



Published in final edited form as:

J Cancer Sci Ther. 2011 September 29; Suppl 2: .

Interventions to Alleviate Symptoms Related to Breast Cancer Treatments and Areas of Needed Research

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Abstract

Treatments for breast cancer produce a host of side effects, which can become debilitating. Some cancer treatment-related side effects occur in up to 90% of patients during treatment and can persist for months or years after treatment has ended. As the number of breast cancer survivors steadily increases, the need for cancer control intervention research to alleviate side effects also grows. This review provides a general overview of recent clinical research studies of selected topics in the areas of symptom management for breast cancer with a focus on cognitive difficulties, fatigue, cardiotoxicity, bone loss, insomnia, and cancer pain. We review both pharmacological and behavioral intervention clinical research studies, conducted with breast cancer patients and survivors. Additionally, clinical perspectives on symptom management and recommendations for areas of needed research are provided.

Keywords

Cancer treatment; Symptom management; Side effects; Interventions; Intervention mechanisms

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Symptoms Associated with Breast Cancer Treatment Discussed in this Review

While advances in breast cancer therapies have resulted in improved survival, side effects stemming from these treatments can be persistent and debilitating. Research suggests that chemotherapy, radiation therapy and hormonal therapy can all contribute to the development and persistence of side effects, including cognitive impairment [1-17], fatigue [18-22], sleep difficulty [23], pain [24-27], cardiotoxicity [28-29], and bone loss, [30-32] the areas of focus in the current review. Many of these symptoms co-occur; however, the underlying etiological pathways leading to each of these side effects may be distinct. Key pathways likely involved in the development of many treatment-related symptoms include immune system dysfunction, genetic pathways, hypothalamic-pituitary-adrenal axis dysfunction, and apoptosis of non-neoplastic cells [33-44].

Side effects from breast cancer treatments can negatively influence quality of life and activities of daily living, lead to non-compliance treatments, and ultimately affect prognostic and survival outcomes [45,46]. Interventions to alleviate side effects are needed to reduce symptom burden, enhance quality of life and functional capacity, and improve adherence to therapy. This review summarizes recent clinical trials and other clinical research studies in the areas of symptom management for breast cancer with a focus on cognitive difficulties, fatigue, cardiotoxicity, bone loss, insomnia, and cancer pain.

Pharmacological Interventions to Treat Symptoms in Breast Cancer

Psychostimulants

Methylphenidate, which enhances levels of dopamine in the brain, is commonly used to treat attention deficit disorder. Several randomized controlled trials have assessed the effects of methylphenidate or its derivatives in trials of cancer-related fatigue and have revealed some promising preliminary results, although these studies have been conducted with relatively small samples. Bruera and colleagues [47] found significant improvements in fatigue in both methylphenidate and placebo groups. Lower and colleagues demonstrated that dexmethylphenidate, the D-isomer of methylphenidate, led to a significant reduction in fatigue in patients who had received chemotherapy [48]. Auret and colleagues showed that the psychostimulant dexamphetamine had no significant effect on fatigue compared to placebo [49].

Modafinil is a wakefulness-promoting agent that is effective in treating sleep disorders and has also been shown to have cognition-enhancing functions. Modafinil can alleviate cancer-related cognitive difficulties (i.e. speed of memory, episodic memory quality) in breast cancer survivors [50]. In patients receiving chemotherapy, modafinil also reduced severe fatigue but had no benefit in those with mild or moderate fatigue [51]. Interestingly, in that same study modafinil did not improve depression, suggesting that while some symptoms, like fatigue and depression, co-occur, they may have underlying distinct pathways and warrant separate interventions.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are typically used as anti-depressants to treat depressive and anxiety disorders. Recent studies have been conducted to assess the effects of paroxetine on cancer-related fatigue. Two studies have shown that paroxetine alleviated depression but not fatigue in breast cancer patients receiving chemotherapy [52,53], and another study showed that paroxetine is as good as amitriptyline for treating depressive

symptoms in cancer patients [54]. Paroxetine represents another interesting example where alleviating one symptom does not alleviate another.

