Management of Treatment-Related Symptoms in Patients With Breast Cancer:
Current Strategies and Future Directions

Sabrina Brem, BA, and Nagi B. Kumar, PhD, RD, FADA

Although the benefits of current treatment strategies are well established, many cancer survivors are at risk for developing physiologic and psychological late effects of cancer treatment that might lead to premature mortality and morbidity and compromise their quality of life. Psychological symptoms include anxiety, depression, fatigue, difficulty sleeping, and loss of self-esteem. Physiologic symptoms include pain, numbness, cognitive impairment, weight gain, loss of sexual interest, spontaneous menopause, and peripheral neuropathy. Both length and quality of survival are important end points. The goal of this review is to summarize the psychological and physiologic symptoms related to breast cancer treatment; the prevalence, contributing therapies, and inter-relatedness of these symptoms; current interventions to prevent, ameliorate, or treat these symptoms; and effectiveness and safety of these interventions. The results of this review will identify the gaps in knowledge and assist in the design of assessments and approaches to improve mortality and quality of life and provide the foundation for the development of evidence-based guidelines to standardize palliative care in cancer survivors.

At a Glance

- A significant number of patients with breast cancer experience psychological and physiologic effects of treatment.
- Current clinical practice and future research must focus on evaluation, treatment, and further understanding of the complex etiology and potential multimodal interventions to optimize patient outcomes.
- The review identifies important gaps in the research that can inform approaches to improve quality of life in survivors.

According to the American Cancer Society (ACS, 2010), breast cancer is the most common cancer diagnosed in women and ranks as the second-leading cause of death after lung cancer. Women with primary invasive breast cancer receive systemic treatments, including cytotoxic chemotherapy and hormonal therapy, to minimize recurrences and mortality, as well as local treatments such as surgery and radiation therapy (Shapiro & Recht, 2001). The most common surgical treatments are lumpectomy (surgical removal with clear margins), mastectomy (surgical removal of the breast), and removal of the axillary lymph nodes. Common nonsurgical treatments include chemotherapy, radiotherapy, and targeted biologic therapy. The five-year overall survival rate has increased to 89% because of advances in early detection and improved treatment strategies (ACS, 2010). If the site of the tumor is localized and treated in its early stages, the survival rate increases to 98% (ACS, 2010).

Although life expectancy has increased because of advancements, new complications also have arisen. Patients now experience a wide range of physical and psychological symptoms that impact the survivors' quality of life (see Table 1). Reported psychological symptoms include anxiety, depression, fatigue, difficulty sleeping, worrying, loss of self-esteem, and lack of appetite and sexual interest (Kenne Sarenmalm, Ohlén, Jonsson, & Gaston-Johansson, 2007). Psychological symptoms of distress are reported in 41% of patients with newly diagnosed breast cancer, with 11% diagnosed with major depressive...

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disorder (Fann et al., 2008). Elevated levels of proinflammatory cytokines (interleukin-1), which occur as a result of both surgical and nonsurgical cancer treatment, are documented in patients with those common psychological symptoms (Fann et al., 2008). Psychological distress often amplifies the impact of physical symptoms, especially in patients with breast cancer experiencing depression (Patrick et al., 2004).

Physical and psychological symptoms often are transient, and their long-term effects are debated. For example, patients with breast cancer are most vulnerable to diagnosis of a major depressive disorder within a year following diagnosis of breast cancer rather than in the long term (Fann et al., 2008). One year after treatment, however, only 20%–30% of patients with breast cancer reported severe psychological distress (Bleicker, Pouwer, van der Ploeg, Leer, & Adé, 2000). Anxiety also is transient: Fallowfield, Hall, Maguire, and Baum (1990) reported that although anxiety levels were significantly high at all points following surgical treatments, the highest values were reported at two weeks postoperatively. Some physical symptoms are permanent. For example, even four years following axillary node dissection, breast-conserving surgery, and radiation therapy, 34% of patients reported minor limitation of movement in the arm and shoulder on the treatment side, whereas 13% reported no improvements (Lash & Silliman, 2000).

Both length and quality of survival are important end points (Aziz, 2007). The goal of this article is to summarize the psychological and physiologic symptoms related to breast cancer treatment; the prevalence, contributing therapies, and interrelatedness of the symptoms; and current interventions to prevent, ameliorate, or treat these symptoms. This article will examine three of the most widespread psychological effects of treatment—depression, anxiety, and fatigue—and three of the most prevalent and controversial physiological side effects: pain, cognitive impairment, and early onset of menopause. Based on their review, the authors then identify gaps in knowledge that would guide future research to improve symptom assessment and management toward ultimately improving mortality and quality of care in breast and other cancer survivors.

