Research Paper: Comparing the Effects of Melatonin and Zolpidem on Sleep Quality, Depression, and Anxiety in Patients With Colorectal Cancer Undergoing Chemotherapy

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Introduction: Patients with cancer may have many complications involving their psychosomatic systems, such as sleep disturbance, depression, and anxiety. Thus, many research studies were conducted to reduce these complications. Zolpidem, as a short-term non-benzodiazepine treatment of insomnia, and melatonin as a chronobiological function-regulatory hormone, are commonly used for improving sleep quality. This randomized clinical trial aims to compare the effects of zolpidem and melatonin on sleep quality, depression, and anxiety in patients with colorectal cancer.

Methods: In this single-blinded trial, 90 patients with colorectal cancer undergoing chemotherapy who had obtained a score of 5 or higher on the Pittsburgh Sleep Quality Index (PSQI) were randomly divided into two groups (n=45). One group was treated with 10 mg zolpidem at bedtime, and the other group received 6 mg melatonin at bedtime for 30 days. PSQI on weeks 0, 4, 8, Groningen sleep quality scale, Hamilton rating scale for depression, and Hamilton anxiety rating scale questionnaires were performed to assess patients on weeks 0, 4, and 8. The outcome was then analyzed, and P<0.05 was considered statistically significant.

Results: Both zolpidem and melatonin had significant impacts on sleep quality in week 4 (P<0.05). After stopping the treatments, the conditions were noticeably reversed on week 8 (P<0.05). Zolpidem and melatonin were relatively similar in affecting sleep duration, latency, efficiency, and disturbance. None of the two study medications had any considerable influence on anxiety and depression.

Conclusion: Melatonin and zolpidem are promising agents for treating sleep complications and, to some extent, depression, and anxiety in cancer patients, according to the present study. However, further clinical trials are recommended to confirm the results of this study.

Keywords: Neoplasms, Sleep initiation and maintenance disorders, Depression, Anxiety, Zolpidem, Melatonin

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1. Introduction

The World Health Organization (WHO) report stated that cancer causes more fatalities than coronary artery disease or cerebrovascular accidents (Ferlay et al., 2015). Considering recent studies, colorectal cancers, after lung, prostate, and breast cancers, are classified as the third most common type of cancer in men and the second most prevalent cancer in women (Ferlay et al., 2015). The incidence of colorectal cancer (CRC) has increased probably due to the aging of the population and better screening methods in developed and developing countries. However, the mortality of CRC has been decreased in the past decades, along with the developments in treatment methods (Bretthauer, 2011; Jemal et al., 2009). Chemotherapy, which is mostly used as an adjuvant or palliative cure for CRC, may cause many complications and discomfort in patients, particularly psychosomatic problems (Ragnhammar, Hafström, Nygren, & Glimelius, 2001).

Recently health care providers have become concerned about the psychological aspects of cancer and its therapy and conduct many investigations in this regard (Bultz & Carlson, 2006; Holland, 1992). More than one-third of patients with cancer suffer from comorbidities such as feelings of disappointment, uselessness, and sadness, as well as sleep disturbance, somatization, paranoia, obsessive-compulsive disorder, anxiety, hostility, and depression. These symptoms might be because of possible confrontation to death, complications of the disease, and or adverse effects of treatments (Lee, Robin Cohen, Edgar, Laizner, & Gagnon, 2006; Price et al., 2009; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Specifically, in CRC, previous studies regarded that 31.6% of the patients suffer from such psychosomatic complications (Zabora et al., 2001). It is assumed that the physical and emotional distresses of cancer may be a significant cause of sleep problems (Garland et al., 2014). Sleep difficulties and insomnia are believed to be related to other common psychological problems, including anxiety, fatigue, and depression, and more than a half of cancer patients suffer from such psychosomatic complications (Fiorentino, Risling, Liu, & Ancoli-Israel, 2011; Garland et al., 2014; Van Onselen et al., 2012). Many treatments have been tried, such as Benzodiazepines (BZDs), anti-depressants, beta-blockers, behavioral therapies, even Yoga and meditation (Kwekkeboom, Cherwin, Lee, & Wanta, 2010; Lemoine, Garfinkel, Laudon, Nir, & Zisapel, 2011; Shahrokhi, M., et al. (2021). Melatonin and Zolpidem on Sleep Quality, Depression, and Anxiety. BCN, 12(1), 105-114.

