Melatonin for the Management of Cancer-Related Fatigue in Breast Cancer: An Integrative Review

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Abstract

Breast cancer is the most common cancer in women in the United States. The treatment of breast cancer has multiple side effects, including cancer-related fatigue (CRF). While physical activity has the strongest evidence in treating CRF, it is limited by a patient's functional status, disease, and safety concerns. Several studies have demonstrated that exogenous melatonin has improved depressive symptoms, insomnia, and sleep quality in breast cancer patients. However, few have focused on the effects of melatonin on CRF. This review explores the effect of melatonin on CRF in breast cancer patients. A review of current literature was conducted by searching PubMed, Cochrane, Scopus, and CINAHL databases. One hundred articles resulted, and after applying exclusion criteria, five articles were chosen for this review. Results showed a significant improvement in CRF in the studies utilizing 5 mg and 18 mg of melatonin in breast cancer patients undergoing chemotherapy or radiation. Melatonin can be considered an option for patients with breast cancer experiencing CRF, especially in the context of patients with physical limitations where exercise may not be an option. Additional research is needed to further evaluate the role and ideal dose of melatonin in the management of CRF.

Breast cancer is the most common cancer in women in the United States, with an estimated 316,950 new cases of invasive breast cancer in 2025 (American Cancer Society, 2025). New and emerging treatments continue to develop for this prevalent disease, including surgery, radiation treatment, and systemic therapies. Unfortunately, these treatments carry multiple side effects, including fatigue. It can be challenging for clinicians to identify the etiology of fatigue, which can be attributed to both cancer treatment and the cancer itself. Regardless of the root cause, fatigue can be debilitating to a patient.

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BACKGROUND

Fatigue

The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (NCCN, 2024a). Between 80% and 100% of people with cancer report symptoms of CRF (American Cancer Society, 2024), and it can occur at any time before, during, or after treatment. About one third of patients will have persistent CRF for years after treatment, causing profound impacts on patient quality of life (Bower et al., 2000). Cancer-related fatigue is subjective and is best assessed by patient self-reports (NCCN, 2024a). Several assessments have been utilized to measure CRF, including the Brief Fatigue Inventory (BFI), European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30), Visual Analog Scale (VAS) for fatigue, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue-Short Form. These tools are validated and reasonable to assess CRF (Fisher et al., 2022).

Cancer-related fatigue is multifactorial and is best managed by a multidisciplinary approach involving interventions tailored to the individual. Factors that can contribute to CRF include pain, anemia, emotional distress, and sleep disturbances (NCCN, 2024a, 2024b). The pathophysiology of CRF has yet to be clearly identified; however, some research has indicated that hyperinflammation, neuroendocrine alterations, and autonomic nervous system dysregulation are possible mechanisms (Sedighi Pashaki et al., 2021). Current guidelines recommend initial management with nonpharmacologic methods such as physical activity (NCCN, 2024a), which has the best evidence to date for management of treatment-related CRF. Other nonpharmacologic interventions include massage therapy, acupuncture, cognitive behavioral therapy, and nutrition consultation (NCCN, 2024a). While physical activity has the strongest evidence in treating CRF, it is limited by many factors, including patients' functional status, disease, and safety concerns. Physical activity should be used cautiously in those at risk for pathologic fracture, thrombocytopenia, coagulation disorders, and anemia.

Pharmacologic interventions are sometimes considered for treatment of CRF and include psychostimulants such as methylphenidate and corticosteroids such as dexamethasone. Methylphenidate has side effects including insomnia, irritability, and anorexia, which may make it an incompatible choice in patients who are already struggling with these symptoms (Minton et al., 2008). Dexamethasone has short-term side effects including insomnia, hyperglycemia, and weight gain as well as long-term side effects including immunosuppression and osteoporosis (Minton et al., 2008). Dexamethasone may not be helpful in patients with insomnia, diabetes mellitus, and those at increased risk for infection. Overall, the risks of using methylphenidate and dexamethasone may outweigh the benefits in the treatment of CRF for certain patients.

Melatonin

Melatonin is a hormone that is released by the pineal gland following a circadian rhythm (Liu et al., 2016). Exogenous melatonin acts as an agonist of melatonin receptors in the suprachiasmatic nucleus, which helps regulate circadian rhythms and sleep onset. Melatonin also has a role in immunomodulation, antioxidation, and antiproliferation that is not yet fully understood (Sedighi Pashaki et al., 2021). Previous research involving the role of melatonin in the modulation of the sleep-wake cycle led to a class of melatonin agonists for treating insomnia, circadian rhythms, mood disorders, and cancer (Liu et al., 2016).

