Available online at www.sciencedirect.com
ScienceDirect
General Hospital Psychiatry 30 (2008) 112–126
General Hospital Psychiatry

Psychiatric–Medical Comorbidity

The Psychiatric–Medical Comorbidity section will focus on the prevalence and impact of psychiatric disorders in patients with chronic medical illness as well as the prevalence and impact of medical disorders in patients with chronic psychiatric illness.

Major depression after breast cancer: a review of epidemiology and treatment

Jesse R. Fann, M.D., M.P.H.[a,b,d,e,*], Anne M. Thomas-Rich, M.D.[a], Wayne J. Katon, M.D.[a], Deborah Cowley, M.D.[a], Mary Pepping, Ph.D.[b], Bonnie A. McGregor, Ph.D.[f], Julie Gralow, M.D.[c]

[a]*Department of Psychiatry and Behavioral Sciences, University of Washington, P.O. Box 356560, Seattle, WA 98195, USA*
[b]*Department of Rehabilitation Medicine, University of Washington, Seattle, WA 98195, USA*
[c]*Department of Medicine, University of Washington, Seattle, WA 98195, USA*
[d]*Department of Epidemiology, University of Washington, Seattle, WA 98195, USA*
[e]*Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA*
[f]*Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA*

Received 26 June 2007; accepted 25 October 2007

Abstract

Objective: While many breast cancer patients experience "normal" distress, there is a subset who experience clinically significant depression. We examined the current knowledge about the prevalence, impact and treatment of major depression in women with breast cancer.
Method: We reviewed the evidence for the prevalence of depression in women with breast cancer from the last 20 years and summarized the medical literature on the pharmacology and psychotherapy of depression in this population.
Results: Despite evidence that depression significantly impacts quality of life in breast cancer patients, few studies focus on the epidemiology and treatment of major depression. Treatment studies have focused on distress and mixed depressive states, with resulting lack of replicable studies showing treatment efficacy. Potential biological and psychosocial determinants of major depression following breast cancer are discussed in a proposed model. The need for further research on the epidemiology and treatment of major depression in this population is proposed.
Conclusion: Major depression is a frequent but underrecognized and undertreated condition among breast cancer patients, which causes amplification of physical symptoms, increased functional impairment and poor treatment adherence. More research on the epidemiology and treatment of major depression in this population is needed.

Keywords: Depression; Distress; Breast cancer; Epidemiology; Treatment

1. Introduction

Breast cancer is the most common malignancy among women worldwide, with 178480 new cases in the United States each year [1]. As early detection and treatment have improved, survival rates have increased to the extent that 89% now survive 5 years beyond diagnosis [1]. Thus, focus has turned toward maximizing quality of life (QOL) among survivors who often experience persisting aversive symptoms such as fatigue, cognitive problems and menopausal symptoms [2,3].

Breast cancer diagnosis and treatment, and the months following primary therapy, are stressful times for most women. While many experience "normal" distress, there is a subset that experience clinically significant depression that may benefit from specialized psychiatric intervention.

* Corresponding author. Department of Psychiatry and Behavioral Sciences, University of Washington, P.O. Box 356560, Seattle, WA 98195, USA. Tel.: +1 206 685 4280.
E-mail address: fann@u.washington.edu (J.R. Fann).

0163-8343/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.genhosppsych.2007.10.008

Extensive research has sought to determine rates of general distress and facilitate coping strategies among breast cancer patients; however, few studies have focused on the epidemiology and treatment of the subset of patients with major depressive disorder (MDD).

Studies that examined both distress and depression have found differences in prevalence. A pooled analysis of studies examining the validity of general distress screening tools in detecting major depression showed a high rate of false positives [4]. One study found that while 41% of newly diagnosed breast cancer patients had high levels of distress, only 11% had MDD [5].

Depression is likely underrecognized in many cancer patients [6]. Oncologist–patient agreement for rating patient depression is good only when the patient reports no significant level of depression [7]. Agreement was only 33% for mild to moderate depression and 13% for severe depression, showing that there is a marked tendency to underestimate the level of depressive symptoms in patients who are more severely depressed. Use of depression screening instruments alone in medical settings without systematic changes in the system of care to increase exposure to appropriate evidence-based treatments has not been shown to consistently lead to improved outcomes [8–10].

Because of the unique psychosocial, medical and hormonal factors that may influence mood in breast cancer patients, epidemiological and treatment data on depression from other populations cannot be assumed to generalize to this population. The goals of this paper are to review the medical literature on the epidemiology of depression, particularly MDD, in women with breast cancer; discuss the association between depression and other sequelae of breast cancer, such as fatigue, pain, cognitive impairment, decreased adherence and caregiver burden and review pharmacotherapy and psychotherapy treatment studies for depression in this population. Finally, a model for the high prevalence of depression in breast cancer patients, the basis for pharmacological and psychotherapeutic intervention and the areas in need of further research will be proposed.

2. Methods

We completed a literature review from the last 20 years using PubMed by pairing the words "breast cancer" or "cancer" with the following words: *depression*, *distress* and *psychological disorders*. We also located research based on the bibliographies of the articles located with the PubMed search, including recent reviews. We selected articles that (1) were in the English language, (2) assessed using standardized instruments the prevalence or outcomes of depression symptoms or depressive disorders with patients with breast cancer and (3) were based on examining at least 50 subjects. Finally, we used PubMed to summarize the medical literature on the pharmacotherapy and psychotherapy of depression in breast cancer populations.

3. Results

3.1. Depression rates in women with breast cancer

Most studies of depression in breast cancer have used symptom scales that were not designed to diagnose *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), Fourth Edition (*DSM-IV*) mood disorders and for which validated cutoff scores for MDD are lacking. In studies that have used scales with high predictive value for MDD diagnosis, high rates of probable MDD during the first year after breast cancer diagnosis have been found, including the period following radiation therapy and adjuvant/neoadjuvant chemotherapy. Table 1 shows studies examining rates of clinically significant depression in women following surgery for breast cancer. While the data from these studies show a wide array of estimated depression rates, largely stemming from differences in study population, study design and choice of depression measure, the rate of depression cited in these studies was about 10% to 25%. Estimates based on screening instruments were generally higher and more variable (most ranged from 15% to 30%) than estimates based on structured interviews (most range from 5% to 15%). Women who have received chemotherapy vs. those who have not reported more psychological distress and depression [36,37]. Evidence was lacking for a strong association between cancer stage and depression [38,39].

The first year after diagnosis of breast cancer may be when patients are at highest risk for depression [40], particularly among younger patients [41]. Compared to patients who do not receive adjuvant therapy, patients on adjuvant chemotherapy have higher levels of depression [36,37,42], and adverse symptoms of chemotherapy have been associated with increased depression and decreased health-related QOL [43]. The effects of chemotherapy on fertility, sexuality and menopause-associated health problems (e.g., osteoporosis and cardiovascular disease) can lead to high levels of distress [44]. The selective estrogen receptor modulator (SERM) tamoxifen has also been shown in some studies to affect mood, with some women needing to discontinue tamoxifen secondary to depression [45–48], although other data mostly from prevention studies have not found an association between tamoxifen and depression [2,49–51]. Following primary cancer therapy, patients are often fearful of cancer recurrence and face the loss of support and frequent visits with medical professionals [40,52], contributing to high rates of anxiety [53–56], which is often comorbid with depression [39,56]. They may also continue to suffer significant fatigue and activity restriction as they attempt to resume their normal lives [57–59]. During these critical moments of their cancer journey, patients with breast cancer rated their need for "help with any sad feelings" as higher than patients with other cancer diagnoses [52].

3.2. Depression and physical functioning

Depression has been found to significantly influence the severity and number of side effects of cancer treatment as well as to increase the burden of fatigue, cognitive

dysfunction and anxiety in women receiving breast cancer treatment [60–62]. Several studies have documented the strong association between depression or distress and physical pain [63–65]. Depression likely amplifies and is a secondary consequence of pain [65,66].

In 2002, the National Institutes of Health State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression and Fatigue review reported that 14–100% of cancer patients experienced pain, 1–42% experienced depression and 4–91% experienced fatigue [67]. Gaston-Johannson et al. [68] examined the influence of fatigue, pain and depression on the health status of 127 breast cancer patients. Ninety-one percent reported fatigue, 47% reported pain and 54% reported depression. These symptoms were all significantly correlated with each other and with total health status [69]. Fatigue is also associated with sleep problems [59], which are further exacerbated by depression [64]. Despite studies assessing treatment for fatigue, pain, and depression individually, there has been no study examining a combined treatment modality for the symptom cluster of pain, fatigue and depression [70]. A recent study found that cognitive–behavioral therapy decreased both fatigue and depression as well as increased sleep efficiency in breast cancer patients [71].

Hot flashes and other menopausal symptoms can be extremely troublesome in breast cancer survivors due to potential premature menopause from chemotherapy, the effects of hormonal therapy (e.g., tamoxifen and aromatase inhibitors) and the contraindication of estrogen replacement therapy in this population [2,72]. Unlike natural menopause, which is associated with gradual increase in symptoms, chemotherapy can lead to sudden and intense symptoms that overwhelm coping abilities. Depression is also integrally related to sexual dysfunction in breast cancer patients [73–75], likely both as a consequence and as a cause. The selective serotonin reuptake inhibitors (SSRIs) that are used to treat depression also cause orgasmic dysfunction in up to a third of women. In addition to the above effects on physical functioning, there is also evidence that depression may adversely affect immune function [81–86] and survival in breast cancer patients [76–78].

3.3. Depression and adherence

Depression is associated with decreased acceptance of and compliance with adjuvant therapy in women with breast cancer [79–81], which may, in turn, affect disease outcome. This is consistent with studies of medical treatment adherence in other medical settings [82]. The role of depression on adherence is perhaps most salient in recently diagnosed younger patients for whom tamoxifen or other hormonal agents may be indicated, as these patients are more prone to depression but are also less likely to desire hormone treatment [83].