Highlights

- Melatonin and zolpidem are promising agents for treating sleep complications.
- None of the two study medications had any considerable influence on anxiety and depression.

Plain Language Summary

Sleep disorders, depression and anxiety are some of most common psychosomatic complications in patients with cancer. So many research studies were conducted to reduce these complications. Zolpidem is a non-benzodiazepine sleep aid medicine, and melatonin as an endogenous hormone, are commonly used for improving sleep quality. In this single blinded randomized clinical trial, the authors aim to compare the effect of zolpidem and melatonin on sleep quality, depression and anxiety in patients with colorectal cancer. In this study 90 patients with colorectal cancer who had anxiety based on Pittsburgh sleep quality index were randomly divided into two groups. The first group was treated with 10 mg zolpidem and the second one 6mg melatonin, both at bed time for 30 days. PSQI on weeks 0, 4, 8, Groningen sleep quality scale, Hamilton rating scale for depression, and Hamilton anxiety rating scale questionnaires were performed to assess patients on weeks 0, 4, and 8. At the end of data analyzing, we concluded that both drugs had significant impacts on sleep quality in week 4, and after stopping the treatment, the complication were noticeably reserved on week 8. Both drugs had similar effect on sleep duration, latency, efficiency and disturbance. Melatonin and zolpidem are promising agents for treating sleep complications and, to some extent, depression, and anxiety in cancer patients, according to the present study.
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Mustian et al., 2013). All of these methods have had some beneficial effects as well as a number of adverse effects. BZDs showed the best results among these methods according to several studies but they also bring about light headedness, morning drowsiness, dependency, and so on. Meditation and relaxation, besides hypnoses (mind-body therapy), were shown to be useful as an additional therapy for pain, fatigue, and sleep disturbance in cancer patients.

Melatonin (MT), an indolamine hormone secreted from the pineal gland, plays a prominent role in regulating human endocrine and chronobiological function. MT is known to have potent oncostatic, antioxidant, anti-proliferative, immune-modulating, and endocrine-modulating activities (Srinivasan, Spence, Pandi-Perumal, Trakht, & Cardinali, 2008). Long-term dysregulation of the circadian rhythm is reported to be associated with reduced MT secretion and also increased cancer risk; thus, clinical research suggests possible advantages from MT on reducing morbidities and mortalities in cancer patients (Mills, Wu, Seely, & Guyatt, 2005). There are discrepancies among the studies regarding the efficacy of MT on sleep disturbances; some say it is beneficial while others not (Buscemi et al., 2006; Ferraccioli-Oda, Qawasmi, & Bloch, 2013). MT was also reported to effectively treat anxiety and depression, particularly in patients with cancer (Hansen et al., 2014). Zolpidem, a non-benzodiazepine-imidazopyridine compound that enhances GABA-A receptor function, is declared beneficial in sleep induction, treatment of anxiety, and even depressive disorders with minimal side effects, principally in chronic comorbid sleep problems (Dang, Garg, & Rataboli, 2011).

Because sleep disturbances, anxiety, and depression are the major complications in patients suffering from cancers, we aimed to compare the effects of zolpidem and melatonin on these problems in individuals suffering from colorectal cancers undergoing chemotherapy. In this study, we used established questionnaires for evaluating the impact of treatments on sleep quality, anxiety, and depression.

2. Materials and Methods

1.1. Patients and grouping

In this single-blind clinical trial, the participants were patients aged ≥18 years suffering from colorectal cancer and were receiving chemotherapy between January 21, 2018, and March 21, 2018, at Sina Hospital, Tehran, Iran. They were required to fill the Pittsburgh Sleep Quality Index (PSQI) questionnaire. They were randomly assigned into two groups (n=45). The first group received 2 pills of 5 mg zolpidem (Sobhan Daru, Tehran, Iran) right before sleeping; the dosing was set due to the best efficacy of the medicines according to previous experiences of the authors in these patients. The second group received 2 pills of 3 mg MT (melatonin supplement (Nature™, USA) for 30 nights. Dosing of MT was set according to Hansen et al. (2014). A nurse colleague cooperated with us in pill count and giving the medications to the participants, and the researchers were unaware of the type of drugs given to the patients. All the patients have filled the informed consent form before joining the study after a comprehensive introduction to the study protocol. They were permitted to discontinue their cooperation at any time during the study.