### Methodology

A comprehensive literature review was performed, using Ovid MEDLINE® (1982–2010), and PubMed (1982–2010) using the following nested search terms and text words: breast cancer survivors, treatment effects, late effects of treatment, and breast cancer treatment symptoms. Reports and research involving patients older than 18 years, published in the English language or fully translated, were included. The study population included only breast cancer survivors, and only studies of women were deemed eligible for this article. In total, 74 studies and reports were included in the review and no specific studies related to this topic were eliminated.

### Psychological Symptoms

#### Depression

The overall rate of depression in patients with breast cancer is higher than in most cancers most likely because menopause and estrogen decline are related to depression (Fann et al., 2008). According to the 2002 National Institutes of Health State-of-the-Science Conference (Patrick et al., 2004), 1%–42% of

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>TREATMENTS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Cognitive-behavioral therapies, stress management, guided imagery, progressive muscle relaxation, meditation, and coping skills</td>
<td>Levels of anxiety debated, Lack of comparisons to general population</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Hormonal therapies, antioxidants, growth factors, monoamine oxidase inhibitors, dopamine agonists, cholinesterase inhibitors, and cognitive-behavioral therapies</td>
<td>Use of subjective questionnaires, Cognitive assessments without everyday functioning, Unknown mechanism</td>
</tr>
<tr>
<td>Depression</td>
<td>Stress reduction, cognitive-behavioral therapies, deep breathing, meditation, progressive muscle relaxation, antidepressants, and estrogen</td>
<td>Unknown mechanism of action, Need to identify populations at risk.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Cognitive-behavioral therapies, counseling, stress management, problem solving, and psychological support</td>
<td>Precise data on reduction of fatigue resulting from treatment are limited.</td>
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<tr>
<td>Pain</td>
<td>Analgesics, gabapentin, lidocaine patch 5%, tramadol, tricyclic antidepressants, and anticonvulsants</td>
<td>Empiric studies, Complicated mechanisms, Lack of epidemiologic studies, Lack of standardized diagnostic tools</td>
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<tr>
<td>Spontaneous or early menopause</td>
<td>Alternatives to hormone-replacement therapy and estrogen-replacement therapy: soy products, vitamins, herbal preparations, alternative prescription medications such as clonidine and megestrol acetate, and selective serotonin reuptake inhibitors</td>
<td>Most studies are preliminary, Proof of efficacy of alternate treatments is limited, Studies of prescription medication use (clonidine, megestrol acetate) are not yet published, No specific studies of acupuncture treatment, chiropractor visits, and nonprescription herbal remedies</td>
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patients with breast cancer reported depression. Although the prevalence of major depressive disorder in patients with cancer ranges from 10%–25%, the exact rate of depression is difficult to determine because of a variety of nonstandardized diagnostic tools that may not always based on Diagnostic and Statistical Manual criteria (Fann et al., 2008). Depression in patients with cancer might be attributed to the diagnosis of cancer itself, as well as adjuvant chemotherapy treatment or surgical procedures (Kenne Sarenmalm et al., 2007).

Whether patients with breast cancer experience more depression than the general population still is under debate. Andrykowski et al. (1996) compared psychosocial adjustment attitudes in patients with breast cancer and patients with benign breast problems, and reported no differences in psychological distress between the two groups. In fact, patients with breast cancer responded more positively to their diagnosis than those with benign issues: They noted an improved positive outlook and interpersonal relationships, and deeper spiritual and religious satisfaction (Andrykowski et al., 1996). In some instances, however, no differences in psychological distress are documented. When a subset of patients recently diagnosed with breast cancer at low risk of recurrence was compared with women randomly selected from the population, no significant variations were found in their psychological adjustment scores (Groenvold et al., 1999). In some cases, the breast cancer population reported lower levels of depression and anxiety. In both studies (Andrykowski et al., 1996; Groenvold et al., 1999), the authors acknowledged the limitations involved in collecting data concerning psychosocial symptoms in patients. They identified a lack of standardization among assessment tools for comparison between patients with cancer and control groups (Groenvold et al., 1999), as well as a lack of objective measures for evaluating positive psychosocial adaptation (Andrykowski et al., 1996).