3.4. Depression, adjuvant therapy and cognitive functioning

Depression in women with breast cancer [84] and estrogen deficiency [85,86] have been associated with significant cognitive and functional impairment, with improvements in cognition associated with estrogen and/or antidepressant treatment [87,88]. Levels of brain-derived neurotrophic factor, a trophic protein important in modulating neuronal synaptic plasticity and essential to long-term memory [89], are decreased in depressed patients [90,91] and can be increased with antidepressant treatment [92]. There is some evidence that self-reported cognitive dysfunction is correlated with depressive and fatigue symptoms [36,42,93]; however, cognitive dysfunction in cancer patients cannot be explained exclusively by the presence of depression [36,94,95]. Adjuvant chemotherapy in breast cancer patients has been associated with higher levels of depression and cognitive dysfunction [36,37,42,96]. The number of women suffering negative cognitive effects from chemotherapy ranges from 15% to 33% [36,96–100]. These problems seem to be worse for women actively receiving high-dose chemotherapy, although they can persist for months or years post treatment [42,101,102]. Tamoxifen may also have an impact on cognition and depression; however, the data are somewhat mixed [36,45,103,104].

3.5. Impact of depression on caregivers and families

Patient depression and caregiver burden and distress are significant problems in families of breast cancer patients [105–110]. Of partners, 20–30% suffer from psychological impairment and mood disturbance as a result of the spouse's cancer [106–108], and psychological distress in cancer patients is a major predictor of distress and decreased QOL of their spouses, parents or other caregivers [106–108,111–116]. There is also evidence that untreated depression in cancer patients may cause higher rates of depression in their surviving family members [117]. Evidence from depressed cancer and other patients have shown that depression leads to caregiver burden and stress at levels similar to or exceeding that caused by patients with cognitive or behavioral impairment [115,116,118,119]. Also, children of depressed mothers are at increased risk for developing adjustment problems [120]. Depression has been shown to be disruptive to routines in the home and to the availability of mothers to their children [121].

3.6. Clinical trials of pharmacotherapy in women with breast cancer

Antidepressant studies that have included breast cancer patients are shown in Table 2. Two small placebo-controlled antidepressant trials for MDD in cancer patients have been reported. Both used mianserin, a tetracyclic 5-HT_2, α_2-adrenergic and histamine-H_1 antagonist affecting both serotonergic and noradrenergic neurotransmission that is not available for clinical use in the United States. Costa et al. [126] studied 73 female cancer (47 breast) patients in a 4-week trial, and van Heeringen and Zivkov [127] studied 57 breast cancer patients in a 6-week trial. Both studies showed significantly more improvement on the Hamilton

Table 1
Studies examining rates of depression in women following surgery for breast cancer

Authors	Study design and depression measure	Study population	Rate and onset of depression
Dean [11]	RDC	122 $T_{1,2}$ $N_{0,1}$ patients assessed 3 and 12 months after mastectomy	3 Months postoperative: 9.7% major, 17.7% minor depression 12 months postoperative: 4.5% major, 18.2% minor depression
Fallowfield et al. [12]	PSE semistructured diagnostic interview at 3 times postoperatively	269 Stage I and II patients assessed 2 weeks, 3 months and 12 months after surgery	Postoperatively: 26% depressed 3 Months postoperative: 22% depressed 12 Months postoperative: 20% depressed
Hopwood et al. [13,14]	HADS depression scale, RSCL, diagnostic interview	214 Ambulatory advanced BCA patients, with 1–3-month follow-ups	18% Depressed at first time point by HADS (20% by diagnostic interview), 11% depressed at 1–3-month follow-up by HADS
Love et al. [15]	11-point depression scale at 3, 6, 12, 18, 24 months	Postmenopausal (mean years since menopause, 9.3) 70 on T, 70 on placebo	No difference between groups (baseline: 31–33% depressed, 12 Months: 30–45% 1 T patient with new onset depression
Goldberg et al. [16]	Modified RSCL at 6 and 12 months postoperatively	166 BCA patients	32% Depressed preoperatively, 24% at 6 months postoperative, 21% at 12 months postoperative
Lee et al. [17]	PSE preoperatively, 3 and 12 months postoperatively	197 BCA patients	7% With case depression preoperatively, 7% at 3 months and 4% at 12 months
Cathcart et al. [46]	Clinical interview for depression at visits with oncologist × 12 months after initial therapy	155 on T (median age 59 years) -19 Premenopausal, 47 had chemotherapy 102 Not on T (age 44 years) -55 Premenopausal, 81 had chemotherapy	Depressed: 15% on T (onset within 3–6 months after initial therapy and within first few weeks of starting T)
Pinder et al. [18]	HADS depression scale	86 Hospitalized, 53 ambulatory (on endocrine or no systemic therapy) advanced BCA	12% Probable depression Similar rates of depression among patients with locoregional recurrence and metastatic disease
Pasacreta [63]	CES-D, DIS structured diagnostic interview between 3 and 7 months after diagnosis and surgery	79 Ambulatory patients, 75% Early stage, 47% received chemotherapy, 33% on T	24% With CES-D ≥16 6.3% Met MDD criteria based on DIS
Ganz et al. [19]	CES-D on cross-sectional mailed survey	864 Mean 3 years after Stage 0–II dx, completed adjuvant tx, disease-free on no cancer tx other than T (47%), no disabling medical or psychological condition	Current use of medication for depression: 12%; anxiety: 8.4%. CES-D ≥16 for <50 years old: 28.3%, 50–59 Years: 24.8%, ≥60 Years: 16.9%
Ganz et al. [2]	CES-D on cross-sectional mailed survey	1098 Mean 3 years after diagnosis, completed adjuvant tx at least 4 months ago, disease-free on no cancer tx other than T, no major disabling medical or psychological condition	CES-D ≥16 for No tx group: 24.8%, T only: 26.8%, chemotherapy only: 30.2%, T+chemotherapy: 24.9%
Green et al. [53]	SCID at 4–12 months post cancer treatment	160 Early-stage patients	11% With MDD
Epping-Jordan et al. [54]	SCL-90 Depression scale at dx and 3- and -month follow-up	90 Stage I–IV patients	Clinical depression: 34% at diagnosis, 29% at 3 months; 26% at 6 months
Wenzel et al. [20]	CES-D at recent treatment completion (<2 months)	304 Stages I, II and IIIA patients 161 ≤50 Years old, 143 >50 Years old	≤50 Years, 32% with CES-D ≥16 >50 Years, 20% with CES-D ≥16
Bower et al. [59]	CES-D Assessed between 1 and 5 years after diagnosis	1957 Stage 0-II patients	25% With clinically significant depression (CES-D ≥16)
Broeckel et al. [21]	CES-D on Cross-sectional mailed survey	61 With no current disease who completed adjuvant chemotherapy 3–36 (mean 16) months ago. 61% on T.	Mean CES-D score: 11.75 (26% ≥16) in former chemotherapy patients, 7.59 (14% ≥16) in noncancer controls
Crivellari et al. [22]	PACIS Mood item at 1, 3, 6, 12, 18 months after starting T	Postmenopausal, node-positive 306 on T alone 299 on T+CMF	Mood worse in first 3 months, worse for age <65 years and for T+CMF group at all time points)
Nystedt et al. [23]	HADS Depression scale at baseline, 3–4 months, 12 months	179 Premenopausal, node-negative 37 on no endocrine tx, 38 on goserelin alone, 39 on goserelin+T, 35 on T alone	No significant difference between groups Clinically significant HADS depression score (>8) in Tnly group at: baseline: 12%, 3–4 months: 13%, 12 months: 6%
Akechi et al. [24]	HADS Depression scale postoperatively	148 Patients not currently receiving active cancer treatment (other than hormone therapy)	23% With clinically significant depression (HADS ≥11)
Morasso et al. [25]	SCID at 1st follow-up after chemotherapy	184 Stage I–III patients	10% With MDD at follow-up

(*continued on next page*)

Table 1 (*continued*)

Authors	Study design and depression measure	Study population	Rate and onset of depression
Gallagher et al. [26]	GHQ-12 at 6 months after diagnosis	195 Grade I-III patients (27% chemotherapy, 36% radiation, 32% hormonal therapy)	26% With GHQ-12 scores indicative of psychological morbidity (GHQ-12 ≥4)
Osborne et al. [55]	HADS Depression scale at various time points	731 Stage I–IV patients	3% With probable depression (HADS>10), 12% With possible depression (HADS 8–10)
Rakovitch et al. [27]	Single question about "unhappiness or depression" rated on 1–5 Likert scale	64 With ductal carcinoma in situ (DCIS), 164 with early invasive breast cancer (EIBC) referred to a tertiary cancer center	13% DCIS, 22% EIBC rated as "very often" (score ≥4)
Ganz et al. [28]	CES-D assessed following primary therapy	558 Stage I–II invasive epithelial breast cancer patients	16.9% (Mastectomy only) to 27.7% (mastectomy with chemotherapy) with CES-D ≥16
Manne et al. [150]	HSCL-25 During any treatment	148 Stage I–IIIa BCA	50% had HSCL-25 score ≥43.
Schou et al. [29]	HADS Depression scale at diagnosis, 3, 12 months after surgery	165 Stage I–III BCA treated with surgery	12% had HADS score ≥8 (mea *n*=11.6) at diagnosis, 6% score ≥8 (mean 9.1) at 3 months, 9% with score ≥8 (mean 9.2) at 12 months after surgery.
Coyne et al. [194]	SCID Given to waiting room sample	113 Stage I–IV in active treatment	9% With clinically significant depression
Golden-Kreutz and Anderson [30]	CES-D Given after surgery but before adjuvant therapy	210 Stage II–III BCA patients	18% With CES-D scores ≥10
Kissane et al. [38]	MILP and HADS given after surgery	303 Stage I–II and 200 metastatic BCA	9.6% Early-stage had MDD; 6.5% of metastatic had MDD.
Aukst-Margetic et al. [31]	CES-D Assessed during radiation therapy	115 Stage I–IV BCA	36.5% With CES-D scores ≥16
Ell et al. [39]	PHQ-9 Given in outpatient clinic or via telephone	472 Women undergoing active treatment or in active follow-up. 250 (53%) with BCA (Stage 0–III), 222 (47%) with gynecological cancer	114 (24%) had PHQ-9 ≥10, 71 (62%) had moderate depression (PHQ-9 scores 10–14), 43 (38%) had severe depression (PHQ-9 scores 15–27).
Roscoe et al. [32]	CES-D Given before and during chemotherapy treatments	94 BCA Patients receiving or about to receive chemotherapy	28% With CES-D scores ≥19
Burgess et al. [33]	SCID Diagnosis of MDD, GAD or both in the 5 years after diagnosis	222 Early-stage patients (44% received chemotherapy, 48% received endocrine therapy)	Annual prevalence of depression, anxiety or both: 1st year 48%, 2nd year 25%, 3rd year 23%, 4th year 22%, 5th year 15%
Yen et al. [34]	CES-D Given after treatment for BCA	97 Women with breast tumors who had received treatment for BCA	38.4% of women met criteria for depression CES-D score >16.
Mehnert and Koch [35]	SCID Given postsurgery	127 BCA patients	4.7% had major depression. 3.1% had dysthymic disorder.
Kenne Sarenmalm et al. [56]	HADS Given to outpatients	56 Postmenopausal women with recurrent BCA receiving palliative treatment	10% had HADS depression score ≥11, 21% had score ≥8.