1.2. Inclusion and exclusion criteria

The inclusion criteria were being 18 and over, having any type of colorectal cancer, being under chemotherapy, having sleep disturbances based on PSQI score (score ≥ 5).

The exclusion criteria were being treated with at least one anti-depressant, using sedative-hypnotic drugs, anti-anxiety medications, any kind of sleep aids, having used MT for the last one month, being pregnant, or lactating.

1.3. Data gathering and questionnaires

The participants were asked to write their demographic information, including name, age, gender, marital status, race, education, access number, disease, type of cancer treatment in the beginning. The translated (Farsi) Groningen Sleep Quality Scale (GSQS), Pittsburgh sleep quality index (PSQI), Hamilton Rating Scale for Depression (HRSD), and Hamilton Anxiety Rating Scale (HARS) were used according to previously published paper (Jafarian, Gorouhi, Taghva, & Lotfi, 2008; Mousavi Malek, Zakerimoghadam, Esmaeili, & Kazemnejad, 2018; Tanner et al., 2013). To assess the appropriation of translated entries, a consultation was done with a bilingual neurologist and psychiatrist, who confirmed the validity of the translated questionnaires. A higher score in GSQS means a more disturbed sleep in the previous night. GSQS ranges from 0 to 14; a score of 0-2 is considered a normal refreshing last night’s sleep, and a score of 6 or higher classified as disturbed and insufficient sleep. PSQI consists of 19 items, each is scored similarly by 0-3 Likert-type scale; and has 7 components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) and the total score
ranges from 0 to 21; a score of 5 or higher demonstrates a disturbed sleep (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). The translated questionnaire was validated and used in previous studies (Farrahi Moghaddam, Sheibani, Garrusi, & Amirkafi, 2012; Nazifi, Mokarami, Akbaritabar, Kalte, & Rahi, 2014). HRSD is an observer-rating, well-established, and validated questionnaire consisted of 17 items, including depressed mood, guilt, suicide, insomnia, work and interests, retardation, agitation, anxiety, somatization, genit, hypochondriasis, insight, weight (Trajković et al., 2011). HARS, which is an established clinical test to rate the severity of anxiety, involves 14 items: anxious mood, tension, fears, insomnia, intellectual, depressed mood, muscular, sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic, behavior—each has a scoring of 0-4 (Clark & Donovan, 1994; Kummer, Cardoso, & Teixeira, 2010). In our study, the patients were evaluated according to both HRSD and HARS by two independent spectators at the same time to decrease the inter-physician variances. The final scores of the patients were calculated as means of the scores.

During the study, on weeks 0, 4, and 8, the participants were asked to fill the GSQS and PSQI questionnaires to evaluate their sleep quality. These intervals were set according to previous studies (Donovan & Jacobsen, 2007). Afterward, the individuals were requested to fill the HRSD and HARS at the beginning of the study, then 2, 4, and 8 weeks later (Vural, Acer, & Akbaş, 2008). During the study (8 weeks), the patients were visited regularly by a psychiatrist to be evaluated for any worsening or warning signs of psychiatric problems, particularly depression, to see if the treatments were sufficient. Those who could not continue the study would be dismissed to be treated separately.
1.4. Statistical methods and analysis

The data were collected and analyzed with SPSS software version 19.0. The obtained data were exhibited as either median or Means±Standard Deviations (SD). GSQS, PSQI, HARS, and HRSD questionnaires were analyzed separately regarding their instructions by two individual experts. The 1-sample Kolmogorov-Smirnov test tested data’s normality. The two groups were compared by Fisher exact test for the primary evaluation. To normalize the data for further analysis, a Z score of 2.5 was considered, and 6 participants, 3 from each group was dismissed. A 2-way repeated measures analysis of variance (2-way ANOVA) was used plus Bonferroni post hoc test. The two groups were considered as a between-subjects factor, and the measurements were considered as the within-subjects factor. Moreover, a 1-way ANOVA with Bonferroni post hoc test was performed to compare the data in each group with the other at a similar time. P-value ≤0.05 was considered as statistically considerable.

