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
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

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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.

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

1. Introduction

Breast cancer is the most common malignancy among women worldwide, with 178,480 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).

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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-Johansson 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 [36,73,42,96]. 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-HT2, α2-adrenergic and histamine-H1 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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design and depression measure</th>
<th>Study population</th>
<th>Rate and onset of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean [11]</td>
<td>RDC</td>
<td>122 T1,2 N0,1 patients assessed 3 and 12 months after mastectomy</td>
<td>3 Months postoperative: 9.7% major; 17.7% minor depression</td>
</tr>
<tr>
<td>Fallowfield et al. [12]</td>
<td>PSE semistructured diagnostic interview at 3 times postoperatively</td>
<td>269 Stage I and II patients assessed 2 weeks, 3 months and 12 months after surgery</td>
<td>Postoperatively: 26% depressed 3 Months postoperative: 22% depressed 12 Months postoperative: 20% depressed</td>
</tr>
<tr>
<td>Hopwood et al. [13,14]</td>
<td>HADS depression scale, 11-point depression scale at 1, 3, 6, 12, 18 months postoperatively</td>
<td>214 Ambulatory advanced BCA patients, with 1–3-month follow-ups</td>
<td>18% Depressed at first time point by HADS (20% by diagnostic interview), 11% depressed at 1–3-month follow-up by HADS</td>
</tr>
</tbody>
</table>
| Love et al. [15] | 11-point depression scale at 3, 6, 12, 24 months | Postmenopausal (mean years since menopause, 9.3) | No difference between groups (baseline: 31–33% depressed, 12 Months: 30–45%)
| 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 7% With case depression preoperatively, 7% at 3 months and 4% at 12 months |
| Lee et al. [17] | PSE preoperatively, 1 and 5 years after diagnosis | 197 BCA patients | Depressed: 15% on T (onset within 3–6 months after initial therapy and within first few weeks of starting T) |
| 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 |
| 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 | Similar rates of depression among patients with locoregional recurrence and metastatic disease 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% CES-D ≥16 for No tx group: 24.8%, T only: 26.8%, chemotherapy only: 30.2%, T+chemotherapy: 24.9% |
| 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 | |
| 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 ≤50 Years, 32% with CES-D ≥16 >50 Years, 20% with CES-D ≥16 25% With clinically significant depression (CES-D ≥16) Mean CES-D score: 11.75 (26% ≥16) in former chemotherapy patients, 7.59 (14% ≥16) in noncancer controls |
| Wenzel et al. [20] | CES-D at recent treatment completion (<2 months) | 304 Stages I, II and IIIA patients | | |
| Bower et al. [59] | CES-D Assessed between 1 and 5 years after diagnosis | 161 ≤50 Years old, 143 >50 Years old | No significant difference between groups Clinically significant HADS depression score (>8) in Tnly group at: baseline: 12%, 3–4 months: 13%, 12 months: 6% 23% With clinically significant depression (HADS ≥11) |
| Broeckel et al. [21] | CES-D on Cross-sectional mailed survey | 1957 Stage 0-II patients | 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 | 61 With no current disease who completed adjuvant chemotherapy 3–36 (mean 16) months ago, 61% on T. | 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% 23% With clinically significant depression (HADS ≥11) |
| Akechi et al. [24] | HADS Depression scale postoperatively | 148 Patients not currently receiving active cancer treatment (other than hormone therapy) | 10% With MDD at follow-up |