BCA, breast cancer; CIDI, Composite International Diagnostic Interview; CMF, cyclophosphamide + methotrexate + fluorouracil; DIS, Diagnostic Interview Schedule; dx, diagnosis; GHQ-12, General Health Questionnaire 12; HSCL-25, Hopkins Symptom Checklist 25; PACIS, Perceived Adjustment to Chronic Illness Scale; PHQ-9, Patient Health Questionnaire 9 depression scale; RDC, Research Diagnostic Criteria; RSCL, Rotterdam Symptom Checklist; SCID, Structured Clinical Interview for *DSM-IV*; SCL-90, Symptom Checklist 90; T, tamoxifen; tx, treatment.

Rating Scale for Depression (HAM-D) in the mianserin group compared with the placebo group.

Two randomized, placebo-controlled SSRI studies of depressive symptoms among selected cancer populations have been published. Fisch et al. [128] studied 12 weeks of fluoxetine 20 mg vs. placebo among 163 patients with advanced cancer (27 with breast cancer) who showed at least minimal depressive symptoms on a 2-item depression screener. However, patients with a diagnosis of MDD were excluded. Patients in the fluoxetine group showed modest but greater improvement in QOL and depression scores compared to the placebo group. There were no significant differences between groups in best-change scores or number of responders. Morrow et al. [129] studied 8 weeks of paroxetine 20 mg vs. placebo among 549 patients (259 with breast cancer) undergoing chemotherapy to assess impact on fatigue and depression. Patients were not required to meet criteria for major or minor depression and response rates among patients with these disorders were not separately analyzed. There was no difference in fatigue and a significant difference in depressive symptom reduction from baseline to completion on the Center for Epidemiologic Studies Depression Scale (CES-D) in the paroxetine group (14.8–12.0) compared to the placebo group (15.8–14.8). Razavi et al. [130] did not find the SSRI fluoxetine to be superior to placebo in a 5-week trial in 69 mixed cancer patients with MDD or adjustment disorder. Significantly more people dropped out of the study in the fluoxetine group, although the frequency of side effects was not significantly different between the groups.

Other antidepressant studies that included breast cancer patients examined mixed depressive disorders that included not only major depression but also adjustment disorder,

Table 2
Antidepressant studies in breast cancer

Authors	*n*	Participants/breast cancer stage	Entry criteria	Depression instruments	Intervention	Results
Costa et al. [126]	73	Stage II–IV breast (*n*=47), ovary, uterine/ cervix cancer patients	ZSRDS score ≥41 and HAM-D ≥16	HAM-D	Mianserin 10 mg vs. placebo, 4 weeks	Significant drop in HAM-D scores vs. placebo; mean mianserin HAM-D score at 4 weeks=8.19 vs. 13.2 for placebo; significantly more responders in the mianserin group
Razavi et al. [130]	69	Mixed cancer diagnoses. 42 with breast or gynecological cancer	MDD or Adjustment disorder, HADS ≥13	HADS, MADRS	Fluoxetine 20 mg vs. placebo, 5 weeks	HADS <8 in 11% of fluoxetine vs. 7% of placebo group; HADS response rate (improvement by 50%) was 18% in fluoxetine group vs. 20% in placebo (no group differences).
Van Heeringen and Zivkov [127]	55	Stage I or II breast cancer patients	MDD by clinical interview	HAM-D	Mianserin 60 mg vs. placebo, 6 weeks	Significant drop in HAM-D scores in mianserin group only; 50% drop in HAM-D in 68% of mianserin vs. 37% of placebo group; significantly more placebo patients dropped out prematurely due to lack of efficacy.
Ballin et al. [122]	10	Patients with a solid tumor who received chemotherapy (4 with breast cancer)	No depression criteria required.	HAM-D	Fluvoxamine, 4 weeks	5/10 Had ≥50% decrease in HAM-D scores.
Holland et al. [131]	37	Women with cancer (30 with breast cancer Stages II, III, IV) in active treatment	MDD or adjustment disorder, HAM-D >14	HAM-D, CGI	Fluoxetine vs. desipramine, 6 weeks	HAM-D and CGI-severity mean scores significantly decreased for both medications. Fluoxetine-treated patients also showed a trend toward improvement in pain and mood.
Razavi et al. [123]	18	Women with breast cancer in active treatment	Adjustment disorder, HADS ≥14	HADS, SCL-90-R	Trazodone vs. clorazepate, 4 weeks	Response (global improvement on CGI scale rated "very, much or minimally improved" in 90.9% of trazodone (HADS mean dropped by 9.4) vs. 57.1% of clorazepate (HADS mean dropped by 9.3) group
Moslinger-Gehmayr et al. [132]	179	Woman during treatment of breast cancer	MDD diagnosed by interview	MADRS, CGI	Amitriptyline vs. paroxetine, 8 weeks	Significant improvements in MADRS and CGI in both groups; paroxetine slightly better tolerated
Thompson [133]	20	Women with breast or gynecologic cancer (8 with breast cancer)	Adjustment disorder, mood or anxiety disorder by interview	None used	Mirtazapine 30 mg or 45 mg daily.	19 Patients had improved depression symptoms, improved sleep continuity, decreased nausea and improved appetite.
Pezzella et al. [134]	179	Women with breast cancer and after at least 2 cycles of chemotherapy	MDD, MADRS ≥16	MADRS	Amitriptyline vs. Paroxetine, 8 weeks	≥50% reduction in MADRS in 43.7% of paroxetine vs. 37.9% of amitriptyline group; both groups decreased CGI severity scores similarly (paroxetine: 3.6–2.4, amitriptyline: 3.7–2.6); paroxetine slightly better tolerated
Fisch et al. [128]	163	Patients with advanced, incurable malignancy (27 with breast cancer)	Depression symptoms on 2-item depression screener, MDD excluded	BZSDS	Fluoxetine 20 mg vs. placebo, 12 weeks	Significant improvement in depression scores in fluoxetine (BZSDS: 24.44–21.14) vs. placebo (23.09–22.54); no significant difference in best change scores, number of responders, or tolerability between groups
Morrow et al. [129]	549	Cancer patients receiving chemotherapy (259 with breast cancer)	No prior psych hospitalization, and an indication of fatigue from baseline questionnaires.	CES-D	Paroxetine 20 mg vs. placebo, 8 weeks	No difference in fatigue and a significant difference in depressive symptom reduction from baseline to completion on the CES-D in the paroxetine group (14.8–12.0) compared to the placebo group (15.8–14.8); by 8 weeks, CES-D ≥19 in 21% of paroxetine vs. 29% of placebo group (32% in both groups at baseline)
Grassi et al. [135]	20	Women with breast cancer (any stage)	MDD by clinical interview	HAM-D	Reboxetine 4–10 mg, 8 weeks	HAM-D decreased significantly (21.76–11.61)

(*continued on next page*)

Table 2 (*continued*)

Authors	*n*	Participants/breast cancer stage	Entry criteria	Depression instruments	Intervention	Results
Roscoe et al. [32]	94	Women with breast cancer receiving at least 4 cycles of chemotherapy	No history of mania or taking psychotropic medications	CES-D	Paroxetine 20 mg vs. placebo, stopping 7 days after fourth chemotherapy cycle	Significant drop in CES-D in paroxetine (14.7–8.8) vs. placebo (14.7–12.6) group Of 13 patients with CES-D =19 in each group, 4 (31%) in paroxetine group vs. 13 (100%) in placebo group had CES-D=19 after 4 chemotherapy cycles.
Musselman et al. [124]	35	Women with Stage I–IV breast cancer	MDD by *DSM-III-R* interview, HAM-D	HAM-D	Paroxetine vs. Desipramine vs. placebo	No difference between groups; mean HAM-D change: 11.27 for placebo group, 10.09 for desipramine group, 7.62 for paroxetine group
Torta et al. [125]	35	Cancer patients receiving chemotherapy (19 with breast cancer)	*DSM-IV* MDD, dysthymia, adjustment disorder, subthreshold depression	HADS MADRS CGI	Sertraline 50–100 mg, 12 weeks	HADS depression scores decreased significantly (11.46–7.04). MADRS scores decreased significantly (28.4–13.26). Among the 27 completers, 70.4% were "very much/much improved" on CGI.

