective	Sleep diary	Description of the prescribing patterns	NA	46% of the prescriptions were hypnotics. Decrease in use of hypnotics over time

↓= Not significant compared to placebo, ↑ = Significant improvement, WASO = Wake time After Sleep Onset, PSQI = Pittsburgh sleep quality index, QOL = Quality-of-Life, VAS = Visual Analogue Scale, NA = Not Applicabble

3.2 Systematic Therapy

The effect of zolpidem combined with a selective serotonin reuptake inhibitor (SSRI) or a serotonin and norepinephrine reuptake inhibitor (SNRI) on sleep was investigated in a double-blinded placebo controlled RCT [20]. The primary outcome was change in wake time after sleep onset (WASO) and Pittsburgh Sleep Quality Index (PSQI) from baseline to study end. The secondary outcome measures were improvement in QOL, measured with Quality-of-Life Inventory (QOLI) and objective and subjective measurements of hot flashes. The study included 53 patients with breast cancer, with no history of sleep disorders, having at least 14 hot flashes per week and undergoing adjuvant endocrine treatment (69.7%) or chemotherapy. They were randomly assigned to zolpidem 10 mg (n = 25) or placebo (n = 28). If the patients already were users of a SSRI/SNRI they continued the medication at the same dose concurrent with their randomisation to either zolpidem or placebo. If the patients were non-users of a SSRI/SNRI they were prescribed the SNRI venlafaxine 75 mg/day concurrent with the random assignment to zolpidem or placebo. The study showed that adding zolpidem to a SSRI/SNRI significantly improved sleep in women with breast cancer with over 14 hot flashes pr. week. 40% of the women treated with zolpidem responded to the intervention and 14% of the patients treated with placebo responded to the treatment (p= 0.035). None of the WASO or PSQI measurements reached statistical significance. Furthermore, the patients assigned to zolpidem were most likely to complete the study (p= 0.02). QOL improved significantly in the zolpidem group compared with the placebo group (p = 0.01). There was a reduction in subjectively reported night time hot flashes in the zolpidem group, but it did not reach statistical significance (p= 0.06). When objectively measured with a sternal skin-conductance monitor, no difference in night time hot flashes was seen.

De Bock et al. [21] studied the prescription of hypnotics, antidepressants and anxiolytics in 2172 patients with breast cancer and in adjuvant endocrine treatment (index group). They compared the index group with 8129 age -and family physician matched women without cancer and in no endocrine treatment (reference group). The secondary outcome was to study the prevalence of the prescriptions over time. Patients in the index group had 2.59 more prescriptions of hypnotics than women in the reference group (95% CI 2.34-2.87). The half-year prevalence of hypnotic use was increased after the start of endocrine treatment indicating that hypnotics were used for a longer time than antidepressants and anxiolytics.

3.3 Chemotherapy

In a study by Costantini et al. [22] the primary outcome was to characterize the prescription practice of hypnotics in 124 patients with breast cancer, who had received adjuvant (88.7%) or neoadjuvant (11.3%) chemotherapy. The secondary outcome was to investigate if the menopausal status, prior use of hypnotics or a psychiatric diagnosis had any effect on the use of hypnotics. They showed that 32% were prescribed hypnotics during chemotherapy. The most commonly described hypnotics were lorazepam (31.4%) and zolpidem (29.4%). In this study, the menopausal status was not significantly associated with the use of hypnotics during treatment with chemotherapy. Patients with prior use of hypnotics were more likely to start using hypnotics (p> 0.0001). Furthermore, users of hypnotics were also more likely to take psychiatric medications (p=0.04).

In one study the primary outcome was to characterize the use of hypnotics in 219 patients with breast cancer undergoing adjuvant chemotherapy and one year after the last treatment with chemotherapy [23]. Data were taken from the patients' sleep diary written during a prior

RCT that tested a behavioural sleep intervention before, during and after chemotherapy [24]. The study investigated all kind of sleep aids including hypnotics, alcoholic beverages, antidepressants, analgesics and anti-emetics. During the first treatment with chemotherapy, 42 % of the patients reported use of hypnotics. The use of hypnotics decreased over the seven nights following the first dose of chemotherapy. Furthermore, one year after the first treatment with chemotherapy 39% of the patients reported use of a hypnotic.

4. DISCUSSION

Patients with breast cancer may have severe sleep disturbances, both perioperatively and when undergoing oncological treatment. This is obvious from the high prevalence of hypnotic use. It is therefore an area that needs attention both clinically as well as scientifically. Treatment with the benzodiazepine triazolam showed significant improvement in sleep in the immediate postoperative period [19]. Treatment with the hypnotic zolpidem combined with a SSRI/SNRI showed improvement in sleep in patients with breast cancer having hot flashes and in endocrine treatment [20]. Hypnotics were significantly more prescribed in patients undergoing endocrine treatment compared with healthy women in no endocrine treatment [21], and hypnotics were prescribed to almost every second patient undergoing chemotherapy [23]. Prior users of hypnotics and patients with prior sleep disturbances were also more likely to take hypnotics during chemotherapy [22,23].