Exogenous melatonin is recommended to help treat insomnia in doses between 1 mg and 5 mg, although some products are as high as 20 mg. Exogenous melatonin is available in multiple formulations and is considered a dietary supplement in the United States; prescription formulations are available in other countries.

Side effects of melatonin are not well established due to a lack of placebo-controlled trials to examine adverse effects. Due to melatonin being regulated as a dietary supplement, there are a variety of formulations available with varying amounts of melatonin, making it challenging to fully examine the adverse effects. Commonly reported side

effects include vivid dreams and nightmares, dizziness, daytime sleepiness, headache, short-term feelings of depression, irritability, and stomach cramps. The safety of long-term melatonin has not been established with controlled studies.

Several studies have demonstrated that exogenous melatonin has improved depressive symptoms, insomnia, and sleep quality in breast cancer patients. However, few have focused on the effects of exogenous melatonin on CRF in breast cancer patients. The aim of this review is to present an integrative examination of available research on exogenous melatonin usage in the management of CRF in breast cancer patients.

METHODS

The electronic databases of PubMed, Cochrane, Scopus, and CINAHL were searched using the keywords "breast cancer AND melatonin AND fatigue." One hundred articles published between January 1998 and September 2023 resulted (Figure 1). Of the 100 article results, 82 were unique across the databases. These articles were examined and 60 were determined to be not relevant to breast cancer, fatigue, and melatonin. Articles were also excluded if fatigue was not assessed, if there was no exogenous melatonin administration, or if there were multiple interventions performed in the studies. Two reviews were excluded, and one protocol article was excluded. Five studies were identified for this integrative review: four randomized controlled trials (RCTs) and one prospective phase II trial (Table 1).

RESULTS

Melatonin Dosage: 5 mg

Innominato and colleagues (2016) explored the efficacy of 5 mg of melatonin in managing self-rated CRF in metastatic breast cancer patients. In this prospective phase II trial, 32 breast cancer patients were given 5 mg of melatonin at bedtime for 2 months. Participants included in the study had histologically proven metastatic breast cancer with stable disease receiving bisphosphonates, tamoxifen, aromatase inhibitors, progestins, trastuzumab, or no systemic therapy. The study was based on a repeated-measures design with each patient serving as their own control. This study measured CRF as a secondary endpoint. Participants completed the EORTC QLQ-C30 v3.0 questionnaire at baseline and after 2 months of melatonin treatment. Higher values on the questionnaire indicate a more severe complaint and a clinically significant improvement was defined as a decrease in score of 10 or fewer points. After 2 months of treatment with melatonin, 47.4% of participants reported a clinically significant improvement in self-rated CRF (p = .011).

Melatonin Dosage: 6 mg

Hansen and colleagues (2014) investigated the efficacy of 6 mg of melatonin in managing self-rated CRF in breast cancer patients undergoing a lumpectomy or mastectomy. In this randomized, double-blind, placebo-controlled trial, 54 participants were randomized to the melatonin group (n = 28) or the placebo group (n = 26). Participants included women between the ages of 30 and 75 years with a planned lumpectomy or mastectomy with no neoadjuvant chemotherapy. Participants in the melatonin group received 6 mg daily, 1 hour before bedtime, for 1 week preoperatively and 12 weeks postoperatively. In this study, CRF was measured as a secondary endpoint. Patients kept a daily record of CRF using the VAS. Data were analyzed using area under the curve for CRF as measured by VAS. There was no significant difference in CRF between the melatonin group and placebo group in the short-term postoperative period of 2 days preoperative through 8 days postoperative (p = .91). There was no significant difference in CRF between the melatonin group and the placebo group in the long-term postoperative period of 2 weeks postoperative to 12 weeks postoperative (p = .56).