BZSDS, Brief Zung Self-Rating Depression Scale; CGI, Clinical Global Improvement scale; *DSM-III-R, DSM, Revised Third Edition*; MADRS, Montgomery–Asberg Depression Rating Scale; SCID, Structured Clinical Interview for *DSM-III-R*; SCL-90-R, Symptom Checklist 90-R, ZSRDS; Zung Self-Rating Depression Scale.

minor depression and other depressive and anxiety disorders [131–134], thus making it difficult to determine treatment efficacy for MDD. In the three studies that compared an SSRI to a tricyclic antidepressant (TCA), both medication classes were found to be effective, and the SSRI was generally better tolerated [131,132,134]. Thompson [133] found the novel antidepressant mirtazapine to be effective in eight breast cancer patients (six on tamoxifen) with depressive or anxiety disorders, and Grassi et al. [135] found the norepinephrine reuptake inhibitor reboxetine to be effective in an open study of 20 breast cancer patients with MDD. Several of these studies also found antidepressant treatment to improve QOL. There is some evidence that combining antidepressant therapy with cognitive therapy may enhance long-term recovery from depression compared with cognitive therapy alone [136].

3.7. Clinical trials of psychotherapy in women with breast cancer

Numerous studies have assessed the efficacy of psychosocial interventions to reduce pain, distress and fatigue and improve QOL in breast cancer patients. These studies and several meta-analyses have revealed mixed results on the ability of psychosocial interventions to improve overall mood, distress, anxiety and depression in cancer patients [137–152]. Few randomized controlled studies have assessed psychotherapy efficacy in treating probable MDD in breast cancer patients.

3.8. Studies that screened for depression

In a study of 45 women with metastatic breast cancer, Savard et al. [153] found that eight weekly sessions of cognitive therapy (CT) and three booster sessions were superior to a wait-list control (WLC) condition. Inclusion criteria included a baseline Hospital Anxiety and Depression Scale (HADS) score ≥7 or a Beck Depression Inventory (BDI) score ≥15. Mean HAM-D scores were 14.21 for the CT group and 14.40 for the WLC group. In the CT group, HAM-D response rates at posttreatment, 3 months and 6 months were 73.3%, 50.0% and 76.9%, compared with the WLC group's rate of 16.7%. The analysis was only limited to 21 CT patients and 16 WLC patients with posttreatment data.

A prospective randomized trial by Greer et al. [154], examined the use of adjuvant psychological therapy (APT), a cognitive–behavioral therapy developed for cancer patients to improve QOL in cancer patients showing "psychological morbidity" as defined by the HADS and the Mental Adjustment to Cancer Scale. One hundred fifty-six patients (82 with breast cancer) were randomized to either receive six APT sessions or no intervention and completed the trial. APT significantly reduced the proportion of patients with possible MDD (HADS ≥8: 22% vs. 7%). The study did not make a definitive diagnosis of MDD. Furthermore, a participant could have been classified as a responder by merely lowering their score on the HADS by one point.

3.9. Prevention studies

In a study by Antoni et al. [155], 100 early-stage breast cancer patients were randomized to receive either a 10-week group cognitive–behavioral stress management intervention or, after a 10-week waiting period, receive a 1-day seminar small "dose" of intervention content without the group support. Patients previously treated for major depression were excluded. Depression dropped significantly in the intervention group, with 35% having CES-D scores ≥16 at baseline, 13% immediately following treatment, 17% at 3 months and 13% at 9 months. In the control group, there was no significant improvement, with 28% depressed at baseline and 21% following the 10-week waiting period, at

3 months and at 9 months. The study lacked a differentiation between major and minor depression. Furthermore, because the control group received a small dose of the intervention without the group therapy, the 3- and 9-month follow-up comparisons are not ideal.

In a study by Kissane et al. [156], 303 women with early-stage breast cancer were randomized to 20 sessions of cognitive–existential group therapy plus three relaxation classes vs. three relaxation classes only. Before the intervention, 11% of the intervention group and 8% in the control group had MDD, as determined by the Monash Interview for Liaison Psychiatry (MILP). While there was significant improvement on the HADS over 12 months in both groups, there were no outcome differences between the groups on percentage with MDD or HADS scores. The women in the intervention group did report reduced anxiety and improved family functioning, compared with controls. The lack of significant effect may be due to the relatively low mean baseline HADS scores. The authors did not report outcome separately for the subgroups with major and minor depression. Kissane et al. [157] also conducted a trial among women with advanced breast cancer of supportive–expressive group therapy (SEGT) consisting of 1 year or more of SEGT plus three relaxation therapy classes (n=147) vs. three relaxation therapy classes only (n=80). Although survival was the primary end point, the SEGT arm had a significantly greater proportion than the control arm who improved at 6 months among those who were depressed at baseline (major depression, dysthymia or adjustment disorder on the MILP). Similarly, the SEGT arm had significantly fewer new cases of depression at 6 months.

Burton et al. [158] found that 200 women awaiting mastectomy randomized to preoperative 45–60-min interviews (with or without a one-time 30-min psychotherapeutic intervention or "chat") had significantly less depression on the Present State Examination (PSE) at 1 year than usual care controls. In a small study of 45 women with metastatic breast cancer, Gotay et al. [159] found no significant improvement on rates of depression (CES-D $\geq$16) in a study of 305 women experiencing a first recurrence of breast cancer randomized to four to eight telephone counseling/information sessions vs. standard care.

4. Discussion

While it appears that the prevalence of MDD among breast cancer patients is around 10–25%, the precise rate of MDD has been difficult to determine. Most epidemiological data on depression thus far have used depression symptom screening tools, where cutoffs for clinically significant depression are not clearly validated in breast cancer populations, rather than diagnostic tools based on *DSM* criteria. The depression rate for breast cancer appears to be higher than for most other cancers, with the exception of pancreatic and oropharyngeal cancers [78,160].

One possible reason for the high prevalence of MDD in breast cancer patients is that menopause and estrogen decline are related to depression. The acute onset of premature menopause is a potential troubling effect of chemotherapy. Additionally, endocrine therapy (e.g., ovarian suppression, SERMs) further depletes estrogen levels in both pre- and postmenopausal women. Estrogen is known to increase brain serotonin (5-hydroxytryptamine or 5-HT) postsynaptic responsivity and is believed to cumulatively act as a serotonin agonist [161]. The serotonergic system is known to play an important role in behaviors that are disturbed in affective disorders, including mood, sleep, sexual activity, appetite and cognitive function [162]. In certain brain regions, estrogen also acts as a cholinergic agonist and increases norepinephrine activity [163]. These multiple modulations suggest that estrogen may have an antidepressant-like effect or enhance neurotransmitter activity.

It has been shown that blood 5-HT levels are decreased in postmenopausal women when compared with premenopausal women and that serum estradiol correlates significantly with blood 5-HT levels [164]. Decline in estrogen, not the level of estrogen, remains a leading hypothesis regarding the high rate of reproductive endocrine-associated affective symptoms and depressive disorders seen in periods of acute estrogen decline [165–168]. There is also evidence that depression may independently lower plasma estrogen and increase follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels [169] and lead to an earlier perimenopause [170]. SERMs such as tamoxifen may modulate the central nervous system by estrogen antagonist actions, which, in turn, inhibit serotonergic mechanisms in the brain [171]. The effects of depression on estrogen and age of perimenopause may add to the adverse hormonal effects of chemotherapy and hormonal therapy in breast cancer patients. There is a need for more data on the association between aromatase inhibitors, which are gaining popularity in adjuvant hormonal therapy and hormone-mediated mood states. Several studies examining the effects of aromatase inhibitors on QOL have shown no significant decrease in QOL [172–174]. The effect of the specific SERMs and chemotherapies on the development of MDD require more in-depth study in the breast cancer population. An open study of bupropion in 20 early-stage breast cancer patients on hormone therapy following adjuvant chemoterhapy showed improvement in both sexual functioning and BDI depression scores, although none of the patients were classified as depressed at baseline [175].

There is mounting evidence that fatigue, pain, depression (and perhaps cognitive impairment) share a common biological mechanism — increased levels of proinflammatory cytokines [e.g., interleukin (IL)-1, IL-6}], which occur as a result of cancer treatment [176–179]. Proinflammatory cytokines may be chronically elevated in breast cancer survivors, even 3–5 years after treatment [178,180]. MDD has been associated with increased production of proinflammatory cytokines [181–184].

Proinflammatory cytokines released in response to the tissue damage that occurs during cancer treatment may contribute to the high rates of depression and related symptoms in cancer patients [176,177,185–188]. Antidepressant therapy has been shown to ameliorate depressive symptoms associated with administration of inflammatory cytokines [189,190] and elevated plasma IL-6 levels decline when patients with MDD are successfully treated with fluoxetine [191]. Increased IL-6 production increases levels of cortisol, which can lead to depressive symptoms. In fact, some data suggest that antiglucorticoid treatment can provide an antidepressant response [192].

Despite the high prevalence of MDD in breast cancer patients, there have been very few studies assessing its treatment. Most antidepressant and psychotherapy efficacy studies that have included breast cancer patients have included mixed depressive states, including adjustment disorders and minor depressive disorders. These less severe distress states often resolve spontaneously or have high placebo response rates [193], particularly with resolution of a precipitating stressor. However, about 10–25% of breast cancer patients will suffer from more severe depressive states, such as MDD, that may significantly benefit from more intensive treatment with pharmacotherapy, psychotherapy or a combination of both. Moreover, while several studies have assessed the efficacy of psychotherapy to reduce distress, pain and fatigue and improve health-related QOL after breast cancer [137–140,145,148,154–156], few studies have examined the efficacy of psychotherapy for the treatment of MDD. Antidepressant medications are already widely used in this population [194]; however, there is considerable variability in which antidepressant medications and dosages are used and with whom. Primary care studies show few patients with MDD receive adequate doses and duration of antidepressant medications [195]. Also, despite the evidence that the combination of psychotherapy and pharmacotherapy are effective in treating MDD in some populations [196], there have been no studies examining the effectiveness of this combination for MDD in cancer patients.