3. Results

In this study, as shown in Figure 1, out of 210 visited patients, 101 individuals were randomly assigned into two groups of 51 and 50, including the zolpidem, treated and the MT treated groups, respectively. The treatments were administered until week 4 of the study (day 30), and patients were followed up till week 8. From zolpidem and MT treated groups, 6 and 5 participants were lost on follow-ups or were excluded. The demographic characteristics are shown in Table 1. Age and gender distribution were similar between the two groups.

Table 2 presents sleep quality indexes. Regarding the PSQI results in the treatment receiving groups in week 4 had significantly lower scores compared to week 0 (P ≤ 0.008 in both groups). Regarding the results of GSQS, there was a significant difference in week 4 compared to week 0 (P=0.004 in both groups). However, in both criteria, the results in week 8 were not significantly different from week 0. The outcomes of this PSQI and GSQS questionnaires showed no significant difference between the MT and zolpidem treated groups. The outcome of HARS and HRSD questionnaires from weeks 0, 2, 4, and 8 revealed insignificant contrast between the zolpidem treated and MT treated groups (Table 3). Table 4 and Table 5 depict the most frequent side effects of the medications and the chemotherapy regimen the patients were receiving, respectively. There was no considerable difference between the two groups regarding these variants.

4. Discussion

Sleep disturbance is a significant problem among patients who suffer from chronic diseases, particularly malignancies. Reports show that more than 60% of patients with advanced cancer have sleep problems (Mercadante et al., 2015). Anxiety and depression, besides other psychological complications, are also common in these patients. In the present randomized clinical trial, we compared the effects of zolpidem, as a commonly-used sleep medication, and MT, as a chronobiologic function regulatory hormone, on sleep quality, anxiety,

Table 1. Demographic data of the groups (n=45) receiving either melatonin or zolpidem who suffer from colorectal cancer undergoing chemotherapy*

| Groups   | No.  | Mean±SD | Sex     | Age, y | Marital Status | No. |
|----------|------|---------|---------|--------|----------------|-----|
| Zolpidem | Female: 22 | 64.11±7.93 | Single: 5 | Diploma: 15 | Married: 36 | Under diploma: 2 |
|          | Male: 23   |          | Divorced: 4 | Bachelor: 23 |                |     |
| Melatonin| Female: 20 | 63.62±7.67 | Single: 7 | Diploma: 10 | Married: 33 | Under diploma: 3 |
|          | Male: 25   |          | Divorced: 5 | Bachelor: 28 |                |     |

* No significant difference was found comparing the demographic data between the two groups.
and depression in patients with colorectal cancers receiving chemotherapy. Regarding sleep quality, a study by Lemoine et al. showed that MT not only improved sleep quality and morning alertness in old patients with insomnia but also had no rebound or withdrawal side effects in these patients (Lemoine, Nir, Laudon, & Zisapel, 2007). However, in our study, we observed a rebound effect after discontinuing MT. Nunes et al. (2008) also declared that MT considerably improved global PSQI scores, sleep latency, and sleep duration in patients suffering from chronic obstructive pulmonary disease. Hickie and Rogers (2011) reported that MT not only improves symptoms and signs of depression but also improves sleep quality and reduces the side effects of other standard treatments in these patients. MT also brought about a lower relapse rate than a placebo group. Using zolpidem in sleep disturbed patients helped enhance sleep quality regarding PSQI questionnaires outcome and reduce anxiety in patients with essential hypertension (Huang et al., 2012). Joffe et al. (2010) reported that zolpidem in breast cancer patients using anti-depressants for their hot flashes improved their quality of sleep. According to the literature, zolpidem is rarely used alone for the treatment of depression and anxiety disorders; however, some scientists use it in combination with other medications such as anti-depressants to ameliorate the quality of sleep and thus to amend the depressive or anxious condition of the patients (Ji et al., 2007). It is assumed that MT imposes its anti-depressant influence through MT1 and MT2 melatonergic-agonist and also relatively weak 5HT2C serotonin receptor antagonism (Cardinali, Srinivasan, Brzezinski, & Brown, 2012). There are controversies in the literature about the anxio-