Vitamin D

In recent years, many studies have examined the relationship between breast cancer outcomes and vitamin D. Vitamin D also plays an important role in breast cancer symptom management. Vitamin D supplementation may reduce cancer-treatment-induced bone loss, aromatase inhibitor-induced arthralgias, cognitive difficulties, and cardiotoxicity. Nevertheless, vitamin D deficiency/insufficiency (<30 ng/ml) remains highly prevalent in breast cancer patients, with rates of sub-optimal vitamin D levels ranging from 63-90% [55,56].

Up to 80% of breast cancer patients experience bone loss during treatment [30-32]. While postmenopausal women without cancer lose an annual average of 1% of their bone mineral density (BMD), women receiving treatment for breast cancer can lose 2% to 7% of their BMD annually [57-61], resulting in a 5-fold increased rate of fractures compared to women without cancer [62-64]. Bone loss and the ensuing fractures result in increased mortality, increased need for assisted living, and decreased quality of life [65-68]. The major role of vitamin D in humans is to increase the absorption of calcium and phosphate, which are directly involved in the development and maintenance of the skeleton [69]. The majority of vitamin D is produced in the skin in response to sunlight exposure. When sunlight exposure is limited (e.g. winter months, sunscreen usage), dietary sources such as fatty fish, fortified foods, and supplements become the main source of vitamin D [70]. Randomized controlled clinical trials show that vitamin D supplementation can improve bone metabolism, increase BMD, and decrease fracture incidence [71-74]. Trials in postmenopausal women show that the beneficial bone effects of vitamin D supplementation are strongly dose-dependent [71], with vitamin D supplementation doses <500 IU/day failing to significantly improve bone metabolism biomarkers (BMB) and BMD levels [75-77]. Significant improvements in bone health with higher daily doses of vitamin D (500-1,200 IU/day) have been observed [73,74,78,79], while other studies found no benefit [80-82]. Only a small number of studies have examined the effect of high-dose, weekly vitamin D supplementation (20,000-100,000 IU/week) on bone health, but these studies have yielded positive results in terms of improvements in bone metabolism and BMD levels [83-87]. While strong evidence supports the use of vitamin D supplementation in the preservation bone health, there is no consensus on the ideal amount of vitamin D intake, and further trials are needed to determine the ideal vitamin D supplementation regimen for the prevention of bone loss.

Recent studies have shown that cognitive impairment affects a large number of breast cancer patients and survivors, specifically impacting memory and concentration [88]. In the nervous system, vitamin D functions as a neurosteroid hormone and displays antineurodegenerative actions [89-91]. Observational studies show increased vitamin D levels are associated with increased global cognitive function [90,92,93]. While no clinical trials examining the effect of vitamin D supplementation on cognitive function exist to date, vitamin D supplementation remains a promising treatment for the prevention and alleviation of cognitive impairment in breast cancer patients and further research in this area is needed. Arthralgia (joint pain) is a well-characterized side effect of aromatase inhibitor (AI) therapy [94]. Phase III AI trials indicate that 18-35% of patients complain of arthralgias [24-27], while almost 50% of AI users reported arthralgias in cross-sectional surveys [95]. Arthralgias are the number one reason for non-compliance in AI users [96,98], with up to 25% of AI users discontinuing usage [97,98]. Two recent studies have shown high-dose vitamin D supplementation significantly reduces AI-induced arthralgias. One study found that breast cancer patients who reached the target threshold for vitamin D (25-OH vitamin D > 40 ng/ml) had an 88% reduction in the onset of AI-induced arthralgias when compared to

those who did not reach the target threshold [99]. The other study found that breast cancer patients who were above the median 25-OH vitamin D level (> 66 ng/ml) reported no disability from joint pain 52% of the time while those below the median 25-OH vitamin D level (< 66 ng/ml) reported no disability from joint pain only 19% of the time. While further research is needed, vitamin D shows initial promise in the prevention of AI-induced arthralgias.