Treatment of depression varied widely. Interventions often focus on stress reduction and cognitive behavior strategies such as deep breathing, meditation and relaxation techniques, and progressive muscle relaxation (McGregor & Antoni, 2009). The treatments often are effective in the reduction of biologic markers of breast cancer progression and result in lower cortisol levels and improved cytokine production to anti-CD3 stimulation up to 12 months later (McGregor & Antoni, 2009). Cognitive-behavioral stress management interventions also are effective prevention strategies. In a study by Greer et al. (1992), adjuvant psychological therapy, a cognitive-behavioral therapy developed for patients with cancer, significantly reduced the proportion of patients with possible major depressive disorder on the Hospital Anxiety and Depression Scale (HADS) (HADS ≥ 8: 22% versus 7%). An operational definition of psychological morbidity for depression based on the HADS is a score equal to or more than 8, with increasing scores demonstrating greater depression. The percentage of patients who scored at that level was reduced from 22% to 7% with intervention. According to Fann et al. (2008), antidepressants also are effective treatments for depression in patients with breast cancer; selective serotonin reuptake inhibitors, adrenergic and histamine agonists, and norepinephrine reuptake inhibitors combined with cognitive-behavioral therapy might improve the recovery time more than cognitive treatments alone. However, recent evidence indicates that some selective serotonin reuptake inhibitor (SSRI) antide-

pressants reduce tamoxifen’s effectiveness by inhibiting its bioactivation by cytochrome P450 2D6 (CYP2D6) (Kelly et al., 2010). Evidence also suggests that estrogen might serve as an adjunct to the treatment of depression in postmenopausal women (Fann et al., 2008), but the use of estrogens in women diagnosed with breast cancer is contraindicated. Although the combination of psychotherapy and pharmacotherapy is an effective treatment for major depressive disorder in some populations, the effectiveness of this combination has not been examined in patients with breast cancer experiencing major depressive disorder (Fann et al., 2008). Despite the availability of treatment options that provide maximum benefit to the general population, the choices available to women with breast cancer are limited because of potential unknown effects and interactions with current treatment regimens (Andrykowski et al., 1996; Shapiro & Recht, 2001). Populations at risk for depression, as well as the functional or interpersonal outcomes of psychological interventions must be specifically identified (Andrykowski et al., 1996).

Anxiety

Depression and anxiety often coexist (Van den Beuken-van Everdingen et al., 2009). In a cohort of patients with breast cancer, the prevalence of anxiety and depression was 33% at diagnosis, 15% after one year, and 45% after recurrence (Burgess et al., 2005). According to McGregor and Antoni (2009), because depression and anxiety often copresent, the interventions are similar and focus on cognitive-behavioral stress management. Anxiety-reduction techniques include progressive muscle relaxation, guided imagery, autogenic or a comprehensive relaxation therapy, deep breathing and meditation, cognitive restructuring (i.e., process of learning to refute cognitive distortions with the goal of replacing them with more positive ones), coping skills, and interpersonal skills training conducted in a group therapy setting (McGregor & Antoni, 2009). In a study by Kissane et al. (2003), patients with breast cancer treated with cognitive-existential group therapy plus relaxation classes (versus a control of relaxation classes only) reported lower levels of anxiety than the control group, but no difference was found in the incidence of major depressive disorder. Women receiving cognitive therapy interventions reported lower anxiety levels at 12 months following the intervention. In addition, reduction of cortisol levels was reported immediately after the intervention and increases in cytokine anti-CD3 production were noted at a three-month follow-up (McGregor & Antoni, 2009).

Theories are conflicting regarding levels of anxiety in patients with breast cancer. Groenvold et al. (1999) reported that patients’ self-reported levels of anxiety were similar to those of the general population. However, the results were inconclusive because of biases and a lack of direct comparison between population groups. Future research should be directed at providing more symmetric surveys that would allow for parallel comparisons between the general population and patients with breast cancer.

Fatigue

Fatigue is the most common symptom associated with cancer and its treatment (Cella, Davis, Breitbart, & Curt, 2001). It is a nonspecific, subjective state, with decreasing levels of vitality
as a biologic protective mechanism to avoid further stress (Young & White, 2006). Cancer-related fatigue varies from everyday fatigue in terms of its severity and persistence, as well as its effects on physical, cognitive, and behavioral functioning (Young & White, 2006). It commonly co-occurs with psychological distress, as it causes and is triggered by psychological factors, including mood disturbances (Kenne Sarenmalm et al., 2007). Fatigue is a multidimensional spectrum of symptoms characterized by weakness, lack of energy, mental capacity, and cognition (Kenne Sarenmalm et al., 2007; Portenoy & Itri, 1999). The degree of psychological distress prior to treatment is the strongest predictor of fatigue following cancer therapy (Smets et al., 1998; Young & White, 2006). Cancer-related fatigue is a common effect of chemotherapy, radiation therapy, and other treatments (Portenoy & Itri, 1999; Kenne Sarenmalm et al., 2007).