Melatonin Dosage: 18 mg

Two of the included studies focused on the efficacy of 18 mg of melatonin in managing self-reported CRF in stage I to III breast cancer patients undergoing adjuvant chemotherapy and radiation. Sedighi Pashaki and colleagues (2021) conducted a double-blinded, placebo-controlled trial with 74 patients randomized to either the melatonin group (n = 38) or the placebo group (n = 36). Patients enrolled in the study were undergoing adjuvant chemotherapy and adjuvant radiation within 4 weeks postoperative from breast-conserving surgery or modified radical mastectomy. Participants were given 18 mg of melatonin or placebo 1 hour before bedtime,

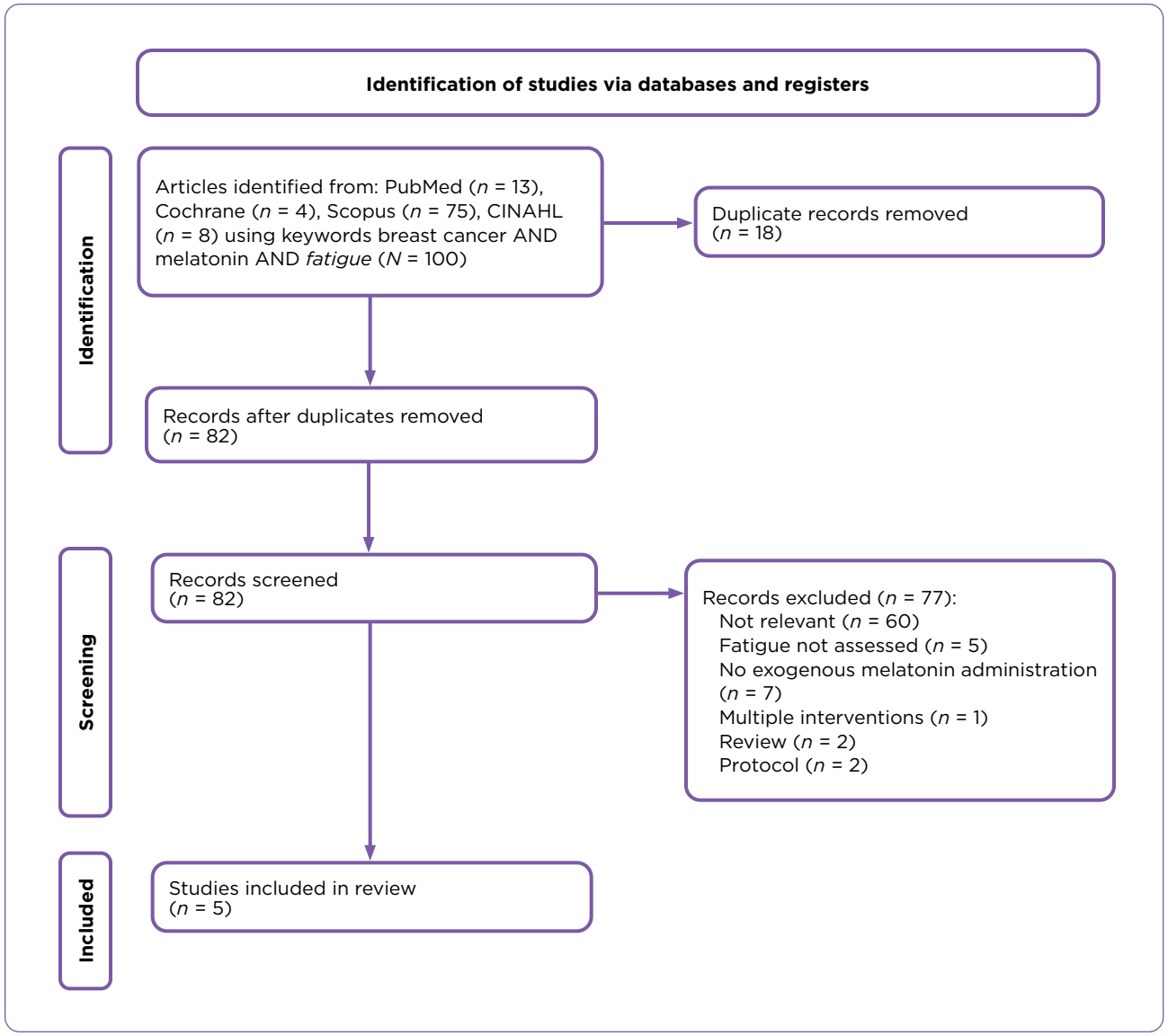

Figure 1. PRISMA flow diagram. Adapted from Moher et al. (2009).

starting 1 week before initiation of adjuvant chemotherapy until 1 month after adjuvant radiation. Patients completed the BFI questionnaire 1 week before the intervention and 4 weeks after the intervention. The total time of the study was 25 weeks. Sedighi Pashaki et al. (2021) found that there was no statistically significant difference in severity and mean score of CRF in the patients 1 week prior to the intervention (p = .393 and p = .10, respectively). The mean CRF score and severity of CRF were significantly lower in the intervention group (p = .001).