### Table 2. The PSQI and GSQS results comparing the effects of melatonin and zolpidem on sleep quality in patients after 30 days of treatment

| Questionnaires                  | Groups        | Mean±SD          | Week 0 | Week 4 | Week 8 |
|---------------------------------|---------------|------------------|--------|--------|--------|
|                                 | Melatonin     | 12.75±1.73       | 6.20±1.42* | 11.95±1.46† |
|                                 | Zolpidem      | 12.91±1.67       | 4.53±1.39† | 12.08±1.42† |
| Pittsburgh sleep quality index  |               |                  |        |        |        |
| 1. Daytime dysfunction          | Melatonin     | 2.11±0.78        | 0.80±0.59† | 1.89±0.68† |
|                                 | Zolpidem      | 2.15±0.74        | 0.82±0.57† | 1.98±0.75† |
| 2. Sleep duration               | Melatonin     | 2.24±0.65        | 1.07±0.54* | 2.18±0.65† |
|                                 | Zolpidem      | 2.24±0.68        | 0.82±0.49† | 2.02±0.69† |
| 3. Sleep latency                | Melatonin     | 2.22±0.47        | 1.11±0.59* | 2.29±0.59† |
|                                 | Zolpidem      | 2.35±0.48        | 0.47±0.51† | 2.35±0.48† |
| 4. Subjective sleep quality     | Melatonin     | 2.15±0.71        | 0.92±0.42† | 1.95±0.71 |
|                                 | Zolpidem      | 2.26±0.65        | 0.80±0.46† | 2.07±0.54 |
| 5. Habitual sleep efficiency    | Melatonin     | 2.07±0.69        | 1.13±0.54* | 2.02±0.62† |
|                                 | Zolpidem      | 2.04±0.71        | 0.73±0.44† | 2.09±0.63† |
| 6. Use of sleeping medication   | Melatonin     | 0.22±0.42        | 0.07±0.25  | 0.07±0.25 |
|                                 | Zolpidem      | 0.20±0.41        | 0.04±0.21  | 0.07±0.25† |
| 7. Sleep disturbances           | Melatonin     | 1.73±0.81        | 1.11±0.57* | 1.56±0.72 |
|                                 | Zolpidem      | 1.69±0.82        | 0.84±0.60† | 1.51±0.84 |
| Groningen sleep quality scale   | Melatonin     | 7.04±2.21        | 3.80±1.34* | 6.47±1.91† |
|                                 | Zolpidem      | 7.58±2.09        | 3.00±1.24* | 6.78±1.78† |

† P-value ≤0.05 compared to the previous estimation; * P-value ≤ 0.003 compared to the previous estimation.
lytic impacts of MT. Some, mostly animal studies, say it is beneficial, and some, mostly human studies, say it has no positive effects (Capuzzo et al., 2006; Papp, Litwa, Gruca, & Mocaër, 2006).

Herein, we found that both zolpidem and MT can improve sleep disturbances by affecting the sleep parameters, including sleep quality, sleep duration, sleep latency, sleep disorders, need for sleeping medicines, sleep efficiency, daytime dysfunction, and also high altitude sleep overnight. These findings are consistent with previous investigations as they declare that zolpidem and MT both improve sleep quality measured by the PSQI questionnaire. In our study, zolpidem and MT showed no significant superiority over each other. However, there were a few considerable differences between these two medications, such as the better impact of zolpidem on sleep latency, efficiency, duration, and disturbances.

