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

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Objective: This study compared the efficacy and safety of paroxetine and desipramine with those of placebo in the treatment of depressive disorders in adult women with breast cancer, stages I–IV.

Method: In a double-blind, placebo-controlled study, 35 female outpatients with breast cancer and DSM-III-R major depression or adjustment disorder with depressed mood were randomly assigned to treatment with paroxetine (N = 13), desipramine (N = 11), or placebo (N = 11) for 6 weeks. Primary efficacy was assessed by change from baseline in score on the 21-item Hamilton Rating Scale for Depression (HAM-D), and the secondary outcome measure was change from baseline in the Clinical Global Impressions-Severity of Illness scale (CGI-S) score.

Results: Mean changes in the total HAM-D and CGI-S scores from baseline to 6-week endpoint for the paroxetine and desipramine groups were not significantly different than those for the placebo-treated group. An unusually high rate of response (defined as ≥ 50% improvement in the HAM-D score) in the placebo group was observed (55% [N = 6]); adverse events precipitated patient discontinuation in the active treatment groups (9% [N = 1] for desipramine, 15% [N = 2] for paroxetine) similar to that in the placebo-treated patients (18% [N = 2]). Improvement on symptom dimensions within the HAM-D and Hamilton Rating Scale for Anxiety (depressive, anxiety, cognitive, neurovegetative, or somatic) was also similar between groups.

Conclusion: The small number of women in this study most likely contributed to the lack of observed differences in efficacy observed during the 6 weeks of treatment. Randomized, placebo-controlled trials of adequate power seeking to determine efficacy of antidepressants in the United States for the treatment of women with breast cancer and comorbid depression remain of paramount importance.

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Depressive disorders (or clinically significant levels of depressive symptoms) hinder a woman's compliance with antineoplastic therapy,[1,2] reduce her quality of life,[3] and diminish her survival.[4–6] Depressive syndromes and major depression are exceedingly common in women with breast cancer, with the prevalence of major depression increasing with neoplastic progression,[7] from an 11% prevalence rate of major depression associated with early-stage, node-negative breast cancer[8] to as great as 50% in women with metastatic breast cancer undergoing palliative therapies.[9,10]

In light of the adverse consequences of major depression in women with breast cancer, it is remarkable that only mianserin, a compound unavailable in the United States, has been scrutinized in placebo-controlled, double-blind, randomized trials. Mianserin, a compound similar to mirtazapine, has been shown to significantly improve depressive symptoms in women with breast cancer and comorbid depression.[11,12] Given this paucity of in-

formation, and some evidence suggesting greater efficacy of tricyclic antidepressants (TCAs) compared to selective serotonin reuptake inhibitors (SSRIs) in patients with more severe depression,[13] we compared the efficacy and safety of paroxetine and desipramine to placebo in the treatment of women with breast cancer and comorbid depression.

METHOD

Study Design

This 2-center, double-blind, randomized, placebo-controlled study was conducted to assess the efficacy and tolerability of paroxetine and desipramine in the treatment of depressive symptoms in women with breast cancer. Outpatients with stages I–IV breast cancer with a major depressive episode or adjustment disorder with depressed mood were enrolled. A 1-week, open-label, placebo period was used to entrain participants for the twice-daily ingestion of study medication during the study and to "wash out" prior mood-altering medications.

Diagnostic procedures included conducting a *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R)[14] multiaxial evaluation, physical examination, psychiatric and medical history, routine laboratory analyses, urinalysis and pregnancy test, electrocardiogram, and administration of the 21-item Hamilton Rating Scale for Depression (HAM-D)[15] and the Clinical Global Impressions scale (CGI).[16] Eligible patients were then randomly assigned to 1 of the 3 double-blind treatment groups.

Patients randomly assigned to paroxetine treatment received 20 mg/day for the first 4 weeks; thereafter, the dose could be increased to 40 mg/day. Patients receiving desipramine began at a dose of 25 mg/evening for the first 3 days, then increased to 50 mg/evening for the next 4 days, with a subsequent forced titration to 125 mg/day at the rate of 25 mg every 7 days during the second, third, and fourth weeks of the study. After this titration period, desipramine dose increases of 25 mg/day were permitted every 3 days up to a maximum dose of 200 mg/day. Dose reduction was permitted if necessary for minimization of adverse events to a minimum dose of 20 mg/day for paroxetine or 125 mg/day for desipramine. Following the 6-week treatment phase, patients defined as responders could continue for an additional 134 days of double-blind treatment and then were gradually tapered off all study medications. Chloral hydrate, maximum of 1.5 g/24 hours, or temazepam, 30 mg, could be given for sleep. For occasional nausea, lorazepam or suppositories containing lorazepam, diphenhydramine, or haloperidol could be used. No other psychotropic drugs were permitted for sleep or nausea during the study.