Cardiotoxicity refers to a diverse range of cardiovascular effects, including heart failure, myocardial infarction, pericardial disease, valvular abnormalities, due to anti-neoplastic therapy [100]. Cardiovascular mortality of cancer survivors is 7-fold higher than the age-matched non-cancer population [28,29]. Anthracyclines, a key component of numerous cytotoxic regimens, is one of the main causes of cardiotoxicity in breast cancer patients [101]. Symptoms of cardiotoxicity, such as decreased left ventricular function, are seen in approximately 25% of breast cancer patients treated with anthracyclines [102]. Trastuzumab, a monoclonal antibody used in the treatment of HER2-positive breast cancer, also contributes to cardiotoxicity. Cardiotoxicity is seen in 3-7% of patients who use Trastuzumab alone and close to 30% when it is combined with anthracyclines [103]. Large randomized trials are currently under way evaluating the effect of vitamin D supplementation on cardiovascular outcomes [104]. Based on the evidence of ongoing trials, vitamin D supplementation may eventually be used as a cardioprotective agent in breast cancer patients.

Pharmacologic Interventions for Neuropathic Pain Related to Surgery

Between 20 and 50% of breast cancer patients develop chronic neuropathic pain in the breast, axilla, and arm [105-107]. Pharmacological interventions for neuropathic pain include opioid analgesics, antidepressants, and anti-epileptic drugs (reviewed in 108). Few drugs have been systematically tested in randomized clinical trials for efficacy specifically in post-mastectomy/ lumpectomy pain (PMLP). However, gabapentin, an antiepileptic drug, and venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), have proven effective in multiple trials involving PMLP. Both drugs decreased existing chronic pain in women who had previously received breast cancer surgery [109-110]. When administered starting before surgery, gabapentin decreased the time to first post-operative analgesic as well as pain scores and adjuvant analgesic use within the first 10 days. However, no effect was observed on long-term chronic pain in the two studies that inquired 3 and 6 months post-surgery [111-113]. However, treatment with venlafaxine beginning prior to surgery decreased pain scores and the need for analgesic use 6 months after surgery in two separate trials [111,114]. Venlafaxine decreased analgesic consumption between 2 and 10 days post-surgery in 1 out of the 2 studies [111]. An eutectic cream mixture of local anesthetics (EMLA) also demonstrated promise as a pre-surgical treatment preventing chronic post-operative pain. When applied to the breast and arm area beginning one day prior to surgery, EMLA decreased analgesic consumption between 2 and 6 days post-surgery and the incidence and intensity of pain 3 months after surgery [115]. Similar results were obtained when the same investigators combined EMLA and gabapentin in pre-operative treatment [116].

Addition of a paravertebral nerve block (PVB) anesthetic component during breast cancer surgery has been reported to decrease acute pain and opioid consumption immediately following surgery in multiple randomized clinical trials [117-120]. However, the effects of PVB implementation on pain levels and analgesic consumption after discharge vary between studies. Kairaluoma et al. [117,118] reported decreased pain at 14 days as well as 6 and 12 months after surgery in their PVB group. Conversely, Boughey et al. [121] detected differences at 1 and 3 hours post surgery, but not at one week. Moller et al. [119] reported

significant differences in median pain intensity in the post-anesthesia care unit (PACU), but not after discharge. However, the very low pain levels in all study participants after discharge decreased the probability of detecting significant differences. Together these studies suggest that the use of PVB is beneficial for acute post-operative pain in breast cancer patients; however refinement of study methods and dosage are needed to provide prolonged effects and reduced PMLP.