One study showed that short term use of the benzodiazepine triazolam was significant in initiating and maintaining sleep three nights after surgery for breast cancer [19]. Triazolam may produce cognitive and psychomotor disturbances [25] even after short term use [26] (duration less than 14 days). Therefore, it would have been of interest if the study had monitored these parameters in the perioperative period .This study was the only one that investigated pharmacological intervention on sleep disturbances before the adjuvant treatment period.

In the study where an SSRI/SNRI combined with zolpidem improved sleep in patients with treatment induced hot flashes and in endocrine treatment, both objective and subjective measurements of sleep were used [20]. The strength in the study was that WASO was objectively measured with actigraphy. Actigraphy is a reliable way to measure sleep [27] and has shown sensitivities and specificities up to 90 % in various patient populations compared with the golden standard polysomnography [28]. Furthermore, the patients subjectively reported fewer hot flashes. Hot flashes are a common side effect to endocrine oncological treatment [29]. Studies have shown that SSRI/SNRI are effective in treating hot flashes [29–31]. Therefore, reduction in hot flashes in both groups (placebo and zolpidem) could be expected. Those randomly assigned to zolpidem were more likely to complete the study, had improved sleep and a significant improvement of QOL compared with the placebo group. Thus, the effect of zolpidem is probably not secondary to an effect on hot flashes. In the clinical setting, adding a hypnotic to patients with breast cancer and hot flashes, could improve sleep. This should be confirmed in future randomized clinical trials and also psychomotor disturbances should be investigated. However, concerns have been raised regarding the interaction of SSRI's and the anti-hormone Tamoxifen cytochrome P450 enzyme CYP2D6 system. This interaction has shown to reduce the effects of the antihormone treatment in women with breast cancer. Thus, any potential SSRI's chosen for the treatment of women with breast cancer and sleep problems, should be non-inhibitors of CYP2D6 [32,33].

Three studies focused on use of hypnotics as an indicator of sleep problems in patients undergoing oncological treatment with chemotherapy or endocrine treatment [21-23]. The studies showed that during the adjuvant treatment period prior users of hypnotics were more likely to start using hypnotics and that this group of patients also was more likely to take psychiatric medication [21–23]. This is in line with studies on use of hypnotics in correlation with other types of cancer [34]. The use of hypnotics were increased in patients undergoing endocrine treatment compared with healthy patients, and patients used hypnotics for a longer time than they used anti-depressants [21]. This is in line with a study that concluded that the strongest and most consistent predictor of sleep disturbance in patients with breast cancer three to four month after surgery was the presence of depressive symptoms, in both pre- and postmenopausal women [35]. Thus, the presence of depressive symptoms or prior depressive symptoms is a strong predictor of sleep disturbance and potential use of hypnotics in patients with breast cancer [4,36,37]. Newer generation of antidepressants, with a more pronounced effect on sleep and circadian regulation [38], might be expected to have a more pronounced effect on depressive symptoms involving sleep and thus the general well being for patients with breast cancer.

Almost every second patient receiving adjuvant chemotherapy was prescribed a hypnotic during chemotherapy treatment [23]. Although there was a decrease over time in the use of hypnotics, it is of concern that so many patients receive hypnotics. This could potentially be an indicator for increased presence of depression or depressive symptoms in this patient population. Sleep experts recommend that the use of hypnotics is limited to a maximum period of two to four weeks [39] and Danish guidelines recommend only one to two weeks of use, and that the doctors should only prescribe an amount of hypnotics equivalent to this period [40]. It is known that treatment with certain hypnotics may result in cognitive and psychomotor disturbances [25]. Treatment with hypnotics and especially benzodiazepines can lead to a potential dependency problem and the long term effect is unknown [26,41]. It is therefore important to focus on treatment of depression or depressive symptoms, and if a hypnotic is needed, then it should be a drug with as few adverse effects as possible. Melatonin, a central chronobiotic with hypnotic properties [42,43], could be investigated in this patient population based on its reduced psychomotor effects, no risk of dependency [44] and its effect on depression [45,46].

Despite the great clinical problem of sleep disturbances, there is a lack of studies with focus on pharmacological intervention against sleep disturbances in patients with breast cancer. Furthermore, the sparse literature is insufficient, heterogeneous and low in patient numbers. Only two RCTs were found and these studies investigated pharmacological intervention in different time periods after the diagnosis of breast cancer. There is a great difference in prescription patterns among different doctors and different hospitals treating patients with malignant diseases [47]. Therefore, there is a need for population based studies describing the magnitude of sleep disturbances and hypnotic use in patients with breast cancer.

5. CONCLUSION

In conclusion, the literature concerning sleep disturbances in patients with breast cancer is limited and some of the studies are of poor quality. The few studies that have been performed within this field show that sleep disturbances occur frequently in patients treated for breast cancer, with almost half of patients receiving hypnotics during their adjuvant treatment period. The challenge is to identify the patients at risk for developing sleep disturbance and the patients who will need treatment. The pathogenesis for sleep disturbances may have different components when looking at the immediate postoperative

period compared with the prolonged period undergoing adjuvant therapy with chemotherapy, endocrine treatment and/or radiation. It is therefore important in future studies to distinguish between these time periods in order to rationalize interventional regimens.

CONSENT

Not applicable for this article.

ETHICAL APPROVAL

Not applicable for this article.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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