| Morasso et al. [25] | SCID at 1st follow-up after chemotherapy | 184 Stage I–III patients | | (continued on next page)
Table 1 (continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design and depression measure</th>
<th>Study population</th>
<th>Rate and onset of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallagher et al. [26]</td>
<td>GHQ-12 at 6 months after diagnosis</td>
<td>195 Grade I-III patients (27% chemotherapy, 36% radiation, 32% hormonal therapy)</td>
<td>26% With GHQ-12 scores indicative of psychological morbidity (GHQ-12 ≥4)</td>
</tr>
<tr>
<td>Osborne et al. [55]</td>
<td>HADS Depression scale at various time points</td>
<td>731 Stage I–IV patients</td>
<td>3% With probable depression (HADS &gt;10), 12% With possible depression (HADS 8–10)</td>
</tr>
<tr>
<td>Rakovitch et al. [27]</td>
<td>Single question about “unhappiness or depression” rated on 1–5 Likert scale</td>
<td>64 With ductal carcinoma in situ (DCIS), 164 with early invasive breast cancer (EIBC) referred to a tertiary cancer center</td>
<td>13% DCIS, 22% EIBC rated as “very often” (score ≥4)</td>
</tr>
<tr>
<td>Ganz et al. [28]</td>
<td>CES-D assessed following primary therapy</td>
<td>558 Stage I–II invasive epithelial breast cancer patients</td>
<td>16.9% (Mastectomy only) to 27.7% (mastectomy with chemotherapy) with CES-D ≥16</td>
</tr>
<tr>
<td>Manne et al. [150]</td>
<td>SCID Given after surgery but before adjuvant therapy</td>
<td>113 Stage I–IV in active treatment</td>
<td>9% With clinically significant depression</td>
</tr>
<tr>
<td>Schou et al. [29]</td>
<td>HADS Depression scale at diagnosis, 3, 12 months after surgery</td>
<td>118 Stage I–II BCA patients</td>
<td>50% had HADS score ≥4</td>
</tr>
<tr>
<td>Coyle et al. [194]</td>
<td>SCID Given to waiting room sample</td>
<td>210 Stage II–III BCA patients</td>
<td>12% had HADS score ≥8 (mean 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.</td>
</tr>
<tr>
<td>Golden-Kreutz and Anderson [30]</td>
<td>CES-D Given after surgery but before adjuvant therapy</td>
<td>303 Stage I–II and 200 metastatic BCA</td>
<td>9.6% Early-stage had MDD; 6.5% of metastatic had MDD.</td>
</tr>
<tr>
<td>Kissane et al. [38]</td>
<td>MILP and HADS given after surgery</td>
<td>115 Stage I–IV BCA</td>
<td>36.5% With CES-D scores ≥16</td>
</tr>
<tr>
<td>Aukst-Margetic et al. [31]</td>
<td>CES-D Assessed during radiation therapy</td>
<td>472 Women undergoing active treatment or in active follow-up. 250 (53%) with BCA (Stage 0–III), 222 (47%) with gynecological cancer</td>
<td>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).</td>
</tr>
<tr>
<td>Ell et al. [39]</td>
<td>PHQ-9 Given in outpatient clinic or via telephone</td>
<td>111 BCA Patients receiving or about to receive chemotherapy</td>
<td>28% With CES-D scores ≥19</td>
</tr>
<tr>
<td>Roscoe et al. [32]</td>
<td>CES-D Given before and during chemotherapy treatments</td>
<td>222 Early-stage patients (44% received chemotherapy, 48% received endocrine therapy)</td>
<td>Annual prevalence of depression, anxiety or both: 1st year 48%, 2nd year 25%, 3rd year 23%, 4th year 22%, 5th year 15%</td>
</tr>
<tr>
<td>Burgess et al. [33]</td>
<td>SCID Diagnosis of MDD, GAD or both in the 5 years after diagnosis</td>
<td>97 Women with breast tumors who had received treatment for BCA</td>
<td>38.4% of women met criteria for depression CES-D score &gt;16.</td>
</tr>
<tr>
<td>Yen et al. [34]</td>
<td>CES-D Given after treatment for BCA</td>
<td>127 BCA patients</td>
<td>4.7% had major depression. 3.1% had dysthymic disorder.</td>
</tr>
<tr>
<td>Mehnert and Koch [35]</td>
<td>SCID Given postsurgery</td>
<td>56 Postmenopausal women with recurrent BCA receiving palliative treatment</td>
<td>10% had HADS depression score ≥11, 21% had score ≥8.</td>
</tr>
<tr>
<td>Kenne Sarenmalm et al. [56]</td>
<td>HADS Given to outpatients</td>
<td>56 Postmenopausal women with recurrent BCA receiving palliative treatment</td>
<td>10% had HADS depression score ≥11, 21% had score ≥8.</td>
</tr>
</tbody>
</table>