Table 3. The HRS for depression and HARS comparing the effects of melatonin and zolpidem in patients during 30 days of treatment in both groups

| Questionnaires | Groups      | Mean ±SD                  |
|----------------|-------------|---------------------------|
|                | Melatonin   | Week 0  | Week 2  | Week 4  | Week 8  |
| Hamilton Rating Scale for Depression | 20.76±9.81 | 20.46±9.71 | 17.84±8.46 | 20.33±9.36 |
|                | Zolpidem    | 21.36±10.17 | 20.91±9.54 | 20.31±9.07 | 20.60±9.13 |
| Hamilton Anxiety Rating Scale | 20.91±8.26 | 20.71±8.03 | 21.09±8.09 | 20.87±8.12 |
|                | Melatonin   | 20.66±8.23 | 20.62±8.16 | 20.62±8.42 | 21.04±7.89 |
|                | Zolpidem    | 20.91±8.26 | 20.71±8.03 | 21.09±8.09 | 20.87±8.12 |

Table 4. The main side effects of MT and zolpidem in patients with colorectal cancer undergoing chemotherapy*

|                  | Zolpidem | Melatonin |
|------------------|----------|-----------|
| Hallucination    | n=2      | n=2       |
| Fatigue          |          |           |
| Next morning Dizziness | n=12     | n=10      |
| Gastrointestinal effects |         |           |
| Next morning Dizziness |         | n=1       |

* There was no significant difference between the two groups regarding the side effects of the medications.

Table 5. The chemotherapy regimen in patients with colorectal cancer being treated with zolpidem or melatonin*

| Groups | Mean±SD | Chemotherapy Regimen |
|--------|---------|----------------------|
|        | Number of Chemotherapy Courses at the Beginning | FOLFOX*: 21 |
|        | Zolpidem | 6.5±0.93 |
|        | Melatonin | 7.1±0.43 |

* There was no significant difference between the two groups regarding the type of chemotherapy and the duration (P>0.05).

1. FOLFOX: Folinic acid (leucovorin), fluorouracil, oxaliplatin; 2. FOLFIRI: Folinic acid (leucovorin), fluorouracil, irinotecan; 3. XELOX: capecitabine, oxaliplatin.
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The authors declared no conflict of interest.

References

Brethauer, M. (2011). Colorectal cancer screening. Journal of Internal Medicine, 270(2), 87-98. [DOI:10.1111/j.1365-2796.2011.02999.x]

Bultz, B. D., & Carlson, L. E. (2006). Emotional distress: The sixth vital sign-future directions in cancer care. Psycho-oncology, 15(2), 93-95. [DOI:10.1002/pon.1022]

Buscemi, N., Vandermeer, B., Hooton, N., Pandya, R., Tjosvold, L., & Hartling, L., et al. (2006). Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. The BMJ, 332(7538), 385-393. [DOI:10.1136/bmj.38751.s32766.f6]

Buyse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: Anew instrument for psychiatric practice and research. Psychiatry Research, 28(2), 193-215. [DOI:10.1016/0165-1781(89)90047-4]

Capuzzo, M., Zanardi, B., Schifflino, E., Buccoliero, C., Gragnaniello, D., & Bianchi, S., et al. (2006). Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. Anesthesia & Analgesia, 103(1), 121-3. [DOI:10.1213/01.ane.000022476.62547.ed]

Cardinali, D. P., Srinivasan, V., Brezieszki, A., & Brown, G. M. (2012). Melatonin and its analogs in insomnia and depression. Journal of Pineal Research, 52(4), 365-75. [DOI:10.1111/j.1600-079X.2011.00962.x]

Clark, D. B., & Donovan, J. E. (1994). Reliability and Validity of the Hamilton Anxiety Rating Scale in an adolescent sample. Journal of the American Academy of Child & Adolescent Psychiatry, 33(5), 354-60. [DOI:10.1097/00004583-199405000-00009]

Dang, A., Garg, A., & Rataboli, P. V. (2011). Role of zolpidem in the management of insomnia. CNS Neuroscience & Therapeutics, 17(5), 385-7. [DOI:10.1111/j.1755-5949.2010.00138.x]

Donovan, K. A., & Jacobsen, P. B. (2007). Fatigue, depression, and insomnia: evidence for a symptom cluster in cancer. In Seminars in Oncology Nursing, 23(2), 127-35. [DOI:10.1016/j.soncn.2007.01.004]

Farrahi Moghaddam, J., Nakhaei, N., Sheibani, V., Garrusi, B., & Amirkafi, A. (2012). Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). Sleep and Breathing, 16(1), 79-82. [DOI:10.1007/s11325-010-0478-5]

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., & Rebelo, M., et al. (2015). Cancer incidence and mortality
worldwide. Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer, 136(5), E359-386. [DOI:10.1002/ijc.29210]