The study was approved by the institutional review board at each of the participating centers, and each patient provided written informed consent before entry into the study.

Patient Selection

Thirty-five female patients with a diagnosis of breast carcinoma (stage I, II, III, or IV) and a diagnosis of major depression for at least 2 weeks (no patients had adjustment disorder with depressed mood) volunteered to participate in this 6-week, double-blind trial of desipramine and paroxetine versus placebo. Inclusion criteria included the following: female outpatients aged 18 to 75 years with a concurrent diagnosis of breast carcinoma (stage I, II, III, or IV), DSM-III-R criteria for major depression (except duration of illness had to be at least 1 month) or adjustment disorder with depressed mood for at least 2 months,[14] HAM-D score of at least 14 on the first 17 items of the 21-item HAM-D, and last cancer treatment within the last 5 years.

Exclusion criteria included the following: pregnant women and women of childbearing potential not using contraception; lactating women; serious suicidal risk; history of urinary retention; intracranial metastases; history of angina pectoris, myocardial infarction, arrhythmia, presence of conduction defects, or any serious cardiac disease; and serious illness including cardiac, hepatic, renal, respiratory, endocrinologic, neurologic, or hematologic disease of such instability that hospitalization for treatment was likely within the next 2 months. Other exclusion criteria included having a DSM-III-R diagnosis of organic mental disorder, alcohol and/or substance use disorder, paranoid or psychotic symptoms, or bipolar disorder. Patients with breast cancer who might require hospitalization for antineoplastic treatment were eligible for the study.

Assessment

Patients were assessed for both efficacy and adverse events at baseline, weekly during weeks 1 through 6, and on a monthly basis thereafter for a total of 6 months of double-blind, randomized treatment. At each evaluation, patients were administered a battery of observer-rated and self-report psychiatric assessments including the 21-item observer-rated HAM-D[15] and the 14-item observer-rated Hamilton Rating Scale for Anxiety (HAM-A).[17] Laboratory evaluations were performed at the screening visit and at termination from the study. A drug level test was performed after 4 weeks of active treatment and again at termination from the study. A plasma desipramine concentration of 500 ng/mL was considered toxic.

The primary efficacy parameter was the mean change from baseline in the total score of the 21-item HAM-D. The secondary outcome measure was the mean change from baseline in the Clinical Global Impressions-Severity

of Illness scale (CGI-S) score. Clinical response was defined as achieving a reduction of ≥ 50% from baseline HAM-D score or a CGI global improvement score ≤ 2. Clinical remission was defined as achieving a HAM-D score ≤ 7.

Symptoms were grouped into dimensions corresponding to mood, cognitive function, neurovegetative, and somatic symptoms. The dimension of mood included depressive symptoms (depressed mood, feelings of guilt, and suicidal thoughts assessed by the HAM-D) and anxiety symptoms (anxious mood, tension/irritability, and fear assessed by the HAM-A). The dimension of cognitive symptoms included self-reported symptoms of difficulty concentrating and poor memory as assessed by the HAM-A. The dimension of neurovegetative symptoms included symptoms of weight loss, abnormal sleep, and psychomotor retardation as assessed by the HAM-D. Lastly, the dimension of somatic symptoms included somatic sensory symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and somatic muscular symptoms as assessed by the HAM-A.

Safety evaluations were based on routine adverse event monitoring and vital assessments. At each post-baseline assessment, adverse events were elicited by asking the patient nonleading questions, subsequently investigated, and documented on the case report form.

Data Analysis

On the basis of the standard deviations of HAM-D scores in patients with breast cancer,[11] the study was designed to have 85% power to detect an 11-point difference in scores on the HAM-D at 6 weeks between any 2 of the 3 treatment groups (15 patients per group) with a 2-sided significance level of 0.05/3.

Data are presented from the intent-to-treat population. Baseline demographic and clinical characteristics among paroxetine-, desipramine-, and placebo-treated groups were compared using the Kruskal-Wallis test or Fisher exact test. Patients' symptom scores at baseline, week 4, and week 6 were used for the statistical analysis. The last-observation-carried-forward approach was applied for the missing data due to early dropout in the study.