The literature varies greatly regarding prevalence of chemotherapy-related fatigue. Kenne Sarenmalm et al. (2007) identified fatigue in 88% of patients with recurrent breast cancer; fatigue was indicated by a lack of energy (67%) and tiredness (87%). Although the prevalence is high in that population, it varies widely in cancer survivors, ranging from 4%–91% (Kenne Sarenmalm et al., 2007). Cella et al. (2001) noted that the most frequently reported range is 60%–90%, which is consistent with the number of cancer survivors in their study who reported fatigue after treatment (chemotherapy alone or in combination with radiation therapy) more than five years before. Young and White (2006) provided additional support when 57% of participants in their study reported severe fatigue. Cella et al. (2001) reported the lowest value (17%) of chemotherapy-related fatigue, which they attributed to strict criteria as a significant number of fatigue-related disruptions were required to assign it as a diagnosis. Because of its significant impact on the cancer population, standardized diagnostic tools must be developed to provide optimal patient outcomes (Cella et al., 2001).

According to Servaes, Verhagen, and Bleijenberg (2002), intervention strategies to control patient fatigue usually are cognitive-behavioral in nature and include individual counseling, stress-management skills, problem solving, and psychological support. The interventions can produce positive results, with less fatigue reported than in the control groups (Servaes et al., 2002). Others have examined interventions with increasing purposeful physical activity because physical activity levels have been shown to significantly predict fatigue level, regardless of age. Physical activity interventions aimed at improving functional strength have been shown to mitigate persistent fatigue in breast cancer survivors (Lueckar-Flude, Groll, Woodend, & Tranmer, 2009; Winters-Stone, Bennett, Nail, & Schwartz, 2008). The physiologic basis of fatigue has been examined and initial reports have correlated fatigue with clinically overt or subclinical hypothyroidism in the patient population (Kumar et al., 2004). Intervention trials with systematic assessment of these phenomena and testing interventions that may treat hypothyroidism and reduce fatigue are still pending. Precise statistical data on the efficacy and safety of treating fatigue with these interventions are limited. Future studies should examine the physiologic and psychological basis of fatigue in patients with breast cancer and develop targeted interventions to prevent and treat this symptom.

### Physiologic Symptoms

#### Pain

Pain and other symptoms of psychological distress often are concurrent (Fann et al., 2008), as many breast cancer survivors who experience pain also report anxiety or depression (Kenne Sarenmalm et al., 2007). In a study of 97 patients with breast cancer, 47% reported cancer-related pain (Stevens, Dibble, & Miaskowski, 1995). The most common physical effect of pain is directly correlated to higher levels of axillary lymph node involvement in older adult patients (Den Oudsten, Van Heck, Van der Steeg, Roukema, & De Vries, 2009). Axillary lymph node dissection (ALND), which was the standard surgical treatment for patients with invasive breast cancer for many decades, resulted in pain, numbness, or loss of strength in 21% of patients with breast cancer following surgery, none of which lessened over time (Ververs et al., 2001). The rate of reported levels of pain often varies; in a study by Hack, Cohen, Robson, and Goss (1999), 72% of breast cancer survivors reported pain, numbness, or weakness of the arm and shoulder following ALND. Although most survivors reported average and worst pain ratings after treatment, Jensen et al. (2010) showed significant associations of pain with physical functioning, severity of sleep problems, and psychological functioning.

One of the explanations for the variance in the levels of pain is the numerous mechanistic classifications for pain, which can be nociceptive, neuropathic, or ideopathic in origin (Chong & Bajwa, 2003). Neuropathic pain lasting at least three months is reported in 20%–50% of breast cancer survivors following surgical and nonsurgical treatments, including chemotherapy and radiation therapy (Bokhari & Sawatzky, 2009). First reported by Foley in 1987, this chronic pain syndrome is defined as pain related to abnormal sensory processing in the peripheral or central nervous system (Foley, 1987; Woolf & Mannion, 1999). Although the exact etiologic factors of the pain are not known (Chong & Bajwa, 2003), postsurgical tissue damage, nerve damage, and inflammation are among the known causes of nociceptive and neuropathic pain (Jung, Herrmann, Griggs, Oaklander, & Dworkin, 2005). Postmastectomy pain, a chronic neuropathic pain syndrome that can affect women permanently following mastectomy or lumpectomy for breast cancer, affects 27% of patients with breast cancer (Carpenter et al., 1998).

