Original Article

Pilot Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms

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BACKGROUND: Approximately 50% of postmenopausal women with hormone receptor-positive early stage breast cancer treated with an aromatase inhibitor (AI) develop musculoskeletal symptoms. Standard analgesics are relatively ineffective. Duloxetine is a serotonin norepinephrine reuptake inhibitor with proven efficacy for treatment of multiple chronic pain states. The authors investigated the hypothesis that duloxetine is efficacious for treatment of AI-associated musculoskeletal symptoms. **METHODS:** The authors performed a single-arm, open-label phase 2 study of duloxetine in postmenopausal women with breast cancer who developed new or worsening pain after treatment with an AI for at least 2 weeks. Patients were treated with duloxetine for 8 weeks (30 mg for 7 days, then 60 mg daily). The primary endpoint was a 30% decrease in average pain score over 8 weeks, and secondary outcomes included change in average and worst pain, pain interference, depression, sleep quality, and hot flashes. Statistical analysis was done with *t* tests for paired data. **RESULTS:** Twenty-one of 29 evaluable patients (72.4%) achieved at least a 30% decrease in average pain, and 18 of 23 patients (78.3%) who completed protocol-directed treatment continued duloxetine. The mean percentage reduction in average pain severity between baseline and 8 weeks was 60.9% (95% confidence interval [CI], 48.6%-73.1%), and in maximum pain severity it was 59.9% (95% CI, 47.0-72.7%). The most common adverse events were grade 1 or 2 fatigue, xerostomia, nausea, and headache. **CONCLUSIONS:** Duloxetine appears to be effective and well tolerated for treatment of AI-associated musculoskeletal symptoms. Future randomized, placebo-controlled studies are warranted. ***Cancer*** **2011;117:5469–75.** © *2011 American Cancer Society.*

KEYWORDS: breast cancer, aromatase inhibitor, arthralgia, duloxetine, serotonin-norepinephrine reuptake inhibitor.

Aromatase inhibitors (AIs) have been shown to be more effective than tamoxifen for decreasing the risk of breast cancer recurrence in postmenopausal women with early stage, hormone receptor-positive breast cancer in multiple large, randomized controlled trials.[1,2] Although aromatase inhibition was initially reported to be well tolerated, subsequent studies have demonstrated that up to 50% of patients report new onset or worsening arthralgias and myalgias associated with treatment.[3,4] The underlying mechanism for development of this toxicity remains unknown. Proposed etiologies include estrogen deprivation, local or systemic inflammatory processes, and alterations in the growth hormone/insulin growth factor pathways.[4,5] Standard analgesics do not appear to effectively manage the symptoms for most women,[6] but acupuncture has been shown in a randomized, placebo-controlled trial to lessen joint pain.[6,7] Because standard adjuvant AI therapy is administered for 2 to 5 years, successful treatment of these symptoms is important for both adherence to therapy and improvement in the quality of life of breast cancer survivors.

Duloxetine (Cymbalta, Eli Lilly Pharmaceuticals, Indianapolis, Ind) is a serotonin and norepinephrine reuptake inhibitor (SNRI) that was initially approved by the US Food and Drug Administration (FDA) for treatment of major depressive disorder.[8] Subsequently, it has been found to be efficacious for treatment of multiple chronic pain states, including low back pain and osteoarthritis, and is FDA approved for the treatment of fibromyalgia, diabetic peripheral neuropathic pain, and chronic musculoskeletal pain.[9-12] Small pilot studies have also suggested a potential benefit from

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duloxetine on sleep disturbance and menopausal symptoms such as hot flashes.[13,14] The mechanism by which duloxetine decreases pain is unclear, but it may alter central pain processing.

Because duloxetine is an effective adjunctive treatment for multiple chronic pain states, we performed this open-label pilot study to determine whether it may be effective for management of AI-associated musculoskeletal symptoms. We also performed exploratory analyses to investigate whether duloxetine may impact other AI-associated toxicities, including hot flashes, sleep disturbance, and mood alterations.