Sedighi Pashaki and colleagues (2023) conducted further research focused on the efficacy of 18 mg of melatonin in managing self-reported CRF in stage I to III breast cancer patients undergoing adjuvant chemotherapy and radiation. This double-blinded, placebo-controlled trial increased the sample size from the prior study to 183 patients randomized between the melatonin group (n = 91) and the placebo group (n = 92). Participants received either 18 mg of melatonin or placebo, taken 1 hour before bedtime, from 1 week prior to adjuvant treatment until 2 years after completion of adjuvant radiotherapy. Patients completed the BFI questionnaire 1 week prior to adjuvant treatment, 4 weeks after treatment completion,

Table 1. Summary of Literature Review

Article	No. of patients	Cancer type	Cancer treatment	Study intervention	Duration of study tx	Measures	Results
Innominato et al., 2016; prospective phase II trial	Total: 32 patients	Breast cancer, metastatic with stable disease	Patients receiving bisphosphonates, or hormonal therapy (tamoxifen, aromatase inhibitors, or progestins), or trastuzumab, or no systemic treatment in the palliative setting	5 mg of melatonin	Nightly for 2 months	Repeated measures design. Secondary outcome measure: Self-rated fatigue using the EORTC QLQ-C30, with higher scores indicating more fatigue.	Clinically meaningful decreases (i.e., ≤ 10 points) occurred in 47.4% of patients. There were significantly higher fatigue scores prior to treatment compared to after treatment with melatonin (p = .011).
Hansen et al., 2014; RCT	Total: 54 patients (melatonin group n = 28, placebo group n = 26)	Breast cancer	Patients planned to undergo lumpectomy or mastectomy, receiving no neoadjuvant chemotherapy in the curative setting	6 mg of melatonin	Daily, 1 hour before bedtime for 1 week preoperatively and 12 weeks postoperatively	Secondary outcome measure: Fatigue as measured by VAS.	There was no significant difference in fatigue between the melatonin group and the placebo group in the short-term postoperative period (p = .91). No significant difference in CRF between the melatonin group and placebo group in the long-term postoperative period (p = .56).
Sedighi Pashaki et al., 2021; RCT	Total: 74 patients (melatonin group n = 38, placebo group n = 36)	Breast cancer, stages I to III	Adjuvant chemotherapy and adjuvant RT within 4 weeks post-op from breast conserving surgery or modified radical mastectomy in the curative setting	18 mg of melatonin	Daily, 1 hour before bedtime, starting 1 week before initiation of adjuvant chemotherapy until 1 month after adjuvant RT	Primary outcome measure: Fatigue as measured by BFI, with higher scores indicating more fatigue.	Mean fatigue score was significantly higher in the placebo group compared to the intervention group (p = .001).
Sedighi Pashaki et al., 2023; RCT	Total: 183 patients analyzed (melatonin group n = 91, placebo group n = 92)	Breast cancer, stages I to III	Adjuvant chemotherapy and adjuvant RT within 4 weeks post-op from breast conserving surgery or modified radical mastectomy in the curative setting	18 mg of melatonin	Daily, 1 hour before bedtime, starting 1 week before adjuvant treatments to 2 years after end of breast cancer treatment	Primary outcome measure: Fatigue as measured by BFI, with higher scores indicating more fatigue.	Mean fatigue scores were higher in the placebo group compared to the intervention group at 1 month (p = .007). Mean fatigue scores were higher in the placebo group compared to the intervention group at 2 years after intervention (p = .001)
Mukhopadhyay et al., 2023; RCT	Total: 77 patients (melatonin group n = 39, placebo group n = 38)	Breast cancer, early stage or ductal carcinoma in situ	Outpatient RT treatment with curative intent	20 mg of melatonin	Daily starting the night before RT initiation until 2 weeks post-RT	Primary outcome measure: Fatigue as measured by FACIT-F and PROMIS. Higher FACIT-F scores indicate less fatigue. Higher PROMIS scores indicate more fatigue.	No significant difference in fatigue between melatonin and placebo groups in FACIT fatigue score (p = .83) and PROMIS short-form (p = .34)

Note. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer QLQ-C30; RCT = randomized controlled trial; VAS = Visual Analogue Scale; CRF = cancer-related fatigue; RT = radiation therapy; BFI = Brief Fatigue Inventory; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; PROMIS = Patient-Reported Outcomes Measurement Information System.

and 2 years later. Prior to the intervention, there was no significant difference in severity and mean CRF between the melatonin and placebo groups (p = .751, p = .671, respectively). One month after intervention, the severity and mean CRF scores were significantly lower in the melatonin group compared to the placebo group (p < .001, p = .007, respectively). At 2 years after the intervention, severity of CRF and mean CRF scores were significantly lower in the melatonin group compared to the placebo group (p < .001, p = .001 respectively).