The treatments for neuropathic pain vary greatly, so no consensus has been reached on its optimal management (Chong & Bajwa, 2003). According to Gordon and Love (2004), interventions to reduce peripheral neuropathic pain are challenging because multiple mechanisms might be responsible for one symptom or a single pathway might be responsible for multiple symptoms. First-line drugs for neuropathic pain include gabapentin, lidocaine patch 5%, tramadol, and tricyclic antidepressants (Dworkin et al., 2003). Evidence suggests that anticonvulsants and antidepressants are effective in treating neuropathic cancer pain in patients who do not respond to conventional analgesics, such as opioids (Kloke, Höffken, Olbrich, & Schmidt, 1991). In clinical trials of patients with neuropathic pain treated with analgesic agents, response rates varied from 30%–60% (Dworkin et al., 2003). In many cases, an early combination of compounds affecting different underlying
mechanisms in each patient may be effective in producing some relief. The significant increase in knowledge of the underlying mechanism of pain, related symptoms, and the availability of a combination of drug therapies targeting these mechanisms and symptoms should ultimately result in the design of optimal treatments for the individual patient (Baron, 2009). Treatment is mostly empiric and dependant on the individual (Chong & Bajwa, 2003).

To optimize the management of neuropathic pain, nurses must establish guidelines for regular assessment using knowledge of the patients’ responses to pain (Bokhari & Sawatzky, 2009; Jensen et al., 2010). Pain from nonsurgical treatments, such as chemotherapy and radiation therapy, can be managed best by early detection and cautious dose selection (Jung et al., 2005). Epidemiologic studies are lacking and standardized diagnostic protocols are difficult to develop for patients experiencing neuropathic pain (Chong & Bajwa, 2005), so nurses need to bridge these gaps to improve their patients’ quality of life.

**Cognitive Impairment**

One of the most common adverse effects reported by patients with breast cancer is chemobrain or chemofog, a phenomenon of cognitive impairment that is reported in patients treated with chemotherapy for breast and other cancers and lasts anywhere from six months to 10 years (Phillips & Bernhard, 2003; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005). Cognitive deficits are also reported as likely the result of the general effect of cancer diagnosis, such as inflammation, autoimmune responses, anemia, steroid hormone deficit, hypothyroidism, diet and potential genetic polymorphisms, rather than systemic treatment (Jim et al., 2009; Schilder et al., 2010; Small et al., 2010; Smith & Blumenthal, 2010). Cognitive impairment significantly affects survivors’ quality of life (Ahles & Saykin, 2002; Boykoff, Moieni, & Subramanian, 2009). The neuropsychological deficits, more common with respect to verbal-semantic memory and concentration loss (Ahles et al., 2002; Weis, Poppelreuter, & Bartsch, 2009), affect patients’ ability to remember, think, and concentrate (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000), leading to deficits in memory, attention, and processing speeds (Weel, Lenzi, Theriault, Davis, & Meyers, 2004). According to Brezden et al. (2000), patients receiving adjuvant chemotherapy reported statistically significant lower overall cognitive function scores, especially for memory and language.

Although many studies have documented the effects of cognitive impairment resulting from chemotherapy (Ahles et al., 2002; Shilling et al., 2005; Wefel et al., 2004; Weis et al., 2009), the proportion of patients on chemotherapy who demonstrate this dysfunction differs dramatically from 16%–75% (Shilling & Jenkins, 2007). Weis et al. (2009) noted that although cognitive deficits decreased significantly in patients on chemotherapy by the end of cancer treatment, 21% showed long-term clinical cognitive deficits even nine months following treatment. The results are consistent with those of Wefel et al. (2004), in which 61% of women following chemotherapy treatment reported at least one cognitive deficit at a short-term evaluation point and 50% reported cognitive dysfunction at a long-term end point. The discrepancy of the values often is because of methodologic differences between studies and the comparison groups that are observed (Shilling & Jenkins, 2007). With the variety of nonstandardized assessment tools, providing truly objective data is challenging (Shilling et al., 2005). Furthermore, Shilling and Jenkins (2007) stated that future studies must incorporate cognitive assessments that measure everyday functioning to more clearly differentiate cognitive changes that are associated with psychological distress, mood state, and quality of life from those changes from objective cognitive decline. Often, questionnaires used to document patients’ self-report of memory loss, such as the Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald, & Parkes, 1982) are subjective in nature and might not reflect objectively measured cognitive decline (Shilling et al., 2005). Although the study by Shilling et al. (2005) addressed that issue by minimizing depression, anxiety, or quality of life as confounders with a pretreatment baseline, they used questionnaires that are not standardized across studies.