Ferraccioli-Oda, E., Qawasmi, A., & Bloch, M. H. (2013). Meta-analysis: Melatonin for the treatment of primary sleep disorders. PloS One, 8(5), e65773. [DOI:10.1371/journal.pone.0065773]

Fiorentino, L., Rissling, M., Liu, L., & Ancoli-Israel, S. (2011). The symptom cluster of sleep, fatigue and depressive symptoms in breast cancer patients: severity of the problem and treatment options. Drug Discovery Today: Disease Models, 8(4), 167-73. [DOI:10.1016/j.ddmod.2011.05.001]

Garland, S. N., Johnson, J. A., Savard, J., Gehrman, P., Perlis, M., & Carlson, L., et al. (2014). Sleeping well with cancer: A systematic review of cognitive behavioral therapy for insomnia in cancer patients. Neuropsychiatric Disease and Treatment, 10, 1113-24. [DOI:10.2147/NDT.S74790]

Hansen, M. V., Andersen, L. T., Madsen, M. T., Hageman, I., Joffe, H., Partridge, A., Giobbie-Hurder, A., Li, X., Habin, K., Ji, J., Liu, W., Zhang, N., Chen, Z., Zheng, A., & Mei, Q., et al. (2010). Generalized anxiety disorder and the Hamilton Anxiety Rating Scale in Parkinson’s disease. Acta Neuropsychiatria, 8(4), 495-501. [DOI:10.15190/S0004-282X.2010000400105]

Hickie, I. B., & Rogers, N. L. (2011). Novel melatonin-based therapies: Potential advances in the treatment of major depression. The Lancet, 378(9791), 621-31. [DOI:10.1016/S0140-6736(11)6005-0]

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer statistics, 2009. CA: A Cancer Journal for Clinicians, 59(4), 225-249. [DOI:10.3322/caac.20006]

Joffe, H., Partridge, A., Giobbie-Hurder, A., Li, X., Habin, K., & Goss, P., et al. (2010). Augmentation of venlafaxine and selective serotonin reuptake inhibitors with zolpidem improves sleep and quality of life in breast cancer patients with hot flashes: A randomized, double-blind, placebo-controlled trial. Menopause, 17(5), 908-16. [DOI:10.1097/gme.0b013e3181fbee1b]

Kummer, A., Cardoso, F., & Teixeira, A. L. (2010). Generalized anxiety disorder and the Hamilton Anxiety Rating Scale in Parkinson's disease. Anq Neuropsiquiatr, 68(4), 495-501. [DOI:10.1590/S0004-282X.2010000400105]

Lee, Y., Robin Cohen, S., Edgar, L., Laizner, A. M., & Gagnon, A. J. (2006). Meaning-making intervention during breast or colorectal cancer treatment improves self-esteem, optimism, and self-efficacy. Social Science & Medicine, 62(12), 3133-45. [DOI:10.1016/j.socscimed.2005.11.041]

Lemoine, P., Garfinkel, D., Laudon, M., Nir, T., & Zisapel, N. (2011). Prolonged-release melatonin for insomnia-an open-label long-term study of efficacy, safety, and withdrawal. Therapeutics and Clinical Risk Management, 7, 301. [DOI:10.2147/TCRM.S23036]

Lee, Y., Nir, T., Laudon, M., & Zisapel, N. (2007). Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. Journal of Sleep Research, 16(4), 372-80. [DOI:10.1111/j.1365-2699.2007.00613.x]

Mercadante, S., Aielli, F., Adile, C., Ferrera, P., Valle, A., & Cartoni, C., et al. (2015). Sleep disturbances in patients with advanced cancer in different palliative care settings. Journal of Pain and Symptom Management, 50(6), 786-92. [DOI:10.1016/j.jpainsymman.2015.06.015]

Mills, E., Wu, P., Seely, D., & Guyatt, G. (2005). Melatonin in the treatment of cancer: A systematic review of randomized controlled trials and meta-analysis. Journal of Pain Research, 39(4), 360-6. [DOI:10.1111/j.1600-079X.2005.00258.x]