Changes from baseline to week 6 in the efficacy rating scales were compared among treatment groups using analysis of variance. The proportions of patients achieving clinical response and clinical remission were analyzed with Fisher exact test.

For each patient, the mean score for each of the 5 dimensions was calculated as the mean of the scores of the individual symptoms included in that dimension. Repeated-measure analysis of variance with treatment as the independent factor and time of visit as the repeated measure was applied to assess the between-subjects effects (treatments) and within-subjects effects (time) for the 5 major dimensions and individual symptoms within each dimension. For post hoc comparisons, Tukey 95% confidence intervals were reported for pairwise between-treatment differences.

All statistical tests were 2-tailed unless specified otherwise. The general linear model procedure (PROC GLM; SAS; Cary, N.C.) was used to perform the analysis of variance and repeated-measure analysis of variance. The hypotheses were tested at the significance level of .05.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, a total of 35 outpatients were enrolled; 13 patients (mean age = 55 years; range, 41–81 years) were randomly assigned to the paroxetine group, 11 patients (mean age = 48 years; range, 35–65 years) received desipramine, and 11 patients (mean age = 59 years; range, 40–78 years) were given placebo. The paroxetine-, desipramine-, and placebo-treated groups were similar in age, race (92% [N = 12], 91% [N = 10], and 64% [N = 7], respectively, were white; p = .27), relationship status, and history of major depression, concomitant anxiety, or other psychiatric disorders. The stage of cancer was significantly different among the 3 treatment groups; i.e., women in the placebo-treated group were at less advanced stages of breast cancer than the other 2 groups (p = .01). Nearly all of the patients in the paroxetine- and desipramine-treated groups had received chemotherapy in the prior 5 years in comparison to just over half of the placebo-treated women (p = .02); however, the performance status of the paroxetine-treated group was the least impaired at baseline (p = .03).

There was no difference among the treatment groups in the use of psychotropic medications prior to the study (paroxetine: 31% [N = 4]; desipramine: 9% [N = 1]; placebo 27% [N = 3]) (p = .48) or in rates of prior psychotherapy (individual and/or group) (p = .74) among the desipramine (27% [N = 3]), paroxetine (31% [N = 4]), and placebo (45% [N = 5]) treatment groups.

Mean doses at study endpoint (i.e., the last available observation for each patient while receiving treatment) were 31 mg/day for paroxetine (range, 20–40 mg/day) and 113 mg/day for desipramine (range, 50–175 mg/day). Three of the desipramine-treated patients withdrew from the study before reaching the 125-mg/day dose at week 4. The incidence of concomitant use of sleeping medications was similar among the paroxetine-treated (31% [N = 4]), desipramine-treated (27% [N = 3]), and placebo-treated (45.9% [N = 5]) groups. During the study, there was also no difference among the treatment groups in the use of oncologic medications (paroxetine: 69% [N = 9]; desipramine: 45% [N = 5]; placebo: 36%

Table 1. Baseline Demographic and Clinical Characteristics of Patients With Breast Cancer and Comorbid Depressive Disorders Treated With Placebo, Desipramine, or Paroxetine[a]