Melatonin Dosage: 20 mg

Mukhopadhyay and colleagues (2023) investigated the efficacy of 20 mg of melatonin in managing CRF in ductal carcinoma in situ breast cancer patients undergoing radiation therapy (RT). This randomized, double-blind, placebo-controlled phase III trial randomized 77 patients into a melatonin group (n = 39) and placebo group (n = 38). Participants in the melatonin group were given 20 mg of melatonin nightly, starting the night before starting RT and until two weeks post-RT. FACIT fatigue scores and PROMIS fatigue scores were measured at baseline, at completion of RT, 2 weeks post-RT, and 8 weeks post-RT. The researchers reported no significant difference in treatment effect between the melatonin and placebo group CRF as measured by the FACIT fatigue score (p = .8313). There was no significant difference in treatment effect between the melatonin and placebo group CRF as measured by the PROMIS short form (p = .34).

Side Effects

Side effects of melatonin were outlined in the study by Hansen et al. (2014) where participants used a 6-mg melatonin dose in the treatment arm. Fifty-six percent of patients experienced at least one side effect in the melatonin group (15/27) compared to 50% in the placebo group (p = .78). Participants in the melatonin arm reported dizziness (14%), headache (10%), and paresthesia in the mouth region, arms, or legs (10%) most frequently. Participants in the placebo group reported headache (27%), difficulty falling asleep (13%), and nausea (13%) with the greatest frequency. Sedighi Pashaki et al. (2023) reported side effects in the treatment arm, which used an 18-mg dose of melatonin. This included severe nausea within the melatonin group, with 5 out of 102 patients withdrawing from the study. In the study performed by Mukhopadhyay et al. (2023) where a 20-mg melatonin dose was used in the treatment arm, participants in both groups reported somnolence and headache as side effects. They noted one patient experienced grade 3 insomnia that the authors attributed to the study drug. In the studies performed by Innominato et al. (2016) and Sedighi Pashaki et al. (2021), side effects of melatonin usage were not reported (Table 2).

Table 2. Side Effects of Melatonin Compared to Placebo

Study/Dosage	Melatonin	Placebo
Hansen et al., 2014/6 mg	Headache (10%), dizziness (14%), paresthesia of mouth region, arms/legs (10%)	Headache (27%), difficulty falling asleep (13%), nausea (13%)
Sedighi Pashaki et al., 2023/18 mg	Severe nausea (5 out of 102 patients withdrawing from the study)	No withdrawals due to nausea
Mukhopadhyay et al., 2023/20 mg	≤ Grade 2 toxicities of somnolence and headache were most reported. Grade 3 toxicities include fatigue (n = 3), pain (n = 1), dermatitis radiation (n = 1), headache (n = 2), breast pain (n = 1), hypertension (n = 1). Grade 4 toxicities include breast infection (n = 1). There were no grade 5 toxicities reported.	≤ Grade 2 toxicities of somnolence and headache were most reported. Grade 3 toxicities include vertigo (n = 1), fatigue (n = 3), dermatitis radiation (n = 1), myalgia (n = 1), dizziness (n = 1), headache (n = 1), nervous system disorders (n = 1), insomnia (n = 1), acute kidney injury (n = 1), hot flashes (n = 1), hypertension (n = 1). Grade 4 toxicities include hyponatremia (n = 1), confusion (n = 1), depression (n = 1). There were no grade 5 toxicities reported.

Note. Side effects of melatonin compared to placebo in Hansen et al. (2014); Sedighi Pashaki et al. (2021); and Mukhopadhyay et al. (2023). Side effects were not reported in Innominato et al. (2016) and Sedighi Pashaki et al. (2021).