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 misersin 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

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Participants/breast cancer stage</th>
<th>Entry criteria</th>
<th>Depression instruments</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa et al. [126]</td>
<td>73</td>
<td>Stage II–IV breast (n=47), ovary, uterus/cervix cancer patients</td>
<td>ZSRDS score ≥41 and HAM-D ≥16</td>
<td>HAM-D</td>
<td>Mianserin 10 mg vs. placebo, 4 weeks</td>
<td>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</td>
</tr>
<tr>
<td>Razavi et al. [130]</td>
<td>69</td>
<td>Mixed cancer diagnoses. 42 with breast or gynecological cancer</td>
<td>MDD or Adjustment disorder, HADS ≥13</td>
<td>HAM-D, MADRS</td>
<td>Fluoxetine 20 mg vs. placebo, 5 weeks</td>
<td>HADS &lt;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).</td>
</tr>
<tr>
<td>Van Heeringen and Zivkov [127]</td>
<td>55</td>
<td>Stage I or II breast cancer patients</td>
<td>MDD by clinical interview</td>
<td>HAM-D</td>
<td>Mianserin 60 mg vs. placebo, 6 weeks</td>
<td>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. 5/10 Had ≥50% decrease in HAM-D scores.</td>
</tr>
<tr>
<td>Ballin et al. [122]</td>
<td>10</td>
<td>Patients with a solid tumor who received chemotherapy (4 with breast cancer)</td>
<td>No depression criteria required.</td>
<td>HAM-D</td>
<td>Fluvoxamine, 4 weeks</td>
<td></td>
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<tr>
<td>Holland et al. [131]</td>
<td>37</td>
<td>Women with cancer (30 with breast cancer Stages II, III, IV) in active treatment</td>
<td>MDD or adjustment disorder, HAM-D &gt;14</td>
<td>HAM-D, CGI</td>
<td>Fluoxetine vs. desipramine, 6 weeks</td>
<td>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. 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.</td>
</tr>
<tr>
<td>Pezzella et al. [134]</td>
<td>179</td>
<td>Woman during treatment of breast cancer</td>
<td>MDD diagnosed by interview</td>
<td>MADRS, CGI</td>
<td>Amitriptyline vs. paroxetine, 8 weeks</td>
<td>Significant improvements in MADRS and CGI in both groups; paroxetine slightly better tolerated 19 Patients had improved depression symptoms, improved sleep continuity, decreased nausea and improved appetite. ≥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.</td>
</tr>
<tr>
<td>Thompson [133]</td>
<td>20</td>
<td>Women with breast or gynecologic cancer (8 with breast cancer)</td>
<td>Adjustment disorder, mood or anxiety disorder by interview</td>
<td>None used</td>
<td>Mirtazapine 30 mg or 45 mg daily.</td>
<td></td>
</tr>
<tr>
<td>Fisch et al. [128]</td>
<td>163</td>
<td>Women with breast cancer and after at least 2 cycles of chemotherapy</td>
<td>Depression symptoms on 2-item depression screener, MDD excluded</td>
<td>MADRS</td>
<td>Fluoxetine 20 mg vs. placebo, 12 weeks</td>
<td>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.</td>
</tr>
<tr>
<td>Morrow et al. [129]</td>
<td>549</td>
<td>Cancer patients receiving chemotherapy (259 with breast cancer)</td>
<td>No prior psych hospitalization, and an indication of fatigue from baseline questionnaires.</td>
<td>CES-D</td>
<td>Paroxetine 20 mg vs. placebo, 8 weeks</td>
<td>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)</td>
</tr>
<tr>
<td>Grassi et al. [135]</td>
<td>20</td>
<td>Women with breast cancer (any stage)</td>
<td>MDD by clinical interview</td>
<td>HAM-D</td>
<td>Reboxetine 4–10 mg, 8 weeks</td>
<td>HAM-D decreased significantly (21.76–11.61)</td>
</tr>
</tbody>
</table>

(continued on next page)
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.

3.7. Clinical trials of psychotherapy in women with
breast cancer

Numerous studies have assessed the efficacy of psycho-
social 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
morbidty” 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 \( (5\text{-hydroxytryptamine or } 5\text{-HT}) \) postsynaptic responsibility 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]. 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 chemotherapy 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 \[ \text{e.g., interleukin (IL)-1, IL-6} \], 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.](image-url)
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