Characteristic	Placebo (N = 11)	Desipramine (N = 11)	Paroxetine (N = 13)	p Value
Age, mean (SD), year	58.6 (12.8)	47.7 (9.0)	54.6 (12.7)	.13
Major depression	11 (100)	11 (100)	13 (100)	> .99
Level of education				.18
PhD, MD, and/or JD	0 (0)	1 (9)	0 (0)	
Master's degree	0 (0)	0 (0)	2 (15)	
Some graduate school	1 (9)	1 (9)	0 (0)	
Bachelor's degree	1 (9)	2 (18)	2 (15)	
Some college	7 (64)	2 (18)	8 (62)	
Graduate from high school	1 (9)	2 (18)	1 (8)	
Less than high school	1 (9)	3 (27)	0 (0)	
Relationship status				.20
Single	0 (0)	1 (9)	2 (15)	
Married or living as married	6 (55)	6 (55)	10 (77)	
Separated	1 (9)	0 (0)	0 (0)	
Divorced	2 (18)	4 (36)	1 (8)	
Other	2 (18)	0 (0)	0 (0)	
History of major depression	9 (82)	9 (82)	10 (77)	> .99
History of prior psychotherapy	5 (45)	3 (27)	4 (31)	.74
Use of psychotropic medication (immediately prior to study enrollment)	3 (27)	1 (9)	4 (31)	.48
Stage of cancer				
I	7 (64)	0 (0)	3 (23)	.01
II	4 (36)	6 (55)	7 (54)	
III	0 (0)	1 (9)	1 (8)	
IV	0 (0)	4 (36)	2 (15)	
Time elapsed since cancer treatment				.91
Currently in treatment	3 (27)	4 (36)	4 (31)	
Within the past year	6 (55)	3 (27)	6 (46)	
2–5 years	2 (18)	3 (27)	2 (15)	
Type of past cancer treatment				
Mastectomy	4 (36)	7 (64)	7 (54)	.41
Lumpectomy	3 (27)	3 (27)	4 (31)	> .99
Chemotherapy	6 (55)	11 (100)	12 (92)	.02
Hormone therapy	1 (9)	2 (18)	4 (31)	.51
Bone marrow transplant	0 (0)	0 (0)	0 (0)	> .99
Cancer support group	2 (18)	1 (9)	1 (8)	.82
Other	2 (18)	1 (9)	2 (15)	> .99
Type of current cancer treatment				
Chemotherapy	1 (9)	3 (27)	2 (15)	.64
Hormone therapy	1 (9)	2 (18)	3 (23)	.85
Radiation therapy	1 (9)	0 (0)	0 (0)	.63
Cancer support group	1 (9)	1 (9)	1 (8)	> .99
Other	3 (27)	1 (9)	2 (15)	.64
Current performance status				.03
Fully ambulatory with no symptoms	1 (9)	0 (0)	0 (0)	
Fully ambulatory with symptoms	3 (27)	5 (45)	11 (85)	
Bedrest up to half the day	6 (55)	6 (55)	2 (15)	
Bedrest more than half the day	1 (9)	0 (0)	0 (0)	
Anxiety disorder	4 (36.4)	3 (27.3)	6 (46.2)	.62
Miscellaneous psychiatric disorder	3 (27.3)	3 (27.3)	5 (38.5)	.81

[a]Values expressed as N (%) unless otherwise noted.

[N = 4]) (p = .25) or pain medications (paroxetine: 77% [N = 10]; desipramine: 64% [N = 7]; placebo: 100% [N = 11]) (p = .10).

Efficacy

Figure 1 shows the mean HAM-D scores of the study participants. Mean changes in the total HAM-D score and CGI-S score from baseline to endpoint for the paroxetine and desipramine groups were not significantly different than those of the placebo-treated group (Table 2). There was also no significant difference in mean changes on the total HAM-A score (Figure 2 and Table 2) among the 3 groups (p = .58).

For the total intent-to-treat population, there were no statistically significant differences in response rates among those receiving paroxetine, desipramine, or placebo using the HAM-D (38% [N = 5], 45% [N = 5], and 55% [N = 6], respectively [p = .91]) or CGI criteria (46% [N = 6], 45% [N = 5], and 73% [N = 8], respectively [p = .38]). Remission (HAM-D score ≤ 7) was achieved

Figure 1. 21-Item Hamilton Rating Scale for Depression Scores After 6 Weeks of Treatment With Placebo, Desipramine, or Paroxetine in Women With Breast Cancer and Comorbid Depression

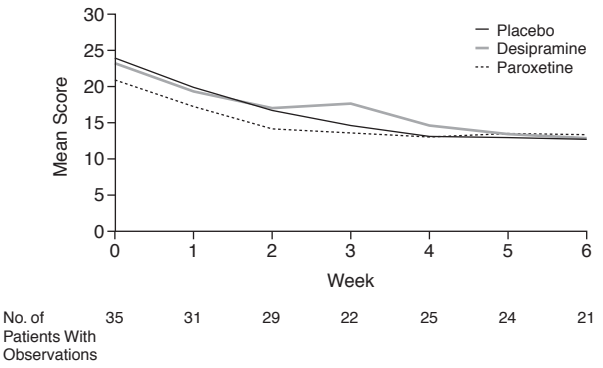


Figure 2. Hamilton Rating Scale for Anxiety Scores After 6 Weeks of Treatment With Placebo, Desipramine, or Paroxetine in Women With Breast Cancer and Comorbid Depression

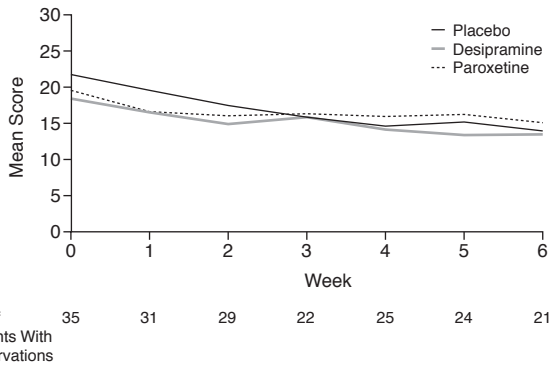


Table 2. Baseline Ratings of Depression and Anxiety Symptoms and Changes in Scores After 6 Weeks for Women With Breast Cancer and Comorbid Depression Randomly Assigned to Treatment With Placebo, Desipramine, or Paroxetine