Behavioral Interventions to Treat Symptoms in Breast Cancer

Exercise

Exercise is a systematic, organized, and consistent routine of participating in physical activity at a dose (frequency, intensity, duration and mode) sufficient to produce improvements in physical (e.g., neurological, cardiovascular, pulmonary, muscular, bone) and/or psychological (e.g., memory, concentration, fatigue, sleep, anxiety, depression) health [123,124]. Exercise can be individually tailored and shows great promise as an intervention capable of improving many side effects stemming from breast cancer and its treatments such as neurotoxicity, impaired immune function, cardiopulmonary toxicities, bone loss, cognitive problems, fatigue, sleep disruption, anxiety, and depression [123-135]. As mentioned earlier in this review, side effects can be acute (starting during treatment and of relatively short duration), chronic (lasting for longer durations i.e., months or years), or late (developing months or years after treatments are completed) and evidence supports the use of exercise to minimize each of these types of side effects [123-135].

Aerobic exercise

Running, cycling, swimming, and walking are modes of aerobic exercise [136]. Research shows exercise to be a valuable intervention for the reduction of many breast cancer and treatment related side effects such as cognitive problems, fatigue, sleep disruption, depression, anxiety, self-esteem, cardiopulmonary function, immune function, body composition, muscular strength, and flexibility as well as many other side effects [122-125,131,134,137-150].

Aerobic exercise can be beneficial when performed during and after treatment. Summaries of a few of these studies are highlighted. Mock and colleagues [151-153] reported that during chemotherapy and radiation for breast cancer, patients who performed home-based walking at a moderate intensity (50-70% of maximum heart rate) reported reductions in cancer-related fatigue CRF, sleep disruption, depression, anxiety, and nausea with improvements in cardiopulmonary function, and QOL. Home-based walking was performed for 10 to 45 minutes per day, 4 to 6 days per week, for one to six months. Female breast cancer survivors undergoing chemotherapy concurrent with participation in an aerobic exercise intervention which was progressive in nature, beginning with 15 minutes per session at 60% of VO_2 peak for 3 sessions per week and progressing to 45 minute sessions at 80% of VO_2 peak, using a treadmill, cycle ergometer, or elliptical trainer showed improvements in anxiety [154]. Courneya and colleagues [154] also found that breast cancer patients who were undergoing chemotherapy treatments could tolerate a higher relative dosage of chemotherapy treatment if performing aerobic exercise [154]. A study of breast cancer survivors who had completed treatment were given a moderate intensity home-based walking exercise intervention in which they walked 2 to 5 days per week for 12 weeks at 55 to 65% of maximum heart rate. Compared to control group participants, the exercise group reported improvements in fatigue, mood, vigor, and body esteem [155].

Resistance exercise

Resistance exercise can come in many forms, including dumbbells, therapeutic resistance bands, or even body weight [136]. Resistance training exercises have been found to benefit breast cancer survivors when performed during and following cancer treatment [122-125,131,134,137-150]. For example, during chemotherapy treatment for breast cancer, performing resistance training that consisted of 2 sets of 8 to 12 repetitions, three times per week, for the duration of chemotherapy resulted in an increase in self-esteem, upper and lower body strength, and lean body mass when compared to a usual care control group and. Further, exercising patients could tolerate higher doses of chemotherapy [154]. Schmitz and colleagues [141] studied the safety and efficacy of resistance training in breast cancer survivors who had recently completed primary treatment. The twice weekly resistance training for 6 to 12 months was safe and resulted in decreased body fat and increased lean body mass. Similarly, Ahmed and colleagues [156] assessed the safety of resistance training for breast cancer survivors who had recently completed treatment. Six months of twice weekly resistance training did not result in any change in arm circumference in participants. A progressive, moderate intensity resistance training and impact training (jump exercises), performed 3 times per week for 1 year, has been found to preserve bone mineral density in the lumbar spine of breast cancer survivors who are taking aromatase inhibitors, when compared to a control condition [157].