MATERIALS AND METHODS

Subject Population

Postmenopausal women who developed new or worsening pain during adjuvant AI therapy for stage I to III hormone receptor-positive breast cancer were enrolled on this pilot study between December 2008 and June 2010 (www.clinicaltrials.gov NCT01028352). Surgical resection, chemotherapy, and radiation therapy, when indicated, were completed before study enrollment. Patients must have been taking standard-dose AI therapy (anastrozole (Arimidex; AstraZeneca Pharmaceuticals, Wilmington, Del) 1 mg, exemestane (Aromasin; Pfizer, New York, NY) 25 mg, or letrozole (Femara; Novartis, Basel, Switzerland) 2.5 mg orally daily for at least 2 weeks before enrollment. Patients were required to have grade 1 or higher musculoskeletal pain or sensory neuropathy that developed or worsened during AI therapy, average pain during the week before enrollment rated at least 4 on a 0 to 10 Likert scale, and Eastern Cooperative Oncology Group performance status 0 to 2. Patients were ineligible if they had new pain specifically because of trauma or fracture, liver dysfunction, creatinine clearance $<$30 mL/min, a clinically significant coagulation disorder, narrow-angle glaucoma, schizophrenia, psychosis, suicidal ideation, seizure disorder, or substance abuse or dependence within the year before enrollment, or if they had taken monoamine oxidase inhibitors (MAOIs) within 14 days before enrollment. Patients were not permitted to take concomitant selective serotonin reuptake inhibitors (SSRIs) or SNRIs, MAOIs, phenothiazines, tricyclic antidepressants, triptans, or other medications as described in the duloxetine package insert, although they were permitted to discontinue the medications at the time of study enrollment. The protocol was approved by the University of Michigan Institutional Review Board before patient enrollment, and all patients provided written informed consent.

Treatment Plan

Enrolled patients were treated with duloxetine 30 mg orally daily for 7 days, then 60 mg daily for 21 days. At that time, patients had the option of continuing duloxetine 60 mg daily or increasing the dose to duloxetine 60 mg twice daily. Patients who developed grade 3 or 4 adverse events based on Common Terminology Criteria for Adverse Events discontinued therapy for up to 7 days and restarted therapy at 60 mg daily once symptoms resolved to grade 2 or less. If symptoms did not resolve within 7 days, study participation was discontinued. In addition, any patient who was unable to tolerate the 60 mg daily dose discontinued study participation. At the completion of the study, patients had the option of continuing duloxetine therapy off protocol. Patients who discontinued duloxetine therapy at any time, regardless of reason, tapered off treatment over 4 to 7 days.

Patients who had been taking a stable dose of medication for treatment of pain (eg, nonsteroidal anti-inflammatory medications, cyclooxygenase-2 inhibitors, opioids, gabapentin, pregabalin, cyclobenzaprine, glucosamine chondroitin) at the time of enrollment were permitted to continue the medication; otherwise, patients were permitted to take up to 2 g of acetaminophen daily for treatment of pain and up to 325 mg of aspirin daily for cardiac prophylaxis, and were instructed to avoid initiation of new treatments for pain during study participation. Patients were also instructed to avoid taking concomitant medications with the potential to interact with duloxetine as described in the package insert.

Subject Assessment

During study participation, patients underwent toxicity assessment every 2 weeks. Patients completed the following questionnaires at baseline and every 2 weeks to evaluate change in pain and functional status: Brief Pain Inventory (BPI),[15] 2-page Health Assessment Questionnaire (HAQ) and Pain Visual Analog Scale,[16] and National Surgical Adjuvant Breast and Bowel Project symptom checklist. To assess depression, menopausal symptoms, and sleep difficulties, the following questionnaires were completed at baseline and every 4 weeks: Center for Epidemiologic Studies-Depression Scale,[17] Menopause-Specific Quality of Life Questionnaire,[18] Hot Flash Related Daily Interference Scale,[19] and Pittsburgh Sleep Quality Index (PSQI).[20,21] Patients also completed a protocol-specific questionnaire specifically designed to collect information about arthralgia severity and management and to assess reasons for continuation or

discontinuation of duloxetine therapy after completion of the trial.

Statistical Analysis

The primary endpoint of the study was assessment of the percentage of patients who achieved at least a 30% decrease in average pain with 8 weeks of duloxetine therapy based on patient-reported scores on the BPI. On the basis of data from duloxetine treatment of other chronic pain conditions,[9-12] we estimated that at least 55% of our patients treated with duloxetine would experience a 30% decrease in average pain with 8 weeks of therapy. We expected that placebo likely would not result in a response rate higher than 40%. With a sample size of 30 patients, a 1-sided 95% confidence interval (CI) for the true proportion of patients who experienced a 30% decrease in average pain was expected to be 40% to 70%. Patients were considered evaluable for the primary endpoint and for toxicity assessment if they met all eligibility criteria and took at least 1 dose of duloxetine. Subjects who did not complete 8 weeks of protocol-directed therapy were considered nonresponders for the primary endpoint.