	Placebo (N = 11)		Desipramine (N = 11)		Paroxetine (N = 13)		
Measure	Baseline, Mean (SD)	Change, Mean (SD)	Baseline, Mean (SD)	Change, Mean (SD)	Baseline, Mean (SD)	Change, Mean (SD)	p Value[a]
Hamilton Rating Scale for Depression	23.91 (4.99)	–11.27 (5.98)	23.00 (6.16)	–10.09 (9.42)	21.00 (5.66)	–7.62 (5.80)	.45
Hamilton Rating Scale for Anxiety	21.82 (8.54)	–7.82 (9.30)	18.45 (6.67)	–5.09 (9.70)	19.62 (7.19)	–4.38 (5.85)	.58
Clinical Global Impressions-Severity of Illness scale	4.18 (0.40)	–1.09 (0.83)	4.00 (0.77)	–1.00 (1.26)	3.85 (0.69)	–0.77 (0.93)	.73

[a]Hypothesis tests with the null hypothesis that there is no difference in the change from baseline to week 6 among the 3 treatment groups.

by 23% (N = 3) of the paroxetine-treated patients, 45% (N = 5) of the desipramine-treated patients, and 36% (N = 4) of the placebo-treated patients (p = .55). Among the study completers, remission (HAM-D score ≤ 7) was achieved by 38% (3/8) of the paroxetine-treated patients, 71% (5/7) of the desipramine-treated patients, and 33% (2/6) of the placebo-treated patients (p = .35).

The temporal changes of the 5 symptom dimensions are displayed in Figure 3. For depressive and neurovegetative symptoms, significant improvements from baseline were observed at both week 4 and week 6 for all 3 treatment groups. Significant improvement for the cognitive symptoms was observed at week 6 for the 2 drug groups but not for the placebo group. The anxiety and somatic symptoms significantly decreased only in the placebo group. No significant intergroup difference was found at any of the 3 time points for the 5 dimensions.