Combined aerobic and resistance exercise

Exercise programs that combine aerobic exercise and resistance training among breast cancer patients and survivors also effectively for reduce side effects [122-125,131,134,137-150]. A few of these studies are presented. Early stage breast cancer survivors receiving chemotherapy and/or radiation who participated in an aerobic and resistance exercise intervention 2 days a week for 12 weeks reported improvements in CRF, QOL, satisfaction with life, and also improved in physical function compared to usual care [156,158]. Mustian and colleagues [159] have also demonstrated the benefits of performing aerobic and resistance exercise during radiation treatment. A four week individually tailored, home based aerobic and resistance training program resulted in improved CRF, QOL, sleep, aerobic capacity, strength and immune function [36,159]. Sprod and colleagues [36] found that breast and prostate cancer patients receiving radiation treatments who exercised for four weeks using the home-based aerobic and resistance training program developed by Dr. Mustian exhibited greater improvements in sleep quality than non-exercising controls. Associations between interleukin-6 and sleep efficiency and duration were demonstrated. While undergoing radiation therapy, participants progressively increased the number of steps walked daily from 5,000 to nearly 12,000 [36,159]. Milne and colleagues [160] also used an exercise intervention that combined aerobic and resistance training for 12 weeks that resulted in improved muscular strength and aerobic fitness in breast cancer survivors who had completed treatment.

Mindfulness-based exercise

Mindfulness-based exercise modes such as Tai Chi Chuan and Yoga provide substantial benefits for cancer patients by relieving side effects, improving physical function and increasing QOL. For example, a community-based 12-week, 15-move, Yang Style Short-Form of Tai Chi Chuan improved aerobic capacity, strength, flexibility, body composition, self-esteem, QOL, bone formation and resorption, and immune function among breast cancer patients post-treatment [128,129,131,161-164].

Exercise for older cancer patients and survivors

More than 60% of people diagnosed with cancer are 65 years of age and over, and by 2030 approximately 70% of cancer patients will be elderly [165]. As cancer survival rates continue to improve, the number of older adults living with a cancer history in the United States will continue to grow. Older cancer survivors, compared to older adults without a cancer history, are at greater risk of developing geriatric syndromes including dementia, depression, osteoporosis, and at a greater risk of falls [166]. Limitations in activities of daily living [166], reduced quality of life [167], and greater frailty [166] are also common in older cancer survivors. Although a majority of cancer patients suffer from a multitude of symptoms and side effects from treatment, younger cancer patients may experience a transient functional decline where as older cancer patients may never fully recover function following treatment [168]. Ongoing research is seeking to identify which assessment tools can best predict outcomes in this population, and thus guide us in tailoring treatments to maximize benefits in older adults with breast cancer.

Very few researchers have specifically targeted older breast cancer survivors with aerobic and resistance exercise interventions despite the promise of such interventions. LaStayo et al. [169] implemented a 12 week eccentric, lower body exercise intervention in older breast cancer survivors. This eccentric exercise intervention involved the use of a recumbent stepper, with participants instructed to resist the motion of the pedals as they moved toward the participant. The force produced by the stepper was greater than could be overcome, so participants quadriceps in particular, elongated under the force of the stepper. This intervention resulted in increases in knee extension strength and power, and aerobic capacity, and decreased time to safely ascend stairs. Physical activity interventions are recommended for all older adults due to their ability to promote muscle mass and muscular strength [170], improve aerobic capacity [171], and reduce falls [172-174]. It is recommended that older adults, including older adults with chronic medical conditions such as cancer, participate in regular aerobic and resistance exercise training, including 150 to 300 minutes of aerobic exercise per week and at least 2 days per week of resistance training [175]. In addition, the Panel on Prevention of Falls in Older Persons of the American Geriatrics Society and British Geriatrics Society recommend that older persons incorporate a customized exercise program, including resistance, balance, gait, and coordination training to be most effective for reducing falls [176]. Older breast cancer survivors report reduced physical activity levels during and immediately following treatment but many attempt to reintroduce physical activity into their lives following treatment [177]. However, some barriers to physical activity following treatment include lack of time, fear of developing lymphedema, and complications from reconstructive surgery [177]. Of note, researchers have found breast cancer survivors with at least two lymph nodes removed who participated in a 13 week weight lifting intervention did not develop lymphedema at a greater rate than a control group that did not participate in resistance training [178]. Exercise interventions show great promise as an intervention that may reduce side effects and combat many of the common age related declines, such as reduce muscular strength and balance.