Mousavi Malek, N., Zakerimoghadam, M., Esmaeili, M., & Kazemnejad, A. (2018). Effects of nurse-led intervention on patients’ anxiety and sleep before coronary artery bypass grafting. Critical Care Nursing Quarterly, 41(2), 161-9. [DOI:10.1097/CNQ.0000000000000195]

Mustian, K. M., Sprod, L. K., Janelins, M., Peppone, L. J., Palesh, O. G., & Chandwani, K., et al. (2013). Multicenter, randomized controlled trial of yoga for sleep quality among cancer survivors. Journal of Clinical Oncology, 31(26), 3233-41. [DOI:10.1200/JCO.2012.43.7707]

Nazifi, M., Mokarami, H., Akbaritabar, A., Kalte, H. O., & Rahi, A. (2014). Psychometric properties of the persian translation of Pittsburgh sleep quality index. Health Scope, 3(2), e15547. [DOI:10.17795/j.healthscope-15547]

Nunes, D., Mota, R., Machado, M., Pereira, E., De Bruin, V., & De Bruin, P. (2008). Effect of melatonin administration on subjective sleep quality in chronic obstructive pulmonary disease. Brazilian Journal of Medical and Biological Research, 41(10), 926-31. [DOI:10.1590/S0100-879X2008001000016]

Papp, M., Litwa, E., Grusa, P., & Mocaer, E. (2006). Anxiolytic-like activity of agomelatine and melatonin in three animal models of anxiety. Behavioural pharmacology, 17(1), 9-18. https://journals.lww.com/behaviouralpharmacology/abstract/2006/02000/Anxiolytic_like_activity_of_agomelatine_and.2.aspx

Price, M. A., Zachariae, R., Butow, P. N., Chauhan, D., Espie, C. A., & Friedlander, M., et al. (2009). Prevalence and predictors of insomnia in women with invasive ovarian cancer: Anxiety a major factor. European Journal of Cancer, 45(18), 3262-3270. [DOI:10.1016/j.ejca.2009.05.030]

Ragnhammar, P., Halström, L., Nygren, P., & Glimelius, B. (2001). A systematic overview of chemotherapy effects in

---
colorectal cancer. *Acta Oncologica*, 40(2-3), 282-308. [DOI:10.1080/02841860151116367]

Srinivasan, V., Spence, D. W., Pandi-Perumal, S. R., Trakht, I., & Cardinali, D. P. (2008). Therapeutic actions of melatonin in cancer: Possible mechanisms. *Integrative Cancer Therapies*, 7(3), 189-203. [DOI:10.1177/1534735408322846]

Tanner, J. B., Tanner, S. M., Thapa, G. B., Chang, Y., Watson, K. L., & Staunton, E., et al. (2013). A randomized trial of temazepam versus acetazolamide in high altitude sleep disturbance. *High Altitude Medicine & Biology*, 14(5), 234-9. [DOI:10.1089/ham.2013.102]

Trajković, G., Starčević, V., Latas, M., Leštarević, M., Ille, T., & Bukumirić, Z., et al. (2011). Reliability of the Hamilton Rating Scale for Depression: A meta-analysis over a period of 49 years. *Psychiatry Research*, 189(1), 1-9. [DOI:10.1016/j.psychres.2010.12.007]

Van Onselen, C., Cooper, B. A., Lee, K., Dunn, L., Aouizerat, B. E., & West, C., et al. (2012). Identification of distinct subgroups of breast cancer patients based on self-reported changes in sleep disturbance. *Supportive Care in Cancer*, 20(10), 2611-9. [DOI:10.1007/s00520-012-1381-3]

Vural, M., Acer, M., & Akbaş, B. (2008). The scores of Hamilton depression, anxiety, and panic agoraphobia rating scales in patients with acute coronary syndrome. Anatolian Journal of Cardiology/Anadolu Kardiyoji Dergisi, 8(1), 43-7. [jag.journalagent.com/anatoljcardiol/pdfs/AnatolJCardiol_8_1_43_47.pdf]

Zabora, J., BrintzenhofeSzoc, K., Curbow, B., Hooker, C., & Piantadosi, S. (2001). The prevalence of psychological distress by cancer site. *Psychoncology*, 10(1), 19-28. [DOI:10.1002/1099-1611(200101/02)10:13.0.CO;2-6]