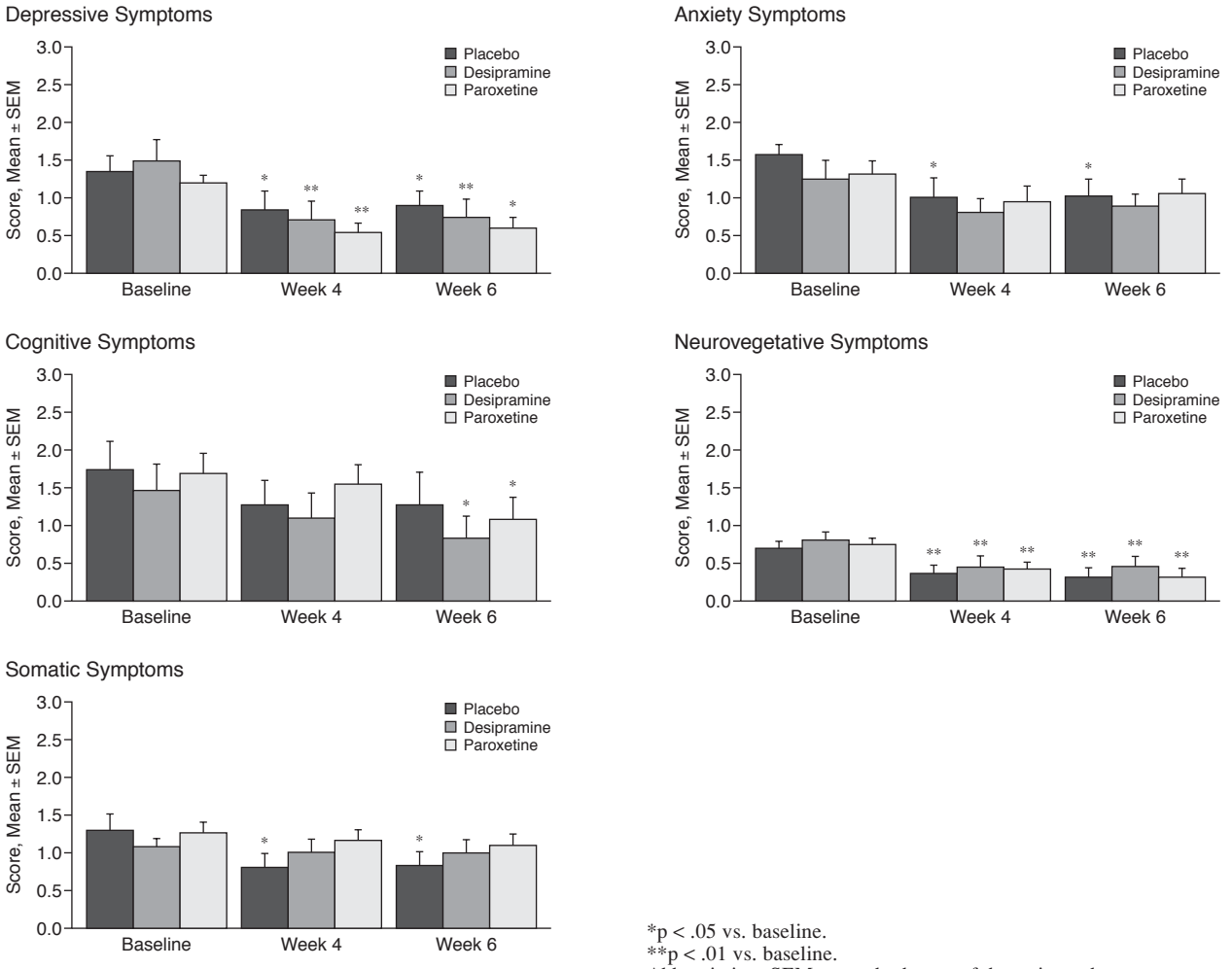
Table 3 illustrates by-treatment mean scores at the 3 visits for the individual symptoms within each of the 5 dimensions. For the placebo group, significant improvement was observed at week 6 for the following symptoms: tension/irritability, abnormal sleep, genitourinary, and somatic muscular symptoms. Depressed mood, feelings of guilt, memory disturbance/concentration, and abnormal sleep were improved in the desipramine-treated patients. Individual symptoms that significantly decreased in the paroxetine-treated group included depressed mood, memory disturbance/concentration, abnormal sleep, and weight loss. At week 6, none of the individual symptoms were significantly different among the 3 treatment groups according to the Type III test of the treatment effect in the repeated-measure analysis of variance and the Tukey tests.

Emergent Adverse Events

Treatment-emergent adverse events were determined by asking open-ended, nonleading questions. Dry mouth (46%, N = 6), nausea (38%, N = 5), and pain (38%, N = 5) were the most frequently reported effects in the paroxetine-treated patients. For the patients in the desipramine group, dry mouth (73%, N = 8), constipation (36%, N = 4), headache (36%, N = 4), and pain (36%, N = 4) were noted most commonly. In the placebo group, headache (45%, N = 5), pain (45%, N = 5), dry mouth (27%, N = 3), and constipation (27%, N = 3) were the most frequently occurring adverse events. Patients treated with desipramine experienced a higher incidence of dry mouth in comparison to the placebo group (p = .09).

Among the total of 35 outpatients, 14 (40%) withdrew from the study by week 6. Adverse events precipitated study discontinuation in 5 (14%) of the study participants:

Figure 3. Scores on 5 Major Symptom Dimensions After 6 Weeks of Treatment With Placebo, Desipramine, or Paroxetine in Women With Breast Cancer and Comorbid Depression



*p < .05 vs. baseline.
**p < .01 vs. baseline.
Abbreviation: SEM = standard error of the estimated mean.

2 (15%) of the paroxetine patients; 1 (9%) of the desipramine patients, who required hospitalization for treatment of her worsening depressive symptoms; and 2 (18%) of the placebo patients. The adverse events associated with active treatment were consistent with the safety profiles for SSRIs and TCAs. Other reasons for withdrawal from the study included lack of efficacy (paroxetine: 15% [N = 2]; desipramine: 18% [N = 2]), patient's wish to discontinue study participation (placebo: 18% [N = 2]; paroxetine: 8% [N = 1]), and difficulty ingesting study medication due to increased debilitation from spread of disease (desipramine: 9% [N = 1]). One placebo-treated patient was lost to follow-up.