Integrative Medicine Approaches

Complementary and Alternative medicine (CAM) or integrative medicine, is a broad area of health care modalities that includes all the techniques that are not a part of conventional medicine and are commonly not prescribed by medical doctors or allied health care professionals. CAM includes natural products, mind body medicine, and manipulative and body-based practices. Women with breast cancer have reported using many of these techniques in conjunction with their treatment or after the completion of their treatment as a way of treating or alleviating their symptoms. In fact, breast cancer patients report CAM usage as high as 75% [179].

Natural products such as herbs, vitamins, and minerals constitute the most widely used CAM techniques among breast cancer patients [180]. Systematic research however, reveals that multivitamins are not helpful in relieving fatigue in breast cancer patients in a double-blind crossover design compared with a placebo [181]. A Significant effect of a Chinese herbal combination on reducing chemotherapy-induced fatigue, nausea, and vomiting has been reported by Situ et al. [182]. Essiac [183] has been used increasingly for relief of symptoms in breast cancer patients; however, no significant effect in improving quality of life and mood states was found in a retrospective cohort study of breast cancer survivors.

Mind body medicine, a part of non-pharmacologic CAM that enables the mind to affect body functions, is being used increasingly by breast cancer patients [184]. A recent study reported 64.2% of breast cancer patients practiced mind body techniques following their diagnosis and this practice was associated with Hispanic race, higher education, low income, and other CAM use [185]. Meditation and yoga are two such areas that have been researched more than other techniques. Thus far studies of meditation and yoga in cancer have focused mainly on patients' quality of life [186-193]; while some studies have looked into symptoms like fatigue [194]. Mindfulness has been reported to improve cognitive functions in healthy and diseased populations [195]; however, studies of the effects of CAM techniques' on cognitive dysfunction in the breast cancer population are needed.

Mindfulness-based stress reduction (MBSR), a program that includes meditation and yoga postures, reported lower levels of total mood disturbance and distress [196] the effects of which persisted until the 12-month assessment [187]; and significant improvements in mood, sleep quality, and fatigue in a mixed cancer population [197]. A recent randomized controlled trial of MBSR program for 6 weeks in breast cancer survivors reported reduced anxiety, depression, and fear of recurrence and better perception of physical functioning [191].

Significant improvements have been reported in breast cancer survivors' persistent fatigue scores after a 12-week practice of yoga [194]. Another trial of yoga has been reported to lead to significantly better general health perception and physical functioning scores, higher levels of intrusive thoughts, and greater benefit finding in women with breast cancer stages 0-III undergoing radiation [198]; reduced fatigue and insomnia in stage II and III breast cancer patients compared to a brief supportive therapy group [199]; better QOL, social and emotional well-being, and spirituality in women with breast cancer from various ethnic backgrounds after chemotherapy [200]; better QOL and mood, less nausea and vomiting [201]; and a smaller decrease in natural killer (NK) cell percentages from pre- to postsurgery and postchemotherapy [202]. A similar study of yoga in women with breast cancer undergoing radiotherapy showed significantly less anxiety, depression, perceived stress, and DNA damage at the end of the treatment in the yoga group versus the control group receiving supportive counseling [203].

Other yoga programs, such as Iyengar yoga (IY) practice in breast cancer survivors, have shown an improvement in fatigue scores as well as emotional well-being [186] and improved pain and vitality scores in addition to other quality of life indices [204]. Similarly, better mental health scores and greater positive affect from a restorative yoga practice in women during active treatment [189]; reduced joint pains, fatigue, and sleep disturbance after practice of "Yoga of Awareness" program in survivors of stages IA-IIB breast cancer [188]; and reduced pain and fatigue in women with metastatic breast cancer after practicing similar yoga techniques have also been reported [205]. Another style, Viniyoga, has been observed to significantly improve fatigue in obese breast cancer survivors [206].