SSRIs and serotonin–norepinephrine reuptake inhibitors may be effective in decreasing menopausal symptoms in breast cancer survivors [72,197–202], although the relationship between depression reduction and menopausal symptom reduction is still under debate. The mechanism for this effect is likely mediated by the serotonergic effects of these agents. Jin et al. [203] found that CYP2D6 inhibiting SSRIs can lower the concentration of endoxifen, the active metabolite of tamoxifen. Although the clinical significance of this is unknown, more studies are needed to evaluate the interactions between SERMs and SSRIs.

Few antidepressant studies have been performed in depressed estrogen-deficient women. Although estrogen alone has not consistently been shown to be an effective antidepressant [204–206], there is evidence that estrogen may serve as an adjunct to the treatment of depression in postmenopausal women. In secondary analyses of randomized, double-blind antidepressant trials for depressed older adults, Schneider et al. [207,208] found that depressed postmenopausal women taking SSRIs had better improvement in depressive symptoms and QOL if they received estrogen replacement therapy (ERT); however, anxiety and cognition improved regardless of ERT status. Therefore, there is a possibility that antidepressant efficacy will be lower in women taking an estrogen antagonist, such as tamoxifen. Studies by Shapira et al. [209] and Amsterdam et al. [210], however, did not find an antidepressant aug-

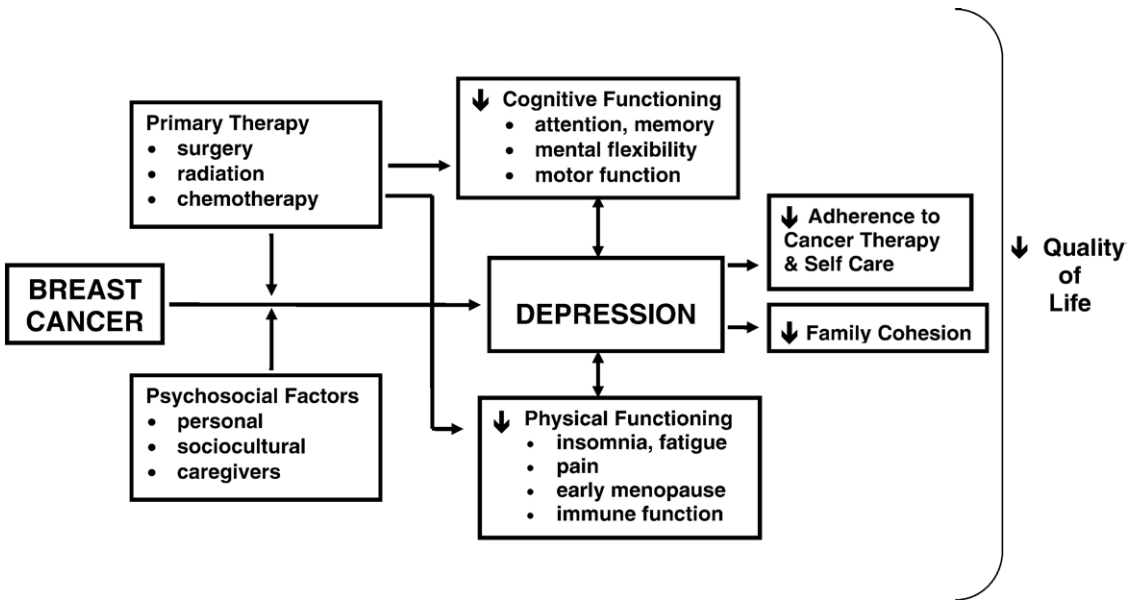

Fig. 1. Theoretical model of depression in women with breast cancer.

menting effect of estrogen. However, Shapira et al. used the TCA imipramine in patients with refractory depression for only a 4-week period.

Two recent Institute of Medicine reports have documented the need for more evidence-based psychosocial interventions for breast cancer survivors [211,212]. Because of the complex and fluctuating nature of depressive symptoms and contributing medical and psychosocial factors, controlled studies are essential to determine the efficacy and safety of specific interventions for MDD in this population. While the widely recognized National Comprehensive Cancer Network practice guidelines for the psychosocial care of cancer patients calls for universal screening for and treatment of distress [213], few evidence-based guidelines have been established for the use of antidepressants and psychotherapy for the treatment of MDD in cancer patients. Data from treatment efficacy studies for MDD in breast cancer patients and, ultimately, long-term maintenance studies, multimodal studies involving stepped care approaches, effectiveness studies testing the cost-effectiveness of different treatment approaches in naturalistic clinical settings (such as those performed in primary care [214]) and dissemination studies promoting cost-effective treatment strategies in community health care delivery systems will ultimately lead to valuable treatment guidelines for depression in breast cancer survivors.

4.1. Conclusion

Major depressive disorder is a frequent but often unrecognized and untreated condition among breast cancer patients, which causes amplification of physical symptoms, additive functional impairment and poor adherence to treatment regimens. Taken together, the set of negative consequences of depression in breast cancer patients is responsible for significant and often prolonged decreases in QOL (Fig. 1). Breast cancer patients within the first year after diagnosis may be at high risk for MDD, particularly if they received chemotherapy, are premenopausal, are less than 65 years old or have a history of depression. The early stages of disease may be the time when intervention is most effective.

Based on the limitations and gaps in our current knowledge, we propose the following recommendations for future research:

1) Epidemiological and treatment studies should study the impact of MDD on important outcomes, such as symptom burden, cognition, functional status, family and caregiver burden, adherence and immune function.
2) Randomized, controlled treatment trials of pharmacotherapy, evidence-based psychotherapy and combination therapy for MDD should be conducted.
3) Randomized, controlled trials of systematic changes in care, such as collaborative care, compared with usual oncology models of care in patients with MDD should be conducted.
4) Prevention studies using psychosocial interventions should stratify randomization on presence of current MDD, prior history of MDD or no current or prior MDD, in order to determine the intervention's differential effects related to depression status.
5) Potential modifiers of depression treatment effect, such as menopausal status and use of adjuvant chemotherapy or hormone therapy, should be studied.

References

[1] American Cancer Society. Cancer facts and figures 2007. Atlanta: American Cancer Society; 2007.
[2] Ganz PA, Rowland JH, Meyerowitz BE, Desmond KA. Impact of different adjuvant therapy strategies on quality of life in breast cancer survivors. Recent Results Cancer Res 1998;152:396–411.
[3] Spiegel D. Cancer and depression. Br J Psychiatry Suppl 1996: 109–16.
[4] Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol 2007;25:4670–81.
[5] Hegel MT, Moore CP, Collins ED, Kearing S, Gillock KL, Riggs RL, et al. Distress, psychiatric syndromes, and impairment of function in women with newly diagnosed breast cancer. Cancer 2006;107: 2924–31.
[6] Hardman A, Maguire P, Crowther D. The recognition of psychiatric morbidity on a medical oncology ward. J Psychosom Res 1989;33: 235–9.
[7] Passik SD, Dugan W, McDonald MV, Rosenfeld B, Theobald DE, Edgerton S. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol 1998;16:1594–600.
[8] Coyne JC, Thompson R, Palmer SC, Kagee A, Maunsell E. Should we screen for depression? Caveats and potential pitfalls. Appl Prev Psychol 2000;9:101–21.
[9] Gilbody SM, House AO, Sheldon TA. Routinely administered questionnaires for depression and anxiety: systematic review. BMJ 2001;322:406–9.
[10] Pignone MP, Gaynes BN, Rushton JL, Burchell CM, Orleans CT, Mulrow CD, et al. Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;136:765–76.
[11] Dean C. Psychiatric morbidity following mastectomy: preoperative predictors and types of illness. J Psychosom Res 1987;31:385–92.
[12] Fallowfield LJ, Hall A, Maguire GP, Baum M. Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. BMJ 1990;301:575–80.
[13] Hopwood P, Howell A, Maguire P. Psychiatric morbidity in patients with advanced cancer of the breast: prevalence measured by two self-rating questionnaires. Br J Cancer 1991;64:349–52.
[14] Hopwood P, Howell A, Maguire P. Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. Br J Cancer 1991;64:353–6.
[15] Love RR, Cameron L, Connell BL, Leventhal H. Symptoms associated with tamoxifen treatment in postmenopausal women. Arch Intern Med 1991;151:1842–7.
[16] Goldberg JA, Scott RN, Davidson PM, Murray GD, Stallard S, George WD, et al. Psychological morbidity in the first year after breast surgery. Eur J Surg Oncol 1992;18:327–31.
[17] Lee MS, Love SB, Mitchell JB, Parker EM, Rubens RD, Watson JP, et al. Mastectomy or conservation for early breast cancer: psychological morbidity. Eur J Cancer 1992;28A:1340–4.
[18] Pinder KL, Ramirez AJ, Black ME, Richards MA, Gregory WM, Rubens RD. Psychiatric disorder in patients with advanced breast cancer: prevalence and associated factors. Eur J Cancer 1993;29A: 524–7.