DISCUSSION

To date, this study is the only placebo-controlled study evaluating the efficacy and tolerability of an SSRI antidepressant in comparison to a TCA for the treatment of unipolar depression in women with breast cancer. Prior placebo-controlled studies of women with breast cancer and comorbid depression have reported that mianserin (up to 60 mg/day) was significantly more effective and tolerable than placebo over 4-week (N = 47)[11] and 6-week (N = 55)[12] treatment periods, respectively. The antidepressant most structurally related to mianserin (a histamine H_1 and 5-HT_2 receptor antagonist) is mirtazapine.

Our study is limited by the small sample size. With 30 patients per group, we would have had 85% power to detect a 7.5-point difference in the HAM-D scores at 6 weeks between any 2 of the 3 treatment groups with a 2-sided significance level of .05/3. During the study, attempts to recruit many potential study participants were deterred by their and their medical providers' preference for open-label, antidepressant treatment. The discrepancy between the planned and actual number of study partici-

Table 3. Baseline Ratings of 5 Major Symptom Dimensions and Changes in Scores After 6 Weeks for Women With Breast Cancer and Comorbid Depression Randomly Assigned to Treatment With Placebo, Desipramine, or Paroxetine

	Placebo (N = 11)			Desipramine (N = 11)			Paroxetine (N = 13)			Intergroup Comparison at Week 6			
											Tukey 95% Confidence Interval for Pairwise Differences		
Symptom Dimension	Baseline	Week 4	Week 6	Baseline	Week 4	Week 6	Baseline	Week 4	Week 6	Overall p Value	Desipramine vs Placebo	Paroxetine vs Placebo	Desipramine vs Paroxetine
Depressive symptoms													
Depressed mood	2.73	1.64*	1.91	2.55	1.09**	1.55*	2.77	1.38**	1.38**	.62	–1.73 to 1.01	–1.84 to 0.79	–1.16 to 1.48
Feelings of guilt	0.82	0.36	0.45	1.18	0.73	0.36**	0.69	0.23	0.38	.95	–0.79 to 0.61	–0.74 to 0.60	–0.70 to 0.65
Suicidal thoughts	0.55	0.55	0.27	0.73	0.27	0.27	0.08	0	0	.46	–0.65 to 0.65	–0.90 to 0.35	–0.35 to 0.90
Anxiety symptoms													
Anxious mood	2.18	1.36*	1.55	1.91	1.18	1.45	1.46	1.08	1.38	.93	–1.18 to 1.00	–1.21 to 0.88	–0.98 to 1.12
Tension/irritability	2.36	1.36**	1.27*	1.73	1.18	1.09	1.92	1.31	1.31	.89	–1.38 to 1.02	–1.12 to 1.19	–1.37 to 0.93
Fear	0.18	0.27	0.27	0.09	0.09	0.09	0.62	0.46	0.46	.29	–0.78 to 0.41	–0.38 to 0.76	–0.94 to 0.20
Cognitive symptoms													
Memory disturbance/ concentration	1.73	1.27	1.27	1.45	1.09	0.82*	1.69	1.54	1.08*	.68	–1.72 to 0.81	–1.41 to 1.02	–1.48 to 0.96
Neurovegetative symptoms													
Loss of weight	0	0	0	0.45	0.09	0.09	0.46	0.08*	0**	.35	–0.09 to 0.27	–0.17 to 0.17	–0.08 to 0.26
Abnormal sleep	1.21	0.67**	0.58**	1.06	0.64*	0.61*	1.05	0.77	0.64*	.97	–0.62 to 0.68	–0.56 to 0.69	–0.66 to 0.59
Psychomotor retardation	0.82	0.45*	0.36	0.91	0.64	0.64	0.69	0.38*	0.31	.54	–0.51 to 1.06	–0.81 to 0.67	–0.42 to 1.08
Somatic symptoms													
Somatic sensory	1.64	1	1	1.09	1	0.82	1.62	1.31	1	.87	–1.16 to 0.79	–0.94 to 0.94	–1.12 to 0.75
Cardiovascular	0.82	0.18*	0.64	0.55	0.45	0.45	0.62	0.69	0.15†	.35	–1.03 to 0.67	–1.30 to 0.33	–0.51 to 1.12
Respiratory	0.64	0.18	0.18	0.73	0.64	0.64	0.85	0.31	0.38	.40	–0.36 to 1.27	–0.58 to 0.98	–0.53 to 1.03
Gastrointestinal	0.55	0.82	0.55	1	0.91	1.45	1.15	1.15	1.31	.05	–0.04 to 1.86	–0.15 to 1.67	–0.76 to 1.06
Genitourinary	2	1.27*	1.27*	1.64	1.45	1.27	1.62	1.54	1.69	.58	–1.19 to 1.19	–0.72 to 1.56	–1.56 to 0.72
Autonomic	1.27	1.27	1	1.45	1.82	1.45	1.23	1.54	1.54	.41	–0.62 to 1.53	–0.50 to 1.58	–1.12 to 0.95
Somatic muscular	2.18	0.91**	1.18**	1	0.73	0.91	1.69	1.54	1.54	.37	–1.41 to 0.87	–0.74 to 1.45	–1.72 to 0.46