Acupuncture is included in mind body as well as manipulative techniques and it has been reported to reduce fatigue along with psychosocial distress in a sample of advanced breast and ovarian cancer patients [207]. One randomized controlled trial of polarity therapy reported significant reduction in fatigue in breast cancer patients undergoing radiation. Hypnosis, another mind body technique, in combination with cognitive behavioral therapy, has been reported to prevent the increase of fatigue increase compared to standard medical care during radiation therapy in breast cancer patients [208]. The same investigators have also observed reduced fatigue in women who underwent lumpectomy for breast cancer following a 15-minute presurgery hypnosis session compared to an attention control group [209]. Practice of a Chinese technique, tai chi, has been reported to increase functional capacity in terms of increased aerobic capacity, muscular strength, and flexibility compared to the control group and as well as improved health-related QOL and self esteem [163,164]. However, other studies of tai chi intervention have not provided consistent results and further research is needed [210].

Overall, integrative medicine research for breast cancer patients has grown in the past decade, yet there is heterogeneity in terms of the study design, the type and length of intervention programs, and the measures used to assess outcomes. Larger studies are needed to confirm the effects of many integrative medicine techniques on common symptoms of breast cancer treatment.

Clinical Perspectives

Assessment and treatment of symptoms is of utmost importance to the oncologist. In addition to affecting quality of life and activities of daily living, symptoms during treatment can lead to dose-reductions, non-compliance, and ultimately affect outcome. The oncologist assessing a complaint of side effects must obtain a thorough history including onset of the symptom in relation to the timing of the treatment, severity of the symptom, extent of symptom interference with activities of daily living, and extent of symptom progression or worsening with time. Some symptoms needing assessment may also appear months or years after treatment has ended.

Symptoms are typically assessed by self-report on a visual analog scale by validated symptom inventory measures used within the clinic. Blood tests may also be employed if anemia, hypothyroidism, or low Vitamin D is suspected. Additional analytic techniques may also be used including echocardiograms for cardiotoxicity, neuropsychological tests for cognitive difficulties and Dual-Energy X-Ray Absorptiometry (DEXA) scans to evaluate bone density.

It is important to inquire about patterns of co-occurring symptoms and obtain details of symptom cluster manifestations. New diagnoses, whether medical or psychiatric, should be considered as possible contributors to side effects. Therefore, communication with the patient's primary care physician can often offer insight that may be useful in understanding the complaint of a new side-effect. Additionally, a full list of medications can also be helpful in understanding what, besides cancer treatments, may be contributing to the symptom burden, as well as a clear assessment of the patient's nutritional status. For example, chemotherapy-associated nausea and vomiting, and mucocitis can lead to poor oral intake, weight loss and a cascade effect of related symptomatology such as loss of energy or fatigue, depression and anxiety.

Management of symptoms is always individualized to the patient depending on their specific circumstances. Methods of possibly reducing symptom burden are included within this review, and every opportunity should be taken to alleviate symptoms to limit dose reductions to treatments, particularly in the curative setting. This underscores the need for

more symptom management research—which is becoming increasingly important for continuing the improvement of quality of cancer.

Conclusion

This review highlights many areas of symptom management for breast cancer which have been recently addressed with systematic research methods. While tremendous progress has been made in the symptom management field, additional rigorous research is needed so that clinical guidelines in specific symptom management areas can be developed or refined. This review underscores the need for more symptom management research—which is becoming increasingly important for improving quality of life for breast cancer patients and involves close collaboration between oncologists and symptom management clinical researchers.

Acknowledgments

The research described in this publication was made possible by a grant from the NCI (Grant No. 1R25CA102618).

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