The potential mechanism related to cognitive impairment has been shown to be multifactorial and contributed by one or more of the following mechanisms—age, vascular injury, oxidative damage, inflammation, direct injury to neuron, autoimmune responses, chemotherapy-induced anemia, abrupt steroid hormone deficit, hypothyroidism, and the presence of the apolipoprotein gene (Abushamaa, Sporn, & Folz, 2002; O’Shaughnessy et al., 2005; Reid-Arndt, 2009; Vearncombe et al., 2009). Current treatment strategies for the loss in cognitive function are limited because of a lack of understanding of the exact etiology (Rugo & Ahles, 2003). To date, interventions with cognitive training alone (Barton & Loprinzi, 2002; Ferguson et al., 2007), pharmacologic agents to treat chemotherapy-induced anemia (Fan et al., 2009; Nelson, Nandy, & Roth, 2007), psycho-stimulants, and antioxidant therapies with vitamins A, C, and E have not demonstrated efficacy or safety in treating cognitive impairment in cancer survivors (Barton & Loprinzi, 2002; Mar Fan et al., 2008; Wen et al., 2006). In addition to the contraindications of using hormone replacement therapy to ameliorate symptoms of cognitive impairment, new trials have provided further evidence against long-term use, cost-effectiveness, and side effects with pharmacologic agents, particularly thrombocytopenic events, and have established the need to identify alternate approaches that can be implemented for longer durations, with fewer side effects and an established safety profile (Schilder et al., 2010). Future research should focus on neuroimaging techniques and the development of animal models than can translate to clinical application to identify the mechanisms that cause cognitive dysfunction in patients on chemotherapy (Ahles & Saykin, 2002). Based on the multiple etiology, the varying manifestation, and extent of cognitive decline documented in this cohort, future research should examine the efficacy and safety of multifaceted interventions, using structured cognitive training along with supplementation with a combination nutritional supplement with antioxidant and anti-inflammatory agents that...
Spontaneous or Early Menopause

The average age of natural menopause has remained 51 years in Western countries during the past three decades (Partridge et al., 2007). Despite inconsistent data, age at natural menopause might be related to certain environmental and reproductive factors, including smoking, marital status, education, parity, history of heart disease, prior use of oral contraceptives, and socioeconomic class (Gold et al., 2001; Partridge et al., 2007; Stanford, Hartge, Brinton, Hoover, & Brookmeyer, 1987). Premature menopause, or ovarian failure, defined as a cessation of menstruation before age 40 (Sklar et al., 2006), often results from adjuvant chemotherapy, surgery, or other cancer treatments (Baud & Brown, 2009). Serious physical and psychosocial consequences, including the development of menopausal symptoms such as hot flashes, genitourinary problems, psychological and psychosexual difficulties, weight gain, sexual dysfunction, palpitations, bone density loss, infertility, vaginal dryness, and short-term memory problems are possible (Baud & Brown, 2009).

Symptoms often manifest through chemotherapy-related amenorrhea (CRA), a common side effect of adjuvant chemotherapy in premenopausal women with breast cancer, which might be temporary or permanent (Partridge et al., 2007). According to Di Cosimo et al. (2004), the risk of CRA is related to patient age and the dose and type of chemotherapeutic agents used. Women older than 40 years are more likely to develop CRA than younger women, and a larger dose of chemotherapy or longer duration of treatment is more likely to cause premature menopause (Di Cosimo et al., 2004). In a study by Partridge et al. (2007), women who received six or seven cycles of chemotherapy with cyclophosphamide, methotrexate, and 5-fluouracil experienced an earlier onset of amenorrhea than women who were treated with one or no cycles of the treatment. Although women of all ages are at risk for permanent ovarian failure when undergoing chemotherapy, women younger than age 42 are more likely to regain ovarian function than women older than age 42 (Di Cosimo et al., 2004). Most women will experience permanent menopause, but 12%–15% of younger women reportedly resumed normal menstrual function following amenorrhea (Shapiro & Recht, 2001). Many premenopausal patients with breast cancer may menstruate during the cytotoxic treatment, but they might ultimately experience menopause earlier than if they had not undergone chemotherapy (Partridge et al., 2007). A woman’s age at treatment is significant in the timing of menopause; the closer a patient is to natural menopause, the less impact the chemotherapy plays on lowering the age of menopause if the woman does not stop having menstrual cycles during or immediately following cytotoxic treatment (Partridge et al., 2007). The risk of CRA declines as time increases since treatment (Sklar et al., 2006).