*p < .05 compared to baseline.
**p < .01 compared to baseline.
†p < .01 compared to week 4.

pants recruited was due at least in part to this reluctance to "risk" placebo therapy. Other limitations of this study were the heterogeneous characteristics among the treatment groups. Indeed, a more homogeneous cohort would have been helpful, as the women treated with placebo had characteristics that might have contributed to a salutary treatment response, i.e., less extensive (i.e., stage I or II) disease, more use of sleeping medications, and less prior exposure to chemotherapy. Of note is that the percentage of study participants who discontinued from this treatment study (40%) is somewhat greater than the "dropout" rates reported in a previous observational study (32%)[18] and clinical trials of antidepressants in medically ill patients (23%–34%).[19,20] Moreover, the potential effect of prior episodes of major depression on treatment response[21] could not be determined, as most of the patients in each of the treatment groups had a history of major depression (Table 1). Given the relatively brief 1-week "washout" period, another factor that might have potentially altered treatment response was psychotropic medications, which were utilized by a minority of our participants immediately prior to study enrollment. Similarly, chemotherapy was received by a minority of women within each group immediately before starting, or during, this study (Table 1).

Although none of the individual symptoms were significantly different among the 3 treatment groups, significant improvement in the depressive and neurovegetative symptom dimensions was observed at week 6 in all 3 groups. Improvement in cognitive symptoms, however, was reported by patients only in the 2 drug treatment groups and not in the placebo-treated women. In contrast, anxiety and somatic symptoms significantly decreased in the placebo group alone. In the only other study reporting symptom dimension response of depressed breast cancer,

Costa and colleagues[11] observed that sleep disturbances and somatic anxiety symptoms were significantly reduced by week 4 in mianserin-treated women in comparison to women treated with placebo.

Multiple tests were performed for dimensional and individual symptoms in Figure 3 and Table 3 to simultaneously compare each of the postbaseline time points, i.e., week 4 and week 6, against the baseline. To account for the increased type I error due to the multiple testing, we report the test results at a more stringent significance level of p = .01 in addition to the commonly used level of p = .05.

Although our study demonstrated no difference in treatment efficacy between paroxetine and desipramine, our results are congruent with other clinical trials comparing SSRI versus TCA treatment of cancer patients with major depression. In a 6-week, double-blind, randomized trial, depressed women with cancer were randomly assigned to treatment with either fluoxetine (N = 21) or desipramine (N = 17). Although the fluoxetine-treated women exhibited greater improvements in quality of life, desipramine was equally effective in reduction of depressive and anxiety symptoms.[20] During an 8-week, double-blind, randomized trial comparing paroxetine versus amitriptyline treatment of depressed women with stages I–IV breast cancer (N = 179),[22] response rates at week 5 to either antidepressant were relatively similar (paroxetine: 22%; amitriptyline: 30%) to those observed in this study (paroxetine: 38%; desipramine: 45%) at week 6. Moreover, by the end of the Holland et al.[20] and Pezella et al.[22] trials, rates of adverse events were also not significantly different between the treatment arms.

This study points to an important set of questions that merit attention and investigation, especially the lack of randomized, placebo-controlled trials demonstrating short-term efficacy of commercially available antidepressants in the United States among breast cancer patients, despite the widespread use of these agents in the treatment of depressive syndromes in breast cancer survivors. Moreover, this small negative study may help counteract potential publication bias, that is, the publishing of small positive, but not negative, studies regarding the treatment of major depression in breast cancer patients.[23] Indeed, given recent information regarding antidepressant efficacy (or lack thereof) in some patient populations,[24,25] depressed women with breast cancer will make the most informed decisions about their "anti-depression" therapy when future studies reveal the incidence of depression in women during cancer therapy, characterize rates of placebo response to antidepressant treatment, and describe the impact of depression treatment on long-term morbidity and mortality of cancer survivors.[26,27]

Drug names: amitriptyline (Limbitrol and others), desipramine (Norpramin and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), haloperidol (Haldol), lorazepam (Ativan and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), temazepam (Restoril and others).

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