[19] Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;16:501–14.
[20] Wenzel LB, Fairclough DL, Brady MJ, Cella D, Garrett KM, Kluhsman BC, et al. Age-related differences in the quality of life of breast carcinoma patients after treatment. Cancer 1999;86:1768–74.
[21] Broeckel JA, Jacobsen PB, Balducci L, Horton J, Lyman GH. Quality of life after adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat 2000;62:141–50.
[22] Crivellari D, Bonetti M, Castiglione-Gertsch M, Gelber RD, Rudenstam CM, Thurlimann B, et al. Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: the International Breast Cancer Study Group Trial VII. J Clin Oncol 2000;8:1412–22.
[23] Nystedt M, Berglund G, Bolund C, Brandberg Y, Fornander T, Rutqvist LE. Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer-self-rated physiological effects and symptoms. Acta Oncol 2000;39:959–68.
[24] Akechi T, Okuyama T, Imoto S, Yamawaki S, Uchitomi Y. Biomedical and psychosocial determinants of psychiatric morbidity among postoperative ambulatory breast cancer patients. Breast Cancer Res Treat 2001;65:195–202.
[25] Morasso G, Costantini M, Viterbori P, Bonci F, Del Mastro L, Musso M, et al. Predicting mood disorders in breast cancer patients. Eur J Cancer 2001;37:216–23.
[26] Gallagher J, Parle M, Cairns D. Appraisal and psychological distress six months after diagnosis of breast cancer. Br J Health Psychol 2002; 7:365–76.
[27] Rakovitch E, Franssen E, Kim J, Ackerman I, Pignol JP, Paszat L, et al. A comparison of risk perception and psychological morbidity in women with ductal carcinoma in situ and early invasive breast cancer. Breast Cancer Res Treat 2003;77:285–93.
[28] Ganz PA, Kwan L, Stanton AL, Krupnick JL, Rowland JH, Meyerowitz BE, et al. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. J Natl Cancer Inst 2004;96:376–87.
[29] Schou I, Ekeberg O, Ruland CM, Sandvik L, Karesen R. Pessimism as a predictor of emotional morbidity one year following breast cancer surgery. Psychooncology 2004;13:309–20.
[30] Golden-Kreutz DM, Andersen BL. Depressive symptoms after breast cancer surgery: relationships with global, cancer-related, and life event stress. Psychooncology 2004;13:211–20.
[31] Aukst-Margetic B, Jakovljevic M, Margetic B, Biscan M, Samija M. Religiosity, depression and pain in patients with breast cancer. Gen Hosp Psychiatry 2005;27:250–5.
[32] Roscoe JA, Morrow GR, Hickok JT, Mustian KM, Griggs JJ, Matteson SE, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 2005;89:243–9.
[33] Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330:702.
[34] Yen JY, Ko CH, Yen CF, Yang MJ, Wu CY, Juan CH, et al. Quality of life, depression, and stress in breast cancer women outpatients receiving active therapy in Taiwan. Psychiatry Clin Neurosci 2006; 60:147–53.
[35] Mehnert A, Koch U. Prevalence of acute and post-traumatic stress disorder and comorbid mental disorders in breast cancer patients during primary cancer care: a prospective study. Psychooncology 2007;16:181–8.
[36] Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 1999;85:640–50.
[37] Leedham B, Ganz PA. Psychosocial concerns and quality of life in breast cancer survivors. Cancer Invest 1999;17:342–8.
[38] Kissane DW, Grabsch B, Love A, Clarke DM, Bloch S, Smith GC. Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. Aust N Z J Psychiatry 2004;38: 320–6.
[39] Ell K, Sanchez K, Vourlekis B, Lee PJ, Dwight-Johnson M, Lagomasino I, et al. Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer. J Clin Oncol 2005;23:3052–60.
[40] Rowland J. Anxiety and the blues after breast cancer: how common are they? CNS Spectr 1999;4:40–54.
[41] Compas BE, Stoll MF, Thomsen AH, Oppedisano G, Epping-Jordan JE, Krag DN. Adjustment to breast cancer: age-related differences in coping and emotional distress. Breast Cancer Res Treat 1999;54: 195–203.
[42] van Dam FS, Schagen SB, Muller MJ, Boogerd W, vd Wall E, Droogleever Fortuyn ME, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 1998;90: 210–8.
[43] Longman AJ, Braden CJ, Mishel MH. Side-effects burden, psychological adjustment, and life quality in women with breast cancer: pattern of association over time. Oncol Nurs Forum 1999;26: 909–15.
[44] Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol 1995; 13:2737–44.
[45] Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry 2003;8: 201–16.
[46] Cathcart CK, Jones SE, Pumroy CS, Peters GN, Knox SM, Cheek JH. Clinical recognition and management of depression in node negative breast cancer patients treated with tamoxifen. Breast Cancer Res Treat 1993;27:277–81.
[47] Thompson DS, Spanier CA, Vogel VG. The relationship between tamoxifen, estrogen, and depressive symptoms. Breast J 1999;5: 375–82.
[48] Breuer B, Anderson R. The relationship of tamoxifen with dementia, depression, and dependence in activities of daily living in elderly nursing home residents. Women Health 2000;31:71–85.
[49] Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 1999;17:2659–69.
[50] Day R, Ganz PA, Costantino JP. Tamoxifen and depression: more evidence from the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) Randomized Study. J Natl Cancer Inst 2001;93:1615–23.
[51] Lee KC, Ray GT, Hunkeler EM, Finley PR. Tamoxifen treatment and new-onset depression in breast cancer patients. Psychosomatics 2007; 48:205–10.
[52] McIllmurray MB, Thomas C, Francis B, Morris S, Soothill K, Al-Hamad A. The psychosocial needs of cancer patients: findings from an observational study. Eur J Cancer Care (Engl) 2001;10:261–9.
[53] Green BL, Rowland JH, Krupnick JL, Epstein SA, Stockton P, Stern NM, et al. Prevalence of posttraumatic stress disorder in women with breast cancer. Psychosomatics 1998;39:102–11.
[54] Epping-Jordan JE, Compas BE, Osowiecki DM, Oppedisano G, Gerhardt C, Primo K, et al. Psychological adjustment in breast cancer: processes of emotional distress. Health Psychol 1999;18:315–26.
[55] Osborne RH, Elsworth GR, Hopper JL. Age-specific norms and determinants of anxiety and depression in 731 women with breast cancer recruited through a population-based cancer registry. Eur J Cancer 2003;39:755–62.
[56] Kenne Sarenmalm E, Ohlen J, Jonsson T, Gaston-Johansson F. Coping with recurrent breast cancer: predictors of distressing symptoms and health-related quality of life. J Pain Symptom Manage 2007;34:24–39.

[57] Tierney AJ, Leonard RC, Taylor J, Closs SJ, Chetty U, Rodger A. Side effects expected and experienced by women receiving chemotherapy for breast cancer. BMJ 1991;302:272.
[58] Williamson GM. Extending the activity restriction model of depressed affect: evidence from a sample of breast cancer patients. Health Psychol 2000;19:339–47.
[59] Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743–53.
[60] Badger TA, Braden CJ, Mishel MH. Depression burden, self-help interventions, and side effect experience in women receiving treatment for breast cancer. Oncol Nurs Forum 2001;28:567–74.
[61] Nail LM. My get up and go got up and went: fatigue in people with cancer. J Natl Cancer Inst Monogr 2004:72–5.
[62] de Jong N, Candel MJ, Schouten HC, Abu-Saad HH, Courtens AM. Course of mental fatigue and motivation in breast cancer patients receiving adjuvant chemotherapy. Ann Oncol 2005;16: 372–82.
[63] Pasacreta JV. Depressive phenomena, physical symptom distress, and functional status among women with breast cancer. Nurs Res 1997; 46:214–21.
[64] Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry 2003;54:269–82.
[65] Reddick BK, Nanda JP, Campbell L, Ryman DG, Gaston-Johansson F. Examining the influence of coping with pain on depression, anxiety, and fatigue among women with breast cancer. J Psychosoc Oncol 2005;23:137–57.
[66] Montgomery GH, Bovbjerg DH. Presurgery distress and specific response expectancies predict postsurgery outcomes in surgery patients confronting breast cancer. Health Psychol 2004;23:381–7.
[67] Patrick DL, Ferketich SL, Frame PS, Harris JJ, Hendricks CB, Levin B, et al. National Institutes of Health State-of-the-Science Conference Statement: symptom management in cancer: pain, depression, and fatigue, July 15–17, 2002. J Natl Cancer Inst Monogr 2004:9–16.
[68] Gaston-Johansson F, Fall-Dickson JM, Bakos AB, Kennedy MJ. Fatigue, pain, and depression in pre-autotransplant breast cancer patients. Cancer Pract 1999;7:240–7.
[69] Dodd MJ, Miaskowski C, Lee KA. Occurrence of symptom clusters. J Natl Cancer Inst Monogr 2004:76–8.
[70] Fleishman SB. Treatment of symptom clusters: pain, depression, and fatigue. J Natl Cancer Inst Monogr 2004;1:119–23.
[71] Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive–behavioral therapy for insomnia secondary to breast cancer, Part I: Sleep and psychological effects. J Clin Oncol 2005;23:6083–96.
[72] Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000; 356:2059–63.
[73] Aapro M, Cull A. Depression in breast cancer patients: the need for treatment. Ann Oncol 1999;10:627–36.
[74] Dhodapkar MV, Ingle JN, Cha SS, Mailliard JA, Wieand HS. Prognostic factors in elderly women with metastatic breast cancer treated with tamoxifen: an analysis of patients entered on four prospective clinical trials. Cancer 1996;77:683–90.
[75] Speer JJ, Hillenberg B, Sugrue DP, Blacker C, Kresge CL, Decker VB, et al. Study of sexual functioning determinants in breast cancer survivors. Breast J 2005;11:440–7.
[76] Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jorgensen T. Depression as a prognostic factor for breast cancer mortality. Psychosomatics 2003;44:24–30.
[77] Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. Cancer 2002;94: 2719–27.
[78] Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004:57–71.
[79] Colleoni M, Mandala M, Peruzzotti G, Robertson C, Bredart A, Goldhirsch A. Depression and degree of acceptance of adjuvant cytotoxic drugs. Lancet 2000;356:1326–7.
[80] Ayres A, Hoon PW, Franzoni JB, Matheny KB, Cotanch PH, Takayanagi S. Influence of mood and adjustment to cancer on compliance with chemotherapy among breast cancer patients. J Psychosom Res 1994;38: 393–402.
[81] Bui QU, Ostir GV, Kuo YF, Freeman J, Goodwin JS. Relationship of depression to patient satisfaction: findings from the barriers to breast cancer study. Breast Cancer Res Treat 2005;89:23–8.
[82] DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101–7.
[83] Williamson GM, Jones DJ, Ingram LA. Medical and psychosocial predictors of breast cancer treatment decisions. In: Park DC, Morrell RW, editors. Processing of medical information in aging patients: cognitive and human factors perspectives. Mahwah (NJ): Lawrence Erlbaum Associates, Inc.; 1999. p. 69–91.
[84] Rowland JH, Massie MJ. Breast cancer. In: Holland JC, editor. Psycho-oncology. New York: Oxford University Press; 1998. p. 380–401.
[85] Sherwin BB. Estrogen effects on cognition in menopausal women. Neurology 1997;48:S21–6.
[86] McLay RN, Maki PM, Lyketsos CG. Nulliparity and late menopause are associated with decreased cognitive decline. J Neuropsychiatry Clin Neurosci 2003;15:161–7.
[87] Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, et al. Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry 2000;157:1949–54.
[88] Kuny S, Stassen HH. Cognitive performance in patients recovering from depression. Psychopathology 1995;28:190–207.
[89] Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem 2003;10:86–98.
[90] Lee BH, Kim H, Park SH, Kim YK. Decreased plasma BDNF level in depressive patients. J Affect Disord 2007;101:239–44.
[91] Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 2005;57:1068–72.
[92] Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. J Psychiatr Res 2007;41:979–90.
[93] Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. J Clin Exp Neuropsychol 2004;26:955–69.
[94] Poppelreuter M, Weis J, Kulz AK, Tucha O, Lange KW, Bartsch HH. Cognitive dysfunction and subjective complaints of cancer patients. a cross-sectional study in a cancer rehabilitation centre. Eur J Cancer 2004;40:43–9.
[95] Scheibel RS, Valentine AD, O'Brien S, Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J Neuropsychiatry Clin Neurosci 2004;16:185–91.
[96] Olin JJ. Cognitive function after systemic therapy for breast cancer. Oncology (Huntingt) 2001;15:613–8 [discussion 8, 21–4].
[97] Vardy J, Wong K, Yi QL, Park A, Maruff P, Wagner L, et al. Assessing cognitive function in cancer patients. Support Care Cancer 2006;14:1111–8.
[98] Hermelink K, Untch M, Lux MP, Kreienberg R, Beck T, Bauerfeind I, et al. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer 2007;109:1905–13.
[99] Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FS. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. J Natl Cancer Inst 2006; 98:1742–5.
[100] Tchen N, Juffs HG, Downie FP, Yi QL, Hu H, Chemerynsky I, et al. Cognitive function, fatigue, and menopausal symptoms in women