DISCUSSION

Cancer-related fatigue is common, multifactorial, and affects quality of life for cancer patients. While physical activity has the strongest evidence in treating CRF, it may not be appropriate for every patient based on functional status, disease, and safety concerns. Treatment with medications including methylphenidate or dexamethasone have a greater side effect profile compared to melatonin. The studies assessed in this integrative review had mixed results.

Research done by Innominato et al. (2016) and both studies done by Sedighi Pashaki et al. (2021, 2023) found a significant improvement in CRF in the melatonin interventions. Hansen et al. (2014) and Mukhopadhyay et al. (2023) found no significant difference in CRF between the melatonin and placebo groups. There was no significant improvement in CRF in the studies utilizing 6 mg of melatonin (Hansen et al., 2014) and 20 mg of melatonin (Mukhopadhyay et al., 2023). There was a significant improvement in CRF in the studies utilizing 5 mg of melatonin (Innominato et al., 2016) and 18 mg of melatonin (Sedighi Pashaki et al., 2021; Sedighi Pashaki et al., 2023).

The articles included in this review utilized multiple measures of CRF, including the EORTC QLQ-C30, VAS for fatigue, BFI, and FACIT-F. Innominato et al. (2016) utilized the EORTC QLQ-C30 in screening self-rated fatigue, which is a 30-item quality-of-life questionnaire with three fatigue-specific questions about the prior week. The EORTC QLQ-C30 is a valid tool to screen for CRF (Fisher et al., 2022). Hansen et al. (2014) utilized the VAS for fatigue, which poses one question rating worst fatigue, on a scale of 0 to 10, since the prior clinic visit. The VAS for fatigue has a sensitivity of 69% to 85% and a specificity of 61% to 71% (Fisher et al., 2022). Sedighi Pashaki et al. (2021, 2023) utilized the BFI questionnaire, which is a scale-based measurement of fatigue over the prior 24 hours and the impact on patients' lives. The BFI is a validated tool that has been used reliably across various studies of patients with cancer (Fisher et al., 2022). Mukhopadhyay et al. (2023) utilized the FACIT-F and the PROMIS Fatigue-Short Form in the measurement of fatigue. The FACIT-F instrument is scored on a 5-point Likert scale based on the prior week. The FACIT-F has been extensively tested and validated in assessing CRF (Fisher et al., 2022). The PROMIS Fatigue-Short Form is a 5-point Likert scale that assesses the experience of fatigue and interference of fatigue on daily activities over the past 7 days. The PROMIS Fatigue-Short Form has high internal consistency and is an effective tool for assessment of CRF (Fisher et al., 2022).

The included articles utilized a variety of treatment modalities. It is notable that in the studies where patients underwent chemotherapy, CRF improved compared to studies where patients underwent surgery alone. A possible contributor to these differences could be that patients with more advanced cancer and/or an indication for systemic therapy may have a higher symptom burden, including CRF. These patients may find a more robust benefit from interventions like melatonin. Further studies should be conducted with stratification of results based on stage and treatment modality.

One limitation of this integrative review is the varying dosages of melatonin in the studies. In previous studies, there has been no definitive recommended dose of melatonin for management of CRF. In the United States, melatonin is marketed as a dietary supplement and is only loosely regulated; therefore, it can contain varying amounts of melatonin as well as serotonin (Erland & Saxena, 2017). Patients have greater access to melatonin due to the availability as an over-the-counter supplement; however, the efficacy could be dependent on the formulation. Further studies should be conducted to determine the ideal dosage of melatonin in the management of CRF. Another limitation of this review is the variable lengths of time that melatonin was administered during the studies, with a range of 2 months to 2 years. Outside the confines of a clinical study, patients may stay on melatonin for much longer as CRF can persist for years. Further research should be conducted to analyze the efficacy of melatonin in managing CRF in the long term.

Implications for Advanced Practitioners

Oncology advanced practitioners (APs) are experts in side effect management and patient education. Given the prevalence of CRF approaches 100% of cancer patients, oncology APs will encounter patients experiencing this side effect. Having

patient-centric management strategies for CRF is crucial. Melatonin can be considered for management of CRF in patients with breast cancer who have physical limitations or in addition to exercise. Clinicians should continue to assess CRF at each visit with a validated fatigue assessment tool. Further AP-led research should be considered.

CONCLUSION

Melatonin supplementation can be considered an option for breast cancer patients experiencing CRF. It may be especially useful to manage CRF in the context of patients with physical limitations where exercise may not be an option. The ideal dosage of melatonin in treatment of CRF has not yet been established and should be examined further in future studies.

Disclosure

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