In addition to chemotherapy-related amenorrhea, some women experience early-onset menopause because of hormonal treatments such as tamoxifen therapy and preventive oophorectomy (Ganz, 2005). Treatments for these symptoms are therefore more complex because hormonal therapies might aggravate their symptoms (Ganz, 2005). According to Love, Cameron, Connell, and Leventhal (1991), 48% of tamoxifen users reported persistent vasomotor, gynecologic, and other side effects as opposed to 21% in the control group. Therefore, adherence in long-term treatment using tamoxifen might be problematic (Love et al., 1991). Furthermore, estrogens are a major trigger for the growth of hormone-dependent tumors linked to the pathogenesis of breast cancer (Seifert, Galid, & Kubista, 1999). Estrogen-replacement therapy is discouraged because of concerns that it might promote cancer recurrence (Santen, Pritchard, & Burger, 1998), although no clinical evidence suggests that this risk is likely to occur (Harris, Remington, Trethnam-Dietz, Allen, & Newcomb, 2002). Therefore, breast cancer survivors are more likely to use nonestrogen alternatives, including soy products, vitamins, herbal preparations, and alternative prescription medications such as venlafaxine or clonidine (Harris et al., 2002; Loprinzi et al., 1998). Nevertheless, proof of the efficacy of alternative therapies is limited (Harris et al., 2002). For example, studies documenting the use of prescription medications such as megestrol acetate and clonidine have not yet been published, and no studies of chiropractic visits or nonprescription herbal remedies are available among the breast cancer survivor population. Acupuncture appears to be promising when compared to venlafaxine in small, randomized clinical trials (RCTs) in these patients. However, the number of RCTs compared with a nonpenetrating placebo-control needle or hormone therapy was too small, and the methodologic quality of some of the RCTs was poor (Cho & Whang, 2009; Walker et al., 2010). SSRIs are evaluated as alternative treatments in the management of menopausal symptoms, as they have shown efficacy in reducing the frequency of hot flashes (Loprinzi et al., 2000; Weitzner, Moncello, Jacobsen, & Minton, 2002). However, caution must be used in women who are receiving tamoxifen as it might affect drug metabolism. More controlled studies are needed to evaluate SSRIs’ efficacy as an alternative therapy in the treatment of vasomotor symptoms because most published studies are preliminary reports (Harris et al., 2002; Loprinzi et al., 1998).

Conclusions

Nurses play a central role in the assessment and management of patient symptoms. In the future, nurses will play an even greater role in patient advocacy, education, and coordination of care. Ideally, the focus will be for prevention of symptoms resulting from treatment by earlier identification of at-risk patients and thorough screening of patients to improve health outcomes and prevent symptoms resulting from cancer treatments.

With increasing survival rates in the breast cancer population, symptoms resulting from treatments are inevitable. To alleviate the side effects, nurses must focus on resolving gaps in the literature through ongoing research. Nurses must identify...
assessment tools that evaluate the impact of the polysymptom-
atic nature of interrelated symptoms resulting from treatment,
rather than individual symptoms in isolation. To avoid bias, as-
essment tools should be standardized and expand beyond self-
reports. This would be especially beneficial in the identification
of often-subjective psychological syndromes, including fatigue,
depression, and anxiety. It would also allow for more accurate
comparison across studies, specifically by creating uniform
diagnostic criteria for severe psychological symptoms such
as fatigue, depression, and anxiety. Furthermore, assessments
should evaluate concurrent and interrelated symptoms rather
than focusing on individual symptoms.

The scope of interventions should expand beyond a tradi-
tional behavioral approach. The mechanisms of action resulting
in patient symptoms must be understood to target interventions
from pharmacologic and cognitive-behavioral perspectives. A
deeper understanding of the complexities of the variables influ-
encing symptom distress must occur to recognize, evaluate, and
treat the symptoms effectively. Future research must be directed
at understanding the complex multimodal physiologic and bio-
logic mechanisms of action that impact patient symptoms. The
role of nurses will expand to recognize and evaluate these needs
to optimize patient outcomes.

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References

and inflammation contribute to lung toxicity after a common
breast cancer chemotherapy regimen. American Journal of
Physiology—Lung Cellular and Molecular Physiology, 283(2),
L336–L345.