receiving adjuvant chemotherapy for breast cancer. J Clin Oncol 2003;21:4175–83.
[101] Brezden CB, Phillips KA, Abdolell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 2000;18:2695–701.
[102] Schagen SB, Hamburger HL, Muller MJ, Boogerd W, van Dam FS. Neurophysiological evaluation of late effects of adjuvant high-dose chemotherapy on cognitive function. J Neurooncol 2001;51: 159–65.
[103] Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. Breast Cancer Res Treat 2000;64:165–76.
[104] Jenkins V, Shilling V, Fallowfield L, Howell A, Hutton S. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. Psychooncology 2004;13:61–6.
[105] Rossi Ferrario S, Zotti AM, Massara G, Nuvolone G. A comparative assessment of psychological and psychosocial characteristics of cancer patients and their caregivers. Psychooncology 2003;12:1–7.
[106] Blanchard CG, Albrecht TL, Ruckdeschel JC. The crisis of cancer: psychological impact on family caregivers. Oncology (Huntingt) 1997;11:189–94 [discussion 96, 201–2].
[107] Grunfeld E, Coyle D, Whelan T, Clinch J, Reyno L, Earle CC, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ 2004;170: 1795–801.
[108] Pitceathly C, Maguire P. The psychological impact of cancer on patients' partners and other key relatives: a review. Eur J Cancer 2003;39:1517–24.
[109] Wagner CD, Bigatti SM, Storniolo AM. Quality of life of husbands of women with breast cancer. Psychooncology 2006;15:109–20.
[110] Osborn T. The psychosocial impact of parental cancer on children and adolescents: a systematic review. Psychooncology 2007;16:101–26.
[111] Gilbar O. Parent caregiver adjustment to cancer of an adult child. J Psychosom Res 2002;52:295–302.
[112] Gilbar O. Gender as a predictor of burden and psychological distress of elderly husbands and wives of cancer patients. Psychooncology 1999;8:287–94.
[113] Andrews SC. Caregiver burden and symptom distress in people with cancer receiving hospice care. Oncol Nurs Forum 2001;28:1469–74.
[114] Gilbar O, Rafaeli R. The relationship between adult cancer patients' adjustment to their illness and that of their parents. Fam Syst Health 2000;18:5–17.
[115] Chen ML, Chu L, Chen HC. Impact of cancer patients' quality of life on that of spouse caregivers. Support Care Cancer 2004;12:469–75.
[116] Cohen M, Pollack S. Mothers with breast cancer and their adult daughters: the relationship between mothers' reaction to breast cancer and their daughters' emotional and neuroimmune status. Psychosom Med 2005;67:64–71.
[117] Valdimarsdottir U, Helgason AR, Furst CJ, Adolfsson J, Steineck G. The unrecognised cost of cancer patients' unrelieved symptoms: a nationwide follow-up of their surviving partners. Br J Cancer 2002; 86:1540–5.
[118] Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry 1999;14:866–74.
[119] Scazufca M, Menezes PR, Almeida OP. Caregiver burden in an elderly population with depression in Sao Paulo, Brazil. Soc Psychiatry Psychiatr Epidemiol 2002;37:416–22.
[120] Cummings EM, Davies PT. Maternal depression and child development. J Child Psychol Psychiatry 1994;35:73–112.
[121] Davis Kirsch SE, Brandt PA, Lewis FM. Making the most of the moment: when a child's mother has breast cancer. Cancer Nurs 2003; 26:47–54.
[122] Ballin A, Gershon V, Tanay A, Brener J, Weizman A, Meytes D. The antidepressant fluvoxamine increases natural killer cell counts in cancer patients. Isr J Med Sci 1997;33:720–3.
[123] Razavi D, Kormoss N, Collard A, Farvacques C, Delvaux N. Comparative study of the efficacy and safety of trazodone versus clorazepate in the treatment of adjustment disorders in cancer patients: a pilot study. J Int Med Res 1999;27:264–72.
[124] Musselman DL, Somerset WI, Guo Y, Manatunga AK, Porter M, Penna S, et al. A double-blind, multicenter, parallel-group study of paroxetine, desipramine, or placebo in breast cancer patients (stages I, II, III, and IV) with major depression. J Clin Psychiatry 2006;67: 288–96.
[125] Torta R, Siri I, Caldera P. Sertraline effectiveness and safety in depressed oncological patients. Support Care Cancer 2007 Sept 14 [Epub ahead of print].
[126] Costa D, Mogos I, Toma T. Efficacy and safety of mianserin in the treatment of depression of women with cancer. Acta Psychiatr Scand Suppl 1985;320:85–92.
[127] van Heeringen K, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. Br J Psychiatry 1996;169:440–3.
[128] Fisch MJ, Loehrer PJ, Kristeller J, Passik S, Jung SH, Shen J, et al. Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier Oncology Group. J Clin Oncol 2003;21: 1937–43.
[129] Morrow GR, Hickok JT, Roscoe JA, Raubertas RF, Andrews PL, Flynn PJ, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. J Clin Oncol 2003;21:4635–41.
[130] Razavi D, Allilaire JF, Smith M, Salimpour A, Verra M, Desclaux B, et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatr Scand 1996;94:205–10.
[131] Holland JC, Romano SJ, Heiligenstein JH, Tepner RG, Wilson MG. A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. Psychooncology 1998;7:291–300.
[132] Moslinger-Gehmayr R, Zaninelli R, Contu A, Oberhoff C, Gutschow K, Schindler AE, et al. A double-blind comparative study of the effectiveness and tolerance of paroxetine and amitriptyline in treatment of breast cancer patients with clinically assessed depression. Zentralbl Gynakol 2000;122:195–202.
[133] Thompson DS. Mirtazapine for the treatment of depression and nausea in breast and gynecological oncology. Psychosomatics 2000; 41:356–9.
[134] Pezzella G, Moslinger-Gehmayr R, Contu A. Treatment of depression in patients with breast cancer: a comparison between paroxetine and amitriptyline. Breast Cancer Res Treat 2001;70:1–10.
[135] Grassi L, Biancosino B, Marmai L, Righi R. Effect of reboxetine on major depressive disorder in breast cancer patients: an open-label study. J Clin Psychiatry 2004;65:515–20.
[136] Maguire P, Hopwood P, Tarrier N, Howell T. Treatment of depression in cancer patients. Acta Psychiatr Scand Suppl 1985;320:81–4.
[137] Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. Health Psychol 1995;14:101–8.
[138] Fawzy FI. Psychosocial interventions for patients with cancer: what works and what doesn't. Eur J Cancer 1999;35:1559–64.
[139] Edwards AG, Hailey S, Maxwell M. Psychological interventions for women with metastatic breast cancer. Cochrane Database Syst Rev 2004:CD004253.
[140] Sheard T, Maguire P. The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. Br J Cancer 1999;80:1770–80.
[141] Anderson B. Biobehavioral outcomes following psychological interventions for cancer patients. J Consult Clin Psychol 2002;70: 590–610.
[142] Chujo M, Mikami I, Takashima S, Saeki T, Ohsumi S, Aogi K, et al. A feasibility study of psychosocial group intervention for breast cancer patients with first recurrence. Support Care Cancer 2005;13: 503–14.