Secondary measures included the percentage of patients treated with duloxetine who experienced 1) a 30% reduction in worst pain from baseline to 8 weeks, 2) a 50% decrease in average pain from baseline to 8 weeks, and 3) a 50% reduction in worst pain from baseline to 8 weeks. Descriptive statistics were used for the primary and secondary measures. The change in average and worse pain score, pain interference score, depression score, HAQ score, vasomotor symptom scores, and sleep scores in this patient cohort from baseline to 8 weeks were analyzed using *t* test for paired data. Statistical significance was defined as a P value of $<.05$.

RESULTS

Between December 2008 and May 2010, 35 patients enrolled and completed baseline questionnaires. One subject withdrew from the study before initiating therapy. After initiating protocol-directed duloxetine therapy, 5 patients were found to be ineligible because their baseline average pain as assessed using the BPI was <4 on a 10-point scale, and therefore the primary endpoint could not be assessed (see Fig. 1 for Patient Flow Diagram). The demographics of the 29 eligible, treated patients are summarized in Table 1. All eligible patients reported new or worsening joint aches or pains rated at least 4 on a 10-point scale since starting AI therapy. As assessed using the BPI, mean average pain at time of study enrollment was 5.5 (range, 4-7), mean worst pain was 7.2 (range, 4-10), and mean pain interference score was 4.32 (range, 1.57-7.86).

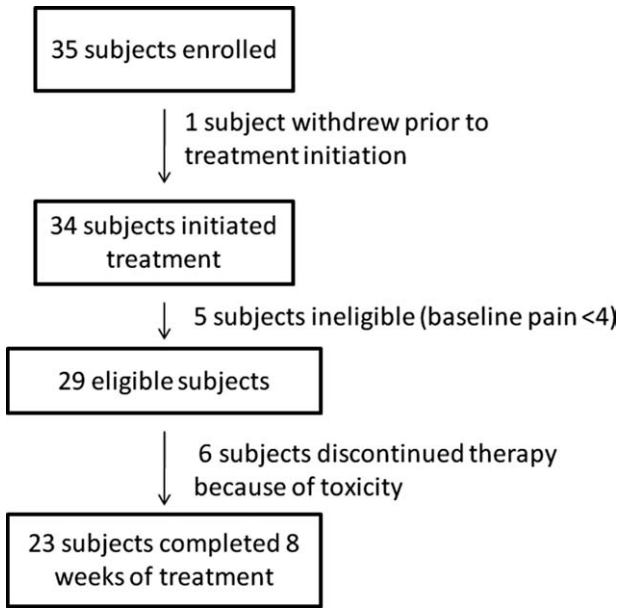

Figure 1. Patient flow diagram is shown.

Fewer enrolled patients were being treated with anastrozole (21%) compared with the other 2 AI medications (approximately 40% each). Approximately 55% of enrolled patients had previously switched from 1 AI to a second AI because of toxicity before study enrollment, and 1 subject had received treatment with all 3 AI medications.

Reduction of Pain With Duloxetine

Of the 29 evaluable patients who initiated protocol-directed therapy, 21 (72.4%) experienced the protocol-specified primary endpoint of at least a 30% decrease in average pain score with 8 weeks of therapy, and 16 (55.2%) experienced at least a 50% decrease in average pain score. Of the 23 patients who completed study therapy, 21 (91.3%) experienced at least a 2 point absolute decrease in average pain between baseline and 8 weeks, and the mean percent reduction in average pain was 60.9%, with a 95% CI of 48.6% to 73.1% (Table 2). Only 1 subject chose to increase the dose of duloxetine to 60 mg twice daily after 4 weeks of daily therapy. The time course of response to duloxetine is pictured in Figure 2.

Of the 29 evaluable patients, 19 (65.5%) experienced at least a 30% decrease in worst pain with 8 weeks of therapy, and 17 (58.6%) experienced at least a 50%

decrease in worst pain. Of the 23 patients who completed study therapy, 20 (87%) experienced at least a 2-point absolute decrease in worst pain between baseline and 8 weeks, and the mean percentage reduction in worst pain was 59.9% (95% CI, 47.0%-72.7%; Table 2).

Change in interference of pain with activities of daily living as measured using the BPI demonstrated that the mean percentage reduction in pain interference with 8 weeks of duloxetine therapy was 78.9% (95% CI, 68.1%-89.8%; Table 2).

Eighteen of the 23 patients (78.3%) who completed all 8 weeks of study treatment chose to remain on duloxetine therapy. After completion of study therapy, 3 patients discontinued treatment because of lack of improvement in pain symptoms, and 2 chose to stop therapy because of duloxetine-associated side effects. Comparison of the baseline characteristics, including duration of AI therapy, prior chemotherