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Report

Effect of paroxetine hydrochloride (Paxil®) on fatigue and depression in breast cancer patients receiving chemotherapy

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Summary

Background. Fatigue can significantly interfere with a cancer patient's ability to fulfill daily responsibilities and enjoy life. It commonly co-exists with depression in patients undergoing chemotherapy, suggesting that administration of an antidepressant that alleviates symptoms of depression could also reduce fatigue.

Methods. We report on a double-blind clinical trial of 94 female breast cancer patients receiving at least four cycles of chemotherapy randomly assigned to receive either 20 mg of the selective serotonin re-uptake inhibitor (SSRI) paroxetine (Paxil®, SmithKline Beecham Pharmaceuticals) or an identical-appearing placebo. Patients began their study medication seven days following their first on-study treatment and continued until seven days following their fourth on-study treatment. Seven days after each treatment, participants completed questionnaires measuring fatigue (Multidimensional Assessment of Fatigue, Profile of Mood States-Fatigue/Inertia subscale and Fatigue Symptom Checklist) and depression (Profile of Mood States-Depression subscale [POMS-DD] and Center for Epidemiologic Studies-Depression [CES-D]).

Results. Repeated-measures ANOVAs, after controlling for baseline measures, showed that paroxetine was more effective than placebo in reducing depression during chemotherapy as measured by the CES-D ($p = 0.006$) and the POMS-DD ($p = 0.07$) but not in reducing fatigue (all measures, $ps > 0.27$).

Conclusions. Although depression was significantly reduced in the 44 patients receiving paroxetine compared to the 50 patients receiving placebo, indicating that a biologically active dose was used, no significant differences between groups on any of the measures of fatigued were observed. Results suggest that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment.

Introduction

Cancer-related fatigue (CRF) is the most commonly reported side effect in patients receiving chemotherapy, with prevalence rates of 70% or greater reported [1–5]. It is up to seven times more likely to occur in cancer patients than in the general population [6]. Patients with cancer often describe their fatigue as involving their whole body and report that it is not related to their level of physical activity nor relieved by rest or sleep [7]. Fatigue can affect compliance with potentially curative treatment for breast cancer and is a common reason given by patients who refuse to enter experimental protocols [7, 8]. Such fatigue can also interfere with a patient's quality of life [8, 9] and can significantly reduce a patient's participation in leisure activities, ability to work, and capacity to sustain meaningful relationships with spouse and family [10]. At the present time, there are neither well-established objective markers nor proven treatments for CRF [11].

The etiology of CRF is unknown. We have summarized several potential pathophysiological hypotheses involving muscle metabolism and ATP synthesis, autonomic nervous system dysfunction, and altered functioning of hypothalamic–pituitary axis that are theoretically plausible and have varying degrees of preclinical support [11, 12]. In addition, it is likely that the disease itself, cancer treatments, and psychological responses (e.g., depression) to the disease or treatments [13, 14] may contribute. Depression has been reported by 40–82% of patients undergoing chemotherapy and frequently correlates with the side effect of CRF [15–17].

The nature of any causal relationship, if one exists, between CRF and depression is unclear. Bower [13] suggests that it may be bi-directional with CRF occurring as a symptom of depression or, conversely, with depression occurring because of 'fatigue interference' with mood, work, and leisure activities (e.g., physical activity). The association between depression and CRF in patients has led researchers to posit that there may be a common pathophysiological mechanism (e.g.,

serotonin insufficiency) involved in the development of both [18, 19]. For example, research suggests that changes in brain 5-hydroxytryptamine (5-HT) are associated with the pathogenesis of both depression [20, 21], and fatigue [22].

Based on the evidence of a strong and consistent relationship between CRF and depression, we hypothesized that both share a final common neural pathway involving serotonin insufficiency. The study reported here examined whether a selective serotonin re-uptake inhibitor (SSRI) antidepressant might mitigate the fatigue associated with cancer treatment by increasing the availability of 5-HT in the synaptic space. We conducted two related research studies to test this hypothesis. Each investigation was a double-blind, placebo-controlled, randomized clinical trial of paroxetine hydrochloride (Paxil®, SmithKline Beecham Pharmaceuticals, Research Triangle Park, NC) to relieve or prevent fatigue in patients receiving chemotherapy. Paroxetine was selected because of its mild side effect profile, rapid onset, and demonstrated efficacy in treating depression.

The first of the two studies was a multicenter randomized, placebo-controlled clinical trial reported previously [23], where cancer patients with any diagnosis undergoing chemotherapy for the first time were assessed for CRF. Patients who reported fatigue at their second chemotherapy cycle were randomized to either 20 mg of oral paroxetine daily or placebo for 8 weeks. Patients ($n = 479$) completed questionnaires on fatigue and depression at home on day seven of cycles two (baseline), three and four (outcome). Baseline measures of fatigue and depression were comparable for patients in the two study groups. Paroxetine significantly reduced depression during chemotherapy ($p < 0.01$), but did not have a significant effect on fatigue ($p > 0.05$), suggesting that modulation of serotonin is not a primary pathophysiological mechanism of CRF in patients beginning chemotherapy.

The current study was run concurrently with the multicenter study and was intended to conceptually replicate the first study in a homogeneous sample in a single institution to reduce potential heterogeneity and consequent error variance due to the 17 geographically diverse sites and multiple types of malignancies included in the first study.

Methods

Procedures

Female patients about to begin or currently receiving treatment for breast cancer were eligible to participate if they were scheduled to receive at least four more cycles of any regimen of chemotherapy and were not undergoing concurrent radiation or interferon treatments. A patient was not eligible to participate if she had a history of seizures or mania, was taking psychotropic medications, or had treatment cycles that were less than 2 weeks apart. If radiation therapy (typically 30 treatments) was sandwiched between chemotherapy cycles, it was allowed and regarded as a treatment cycle. Changes in chemotherapy doses or regimens were permitted. Patients were stratified by type of chemotherapy regimen and were randomized by a computer generated scheme to receive either 20 mg paroxetine or an identical looking placebo daily starting seven days after the first on-study treatment and stopping seven days after the fourth on-study treatment. Patients as well as all medical and study personnel with patient contact were blinded to randomization assignment. Study subjects were recruited from a university medical center and two of its affiliated hospitals. The Institutional Review Boards of each participating institution approved the study, and all patients provided written informed consent.

Outcome measures

General health status was assessed using the Karnofsky Performance Scale at study entry. Three measures of fatigue and two measures of depression were completed at home on the 7th day after each of the four on-study treatments and returned at the subsequent chemotherapy treatment. A phone call was placed to patients on the day the questionnaires were to be completed in order to serve as a reminder and answer any questions.

Fatigue was the primary outcome measure. It was assessed, as in the previous trial, 'at the present moment' by the Fatigue Symptom Checklist (FSCL) [24], over the prior week by question 1 on the Multidimensional Assessment of Fatigue (MAF) [25], and as a mood with the Fatigue/Inertia subscale of the Monopolar Profile of Mood States short form (POMS-FI) [26]. In addition, we assessed 'fatigue interference', which is defined as the degree to which fatigue interferes with an individual's ability to engage in routine daily activities using the Fatigue Interference subscale of the MAF.

The FSCL consists of 30 items in three subscales: drowsiness and dullness, difficulty of concentration, and projection of physical impairment. The presence and intensity of each item is indicated on a five-point rating scale with '1' = 'Absence of' and '5' = 'A great deal'. Reliabilities for the total FSCL score range from 0.92 to 0.94 [24, 27]. Question 1 from the MAF assessed the degree to which patients had experienced fatigue during the prior week using a rating scale anchored by '1' = 'Not at all' and '10' = 'A great deal'. Eleven other questions from the MAF comprise the Fatigue Interference subscale. Each used a rating scale identical in construct to that in question 1 and each queried about the degree to which fatigue interfered with the patient's ability to engage in specific activities (e.g., dressing, cooking, working, walking, exercising) during the prior week.

The POMS-FI consists of five adjectives (fatigued, worn out, exhausted, sluggish, and weary) which subjects rate on a five-point scale with '1' = 'Not at all' and

'5' = 'Extremely' to describe their moods over the past week. The POMS has been used extensively in research with cancer patients and has demonstrated reliability and validity [28, 29].

Depression was a secondary endpoint that was assessed using the Center for Epidemiological Studies Depression Scale (CES-D) [30] and with the Depression/Dejection subscale of the Monopolar Profile of Mood States short form (POMS-DD) [26]. The CES-D is a 20-item depression scale with less emphasis on the physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. Patients indicated how often over the prior week they had experienced 20 symptoms with '1' = 'Rarely or none of the time' and '4' = 'Most or all of the time.' The POMS-DD is identical in construct to the POMS-FI. The five adjectives assessed in this subscale are: sad, unworthy, discouraged, lonely, and gloomy.

Results

Sample characteristics

One hundred twenty-two women consented to participate in the study. We report on 94 women (77% of this sample) who completed the study: 80 (66%) women provided fully evaluable data and 14 (11%) provided baseline data as well as data for at least two of the three following chemotherapy cycles. Eleven (paroxetine = 6, placebo = 5) of the 28 patients who were accrued to the study but failed to provide evaluable data withdrew from the study do to side effects, typically nausea or headache. An additional 11 patients either became too ill to continue, became ineligible due to medication changes, or withdrew from the study prior to starting the study medication. One patient in the placebo group failed to return her questionnaires and one patient in the paroxetine group withdrew because she found the study medication not helpful. Finally, two patients in each group withdrew from the study without providing either evaluable data or a reason for their withdrawal. For analysis purposes, data from the previous treatment cycle was substituted for missing data. The 94 patients include 50 (79%) of the 63 patients randomized to the placebo condition and 44 (75%) of the 59 patients randomized to the paroxetine group. Patients' ages ranged from 31 to 79 (mean = 51.3). Eighty-four (89%) were Caucasian. The patients were all mobile and had an average Karnofsky Performance Status of 88.5 (range = 65 –100). Thirty-five (37%) patients were receiving cyclophosphamide, methotrexate and fluorouracil (CMF) therapy, 42 (45%) patients were receiving chemotherapy regimens containing cyclophosphamide and doxorubicin with or without fluorouracil (CAF or CA), and 17 (18%) patients were receiving other chemotherapy regimens.

Using a CES-D score of 19 or greater to indicate depression, 26 (28%) patients were significantly depressed at baseline. Only five (5%) patients had anemia (hemoglobin level of <11 g/dl) at study entry. Hemoglobin assessments were missing for 18 of the 94 patients at their baseline chemotherapy treatment and values from their next treatment were substituted. There were no significant differences between the 44 patients in the intervention group and the 50 patients in the placebo group in age or in mean baseline measures of fatigue, depression or general health status. There was, however, a significant difference between treatment condition in baseline hemoglobin level, $p < 0.05$ ($\text{mean}_{\text{placebo}} = 12.9$, $\text{mean}_{\text{paroxetine}} = 12.3$). Demographic and other patient variables for the two treatment groups are provided in Table 1.

Depression

A repeated-measures analysis of covariance (ANCOVA), after controlling for the Cycle 1 assessment, showed that paroxetine was more effective than placebo in reducing depression across the remaining three chemotherapy cycles, as measured by the CES-D ($p = 0.006$), the primary measure of depression (Figure 1). A difference between the two study arms was also observed in a parallel ANCOVA examining the POMS-DD scale ($p = 0.07$). By cycle four, only 4 of the original 13 patients in the paroxetine group who had baseline CES-D scores greater than 19, indicating they were depressed at study onset, still had scores above that

Table 1. Demographic and clinical characteristics at baseline by study arm

	Paroxetine $n = 44$	Placebo $n = 50$
Age		
Mean (SD)	52.2 (9.3)	52.2 (10.2)
Range	34–79	31–71
Ethnicity		
White	41 (93%)	43 (86%)
Black	1 (2%)	6 (12%)
Other	2 (5%)	1 (2%)
Chemotherapy regimen		
CAF or CA[a]	18 (41%)	24 (48%)
CMF[b]	18 (41%)	17 (34%)
Other	8 (18%)	9 (18%)
Baseline		
Depression		
CES-D[c] ≥ 19	13 (29%)	13 (26%)
Baseline anemia		
Mean HGB (SD)	12.3 (1.3)	12.9 (1.1)
HGB level of <11 g/dL	4 (9%)	1 (2%)

* $p < 0.1$, $p < 0.01$** (asterisks represent comparison of drug versus placebo groups using repeated measures ANCOVA, controlling for Cycle 1).

[a] Center for Epidemiological Studies Depression.

[b] Depression/Dejection Subscale of Profile of Mood States.

[c] Question 1 of Multidimensional Assessment of Fatigue.

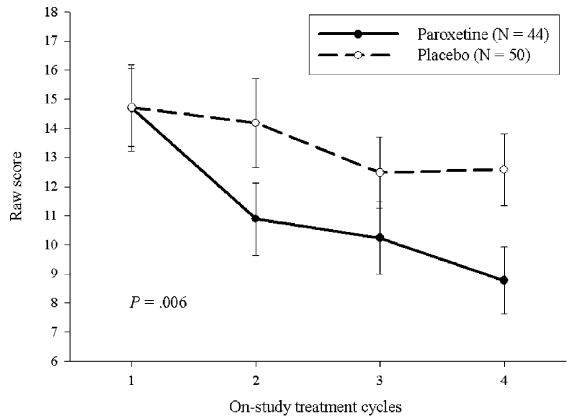

Figure 1. Depression (CES-D) over time by intervention group examined by repeated measures ANCOVA controlling for baseline CES-D.

cutoff point. This compares to all 13 of the initially depressed patients in the in the placebo group remaining above that threshold.

The two depression measures were highly correlated with '*r*' values greater than 0.74 at all treatments and correlations between the first and last treatments greater than 0.49 for each measure. Analyses using paired *t*-tests showed that patients in the intervention group had a significant decrease in both measures of depression between treatments one and four (both, $ps \leq 0.001$). The observed decrease in the control group was statistically significant for the POMS-DD ($p = 0.03$) but not for the CES-D ($p = 0.09$). Mean values for the CES-D and the POMS-DD by study arm for the four treatment cycles are provided in Table 2.

Fatigue

Separate repeated measures ANCOVA, controlling for baseline scores of the measure being analyzed, were used to examine between group differences on question 1 of the MAF (Figure 2), the FSCL, the POMS-FI, and the Interference subscale of the MAF. No significant differences between study arms were observed in the analyses examining these four measures of fatigue (all, $ps > 0.27$). The four fatigue measures had moderate to strong correlations with one another at all four assessment points with '*r*' values ranging from 0.47 to 0.77. Correlations for a given fatigue measure between the first and last treatments ranged

Table 2. Depression and fatigue at the four on-study chemotherapy cycles by paroxetine ($n = 44$) versus Placebo ($n = 50$)

Measure	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Depression								
CES-D[a]								
Drug**	14.7	1.11	10.9	1.11	10.2	1.11	8.8	1.11
Placebo	14.7	1.33	14.1	1.53	12.5	1.22	12.6	1.24
POMS-DD[b]								
Drug*	2.9	0.47	1.7	0.34	1.8	0.35	1.2	0.30
Placebo	3.2	0.48	2.5	0.37	2.1	0.31	2.2	0.34
Fatigue:								
MAF 1[c]								
Drug	5.6	0.35	5.4	0.36	5.1	0.37	4.6	0.38
Placebo	5.8	0.38	5.4	0.35	5.3	0.36	5.0	0.37
POMS-FI[d]								
Drug	7.4	0.75	6.7	0.68	7.1	0.77	6.0	0.70
Placebo	8.4	0.66	8.0	0.71	7.6	0.75	7.1	0.79
FSCL[e]								
Drug	49.6	2.28	46.4	2.65	45.7	2.22	44.6	2.41
Placebo	50.5	2.43	49.4	2.48	48.1	2.24	48.0	2.62
Interference[f]								
Drug	3.8	0.32	3.4	0.28	3.4	0.31	3.1	0.31
Placebo	4.5	0.34	4.2	0.34	4.1	0.33	3.8	0.34

* $p < 0.1$, $p < .01$** (asterisks represent comparison of drug versus. placebo groups using repeated measures ANCOVA, controlling for Cycle 1).
[a] Center for Epidemiological Studies Depression.
[b] Depression/Dejection Subscale of Profile of Mood States.
[c] Question 1 of Multidimensional Assessment of Fatigue.
[d] Fatigue/Inertia Subscale.
[e] Fatigue Symptom Checklist.
[f] Interference with Daily Activities Sub-Scale from MAF.

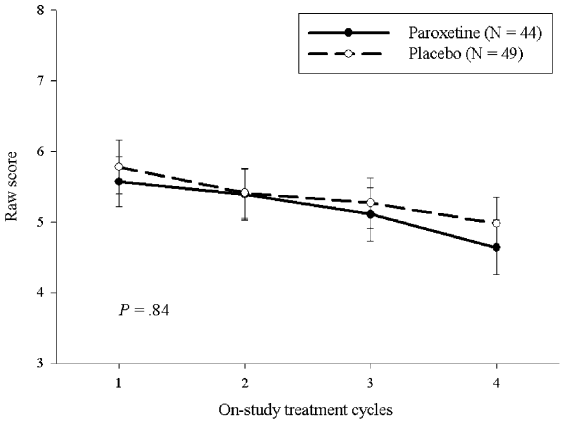

Figure 2. Fatigue (MAF question 1) over time by intervention group examined by repeated measures ANCOVA controlling for baseline MAF question 1.

between 0.52 and 0.63. Analyses using paired *t*-tests showed that mean decrease in fatigue observed in patients receiving paroxetine between treatments one and four was statistically significant for all four fatigue measures, (all, *ps* < 0.04). The decrease in fatigue observed during the same time period in patients in the placebo group was also statistically significant when assessed by the POM-FI and the two components of the MAF (all, $ps \leq 0.05$), but not when assessed by the FSCL, $p = 0.26$. Hemoglobin levels at baseline were not significantly correlated with any of the fatigue measures but decreases in hemoglobin between the first and last assessments were modestly correlated with increases during the same time period on the Interference measure, after controlling for study arm, partial $r = -0.25$, $p = 0.04$. Changes in hemoglobin between the first and last assessments, however, did not significantly correlate with changes in the other measures of fatigue. Mean values for the fatigue measures by study arm and treatment cycles are shown in Table 2.