[143] Rehse B, Pukrop R. Effects of psychosocial interventions on quality of life in adult cancer patients: meta analysis of 37 published controlled outcome studies. Patient Educ Couns 2003;50: 179–86.
[144] Jacobsen P, Donovan K, Swaine Z, Watson I. Management of anxiety and depression in adult cancer patients: toward an evidence-based approach. Philadelphia (Pa): Springer; 2006.
[145] Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. Oncol Nurs Forum 1995;22:1369–81.
[146] Ross L, Boesen EH, Dalton SO, Johansen C. Mind and cancer: does psychosocial intervention improve survival and psychological well-being? Eur J Cancer 2002;38:1447–57.
[147] Fisch M. Treatment of depression in cancer. J Natl Cancer Inst Monogr 2004;1:105–11.
[148] Newell SA, Sanson-Fisher RW, Savolainen NJ. Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. J Natl Cancer Inst 2002;94:558–84.
[149] Classen C, Butler LD, Koopman C, Miller E, DiMiceli S, Giese-Davis J, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. Arch Gen Psychiatry 2001;58:494–501.
[150] Manne S, Sherman M, Ross S, Ostroff J, Heyman RE, Fox K. Couples' support-related communication, psychological distress, and relationship satisfaction among women with early stage breast cancer. J Consult Clin Psychol 2004;72:660–70.
[151] Lepore SJ, Coyne JC. Psychological interventions for distress in cancer patients: a review of reviews. Ann Behav Med 2006;32:85–92.
[152] Williams S, Dale J. The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review. Br J Cancer 2006;94:372–90.
[153] Savard J, Simard S, Giguere I, Ivers H, Morin CM, Maunsell E, et al. Randomized clinical trial on cognitive therapy for depression in women with metastatic breast cancer: psychological and immunological effects. Palliat Support Care 2006;4:219–37.
[154] Greer S, Moorey S, Baruch JD, Watson M, Robertson BM, Mason A, et al. Adjuvant psychological therapy for patients with cancer: a prospective randomised trial. BMJ 1992;304:675–80.
[155] Antoni MH, Lehman JM, Kilbourn KM, Boyers AE, Culver JL, Alferi SM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychol 2001;20:20–32.
[156] Kissane DW, Bloch S, Smith GC, Miach P, Clarke DM, Ikin J, et al. Cognitive-existential group psychotherapy for women with primary breast cancer: a randomised controlled trial. Psychooncology 2003; 12:532–46.
[157] Kissane DW, Grabsch B, Clarke DM, Smith GC, Love AW, Bloch S, et al. Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. Psychooncology 2007;16:277–86.
[158] Burton MV, Parker RW, Farrell A, Bailey D, Conneely J, Booth S, et al. A randomised controlled trial of preoperative psychology preparation for mastectomy. Psychooncology 1995;4:1–19.
[159] Gotay CC, Moinpour CM, Unger JM, Jiang CS, Coleman D, Martino S, et al. Impact of a peer-delivered telephone intervention for women experiencing a breast cancer recurrence. J Clin Oncol 2007;25: 2093–9.
[160] McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB. Depression in patients with cancer. Diagnosis, biology, and treatment. Arch Gen Psychiatry 1995;52:89–99.
[161] Halbreich U, Rojansky N, Palter S, Tworek H, Hissin P, Wang K. Estrogen augments serotonergic activity in postmenopausal women. Biol Psychiatry 1995;37:434–41.
[162] Pearlstein TB. Hormones and depression: what are the facts about premenstrual syndrome, menopause, and hormone replacement therapy? Am J Obstet Gynecol 1995;173:646–53.
[163] Melzer H. Role of serotonin in depression. Ann N Y Acad Sci 1990; 600:486–95.
[164] Gonzales GF, Carrillo C. Blood serotonin levels in postmenopausal women: effects of age and serum oestradiol levels. Maturitas 1993;17: 23–9.
[165] Schmidt PJ, Rubinow DR. Menopause-related affective disorders: a justification for further study. Am J Psychiatry 1991;148:844–52.
[166] Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol 1977;106:203–14.
[167] Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29:85–96.
[168] Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 2004;61: 62–70.
[169] Young EA, Midgley AR, Carlson NE, Brown MB. Alteration in the hypothalamic-pituitary-ovarian axis in depressed women. Arch Gen Psychiatry 2000;57:1157–62.
[170] Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry 2003;60:29–36.
[171] Sumner BE, Grant KE, Rosie R, Hegele-Hartung C, Fritzemeier KH, Fink G. Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine(2A) receptor binding sites and mRNA levels in the brain of ovariectomized rats with or without acute estradiol replacement. Brain Res Mol Brain Res 1999;73:119–28.
[172] Fallowfield LJ, Bliss JM, Porter LS, Price MH, Snowdon CF, Jones SE, et al. Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer. J Clin Oncol 2006;24:910–7.
[173] Whelan TJ, Goss PE, Ingle JN, Pater JL, Tu D, Pritchard K, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in post-menopausal women. J Clin Oncol 2005;23:6931–40.
[174] Fallowfield L, Cella D, Cuzick J, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol 2004;22:4261–71.
[175] Mathias C, Cardeal Mendes CM, Ponde de Sena E, Diasde Moraes E, Bastos C, Braghiroli MI, et al. An open-label, fixed-dose study of bupropion effect on sexual function scores in women treated for breast cancer. Ann Oncol 2006;17:1792–6.
[176] Cleeland CS, Bennett GJ, Dantzer R, Dougherty PM, Dunn AJ, Meyers CA, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer 2003;97:2919–25.
[177] Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. Biol Psychiatry 2003;54:283–94.
[178] Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002; 64:604–11.
[179] Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. Brain Behav Immun 2007;21:251–8.
[180] Nieboer P, Buijs C, Rodenhuis S, Seynaeve C, Beex LV, van der Wall E, et al. Fatigue and relating factors in high-risk breast cancer patients treated with adjuvant standard or high-dose chemotherapy: a longitudinal study. J Clin Oncol 2005;23:8296–304.
[181] Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9:853–8.

[182] Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J Affect Disord 1995;34:301–9.
[183] Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4:317–27.
[184] Musselman DL, Miller AH, Porter MR, Manatunga A, Gao F, Penna S, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. Am J Psychiatry 2001;158:1252–7.
[185] Dantzer R. Cytokine-induced sickness behavior: where do we stand? Brain Behav Immun 2001;15:7–24.
[186] Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 2000;157:683–94.
[187] Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. Brain Behav Immun 2003;17(Suppl 1):S119–24.
[188] Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry 2005;29: 201–17.
[189] Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 2001;344: 961–6.
[190] Capuron L, Hauser P, Hinze-Selch D, Miller AH, Neveu PJ. Treatment of cytokine-induced depression. Brain Behav Immun 2002;16:575–80.
[191] Sluzewska A, Rybakowski JK, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. Ann N Y Acad Sci 1995; 762:474–6.
[192] Wolkowitz OM, Reus VI. Treatment of depression with antiglucocorticoid drugs. Psychosom Med 1999;61:698–711.
[193] Williams JW, Barrett J, Oxman T, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. JAMA 2000; 284:1519–26.
[194] Coyne JC, Palmer SC, Shapiro PJ, Thompson R, DeMichele A. Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. Gen Hosp Psychiatry 2004;26:121–8.
[195] Katon W, von Korff M, Lin E, Bush T, Ormel J. Adequacy and duration of antidepressant treatment in primary care. Med Care 1992; 30:67–76.
[196] Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342: 1462–70.
[197] Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002;20:1578–83.
[198] Stearns V, Isaacs C, Rowland J, Crawford J, Ellis MJ, Kramer R, et al. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. Ann Oncol 2000; 11:17–22.
[199] Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL, Cohen LS. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. J Clin Psychiatry 2003;64:473–9.
[200] Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB. Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. Breast J 2006;12:114–22.
[201] Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003;289:2827–34.
[202] Gordon PR, Kerwin JP, Boesen KG, Senf J. Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population. Menopause 2006;13:568–75.
[203] Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30–9.
[204] Coope J. Is oestrogen therapy effective in the treatment of menopausal depression? J R Coll Gen Pract 1981;31:134–40.
[205] Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. Biol Psychiatry 2004;55: 406–12.
[206] Haines CJ, Yim SF, Chung TK, Lam CW, Lau EW, Ng MH, et al. A prospective, randomized, placebo-controlled study of the dose effect of oral oestradiol on menopausal symptoms, psychological well being, and quality of life in postmenopausal Chinese women. Maturitas 2003;44:207–14.
[207] Schneider LS, Small GW, Clary CM. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. Am J Geriatr Psychiatry 2001;9:393–9.
[208] Schneider LS, Small GW, Hamilton SH, Bystritsky A, Nemeroff CB, Meyers BS. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. Am J Geriatr Psychiatry 1997;5:97–106.
[209] Shapira B, Oppenheim G, Zohar J, Segal M, Malach D, Belmaker RH. Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. Biol Psychiatry 1985;20:576–9.
[210] Amsterdam J, Garcia-Espana F, Fawcett J, Quitkin F, Reimherr F, Rosenbaum J, et al. Fluoxetine efficacy in menopausal women with and without estrogen replacement. J Affect Disord 1999;55:11–7.
[211] Hewitt M, Greenfield S, Stoval E. From cancer patient to cancer survivor: lost in transition. Washington (DC): The National Academies Press; 2006.
[212] Hewitt M, Herdman R, Holland D. Meeting psychosocial needs of women with breast cancer. Washington (DC): The National Academies Press; 2004.
[213] NCCN practice guidelines for the management of psychosocial distress. National Comprehensive Cancer Network. Oncology (Huntingt) 1999;13:113–47.
[214] Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med 2006;166:2314–21.