Ahles, T.A., & Saykin, A.J. (2002). Breast cancer chemotherapy-
related cognitive dysfunction. Clinical Breast Cancer, 3(Suppl.

Skalla, K., . . . Silberfarb, P.M. (2002). Neuropsychologic impact
of standard-dose systemic chemotherapy in long-term survivors
of breast cancer and lymphoma. Journal of Clinical Oncology,

American Cancer Society. (2010). Breast cancer facts and figures

Andrykowski, M.A., Curran, S.L., Studts, J.L., Cunningham, L., Car-
adjustment and quality of life in women with breast cancer
and benign breast problems: A controlled experiment. Journal
of Clinical Epidemiology, 49, 827–834. doi: 10.1016/0895-
4556(96)00028-5

Aziz, N.M. (2007) Cancer survivorship research: State of knowledge,


Barton, D., & Loprinzi, C. (2002). Novel approaches to preventing
chemotherapy-induced cognitive dysfunction in breast cancer: The
art of the possible. Clinical Breast Cancer, 3(Suppl. 3), S121–S127.

Bauld, R., & Brown, R.F. (2009). Stress, psychological distress,
psychosocial factors, menopause symptoms and physical health

Blecker, E.M., Pouwer, F., van der Ploeg, H.M., Leer, J.W., & Adèr,
H.J. (2000). Psychological distress two years after diagnosis of
breast cancer: Frequency and prediction. Patient Education and
Counseling, 40, 209–217. doi: 10.1016/S0167-8270(00)00085-3

Bokhari, F., & Sawatzky, J.V. (2009). Chronic neuropathic pain in
women after breast cancer treatment. Pain Management Nurs-

chemobrain: An in-depth look at survivors’ reports of impact on
work, social networks, and health care response. Journal of Can-

Brezden, C.B., Phillips, K.A., Abdolleh, M., Biston, T., & Tannock, I.F.
(2000). Cognitive function in breast cancer patients receiving adju-
vant chemotherapy. Journal of Clinical Oncology, 18, 2695–2701.

The Cognitive Failures Questionnaire (CFQ) and its correlates.
British Journal of Clinical Psychology, 21, 1–16.

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., &
Ramirez, A. (2005). Depression and anxiety in women with early

Carpenter, J.S., Andrykowski, M.A., Sloan, P., Cunningham, L.,
omy/postlumpectomy pain in breast cancer survivors. Journal of
Clinical Epidemiology, 51, 1285–1292. doi: 10.1016/S0895-
4356(98)00121-8

fatigue: Prevalence of proposed diagnostic criteria in a United
States sample of cancer survivors. Journal of Clinical Oncology,
19, 3385–3391.

menopausal symptoms: A systematic review. Menopause, 16,
1065–1073.

Chong, S.M., & Bajwa, Z.H. (2003). Diagnosis and treatment of
neuropathic pain. Journal of Pain and Symptom Management,

Den Oudsten, B.L., Van Heck, G.L., Van der Steeg, A.F., Roukema,
12 months after surgical treatment of early-stage breast cancer.
Psycho-Oncology, 18, 1230–1237. doi: 10.1002/pon.1518

Di Cosimo, S., Alimonti, A., Ferretti, G., Sperduti, I., Carlini, P.,
py-induced amenorrhea depending on the timing of treatment by
menstrual cycle phase in women with early breast cancer. Annals
of Oncology, 15, 1065–1071. doi: 10.1093/oncology/mdl266

Dworkin, R.H., Corbin, A.E., Young, J.P., Jr., Sharma, U., LaMoreaux,
L., & Bockbrader, H., . . . Poole, R.M. (2003). Pregabalin for the
treatment of postherpetic neuralgia: A randomized, placebo-

chological outcomes of different treatment policies in women with

Fan, H.G., Park, A., Xu, W., Yi, Q.L., Braæna, S., Chang, J., . . . Tann-
function in women following chemotherapy for breast cancer.
Psycho-Oncology, 18, 156–161. doi: 10.1002/pon.1372

Fann, J.R., Thomas-Rich, A.M., Katon, W.J., Cowley, D., Pepping,
standard-dose systemic chemotherapy in long-term survivors
of breast cancer: Five year observational cohort study. BMJ, 330,
702.

Frcan, J.R., Thomas-Rich, A.M., Katon, W.J., Cowley, D., Pepping,
standard-dose systemic chemotherapy in long-term survivors
of breast cancer: Five year observational cohort study. BMJ, 330,
702.


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