The relationship between the measures of depression and fatigue were examined using correlational analyses. Each of the depression instruments had statistically significant correlations with each of the four fatigue measures at baseline (all, *ps* < 0.001) with '*r*' values ranging from 0.42 to 0.57. In addition, an examination of partial correlations, controlling for study arm, revealed the changes in the two depression measures over the course of the study were significantly correlated to changes in the fatigue measures (all, *ps* < 0.01) with partial '*r*' values ranging from 0.33 to 0.55.

Discussion

The hypothesis that paroxetine at a dose of 20 mg once daily would have a beneficial effect on CRF was not supported by our findings in this randomized, placebo-controlled clinical trial of 96 patients with breast cancer. By contrast, paroxetine, at a dose of 20 mg one time a day, significantly reduced depression. These data suggest that, although paroxetine is effective at reducing depression, the drug is not efficacious in relieving CRF among women diagnosed with breast cancer being treated with chemotherapy. These findings, while contrary to our hypothesis, are unfortunately in accordance with results from the larger clinical trial mentioned earlier [23]. In that study of 479 Patients with CRF, 20 mg of oral paroxetine daily was no more effective at alleviating fatigue than placebo. As in the current study, depression was significantly reduced in the patients receiving the active medication, compared to placebo, providing evidence that the dose of paroxetine used in the experiment was clinically active.

We chose 20 mg paroxetine once daily as the treatment dose for the intervention because it is the generally recommended initial dose for this medication and was found to be effective in relieving depression in randomized clinical trials conducted to determine the drug's efficacy [31]. Considering that a noticeable effect from 20 mg of paroxetine on depression was observed within one treatment cycle in both studies, we believe that the dosage and length of time patients took the study medication was adequate to test its potential to reduce fatigue. While it is possible that a higher dose of paroxetine may have been efficacious in reducing CRF, we consider it unlikely in view of the fact that no signs of efficacy in this regard were noted in either study.

Our findings that paroxetine did not reduce fatigue but did positively affect depression, while consistent across both studies, are nonetheless surprising because of the generally high correlation observed between the fatigue and depression measures in each experiment and because fatigue is a symptom of depression [32]. Together, these studies indicate that central serotonin might not be the link that binds depression and fatigue and that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment.

Our data provided no support for a view that anemia was a significant factor in CRF. Baseline anemia was not related to any of the four baseline measures of fatigue and changes in anemia over the course of the study were significantly correlated with concurrent changes over time in only one of these measures, and then only modestly so. Some other studies have shown a relationship between anemia and CRF [33]. It is possible that differences in our sample and that of other studies in regard to treatment, stage, and time since diagnosis may have contributed to our contrary findings of no relationship between anemia and chemotherapy related fatigue.

While low serotonin levels did not appear to be contributing factors to CRF in either study, it is possible, given the high correlations between fatigue and depression in both samples, that pharmacologic interventions for depression using drugs of a different class could have a beneficial effect on fatigue. Similarly, even though these results appear to rule out a 'serotonin insufficiency', as a causal factor in CRF, they do not eliminate the possibility of other neurotransmitters or

biochemical factors being involved [32–36]. Further study is warranted.

Alternative theories regarding the pathophysiology of CRF also exist. One implicates inactivity and suggests that CRF may result from deconditioning of the cardiovascular system or muscle atrophy resulting from lower levels of physical activity after diagnosis and throughout treatment. Should this be the case, interventions involving physical activity might be helpful.[80] Some evidence suggests that disruptions in sleep and/or alterations in circadian rhythms are related to CRF [37, 38], and it is possible that interventions promoting good sleep hygiene practices (e.g., sleep routines, avoidance of stimulants) may also be effective for some patients [39]. Although not yet confirmed in the literature, it is also possible that psychostimulants such as methylphenidate and modafinil may be efficacious in reducing CRF, a suggestion made in a recent review [12].

Maintaining quality of life of cancer patients is extremely important. Cancer-related fatigue continues to be reported by patients as the most frequent and troublesome side effect. At the present time, the specific causes of cancer-related fatigue are largely unknown, preventing identification of effective treatments. Further research on the causes and management of CRF is crucial.

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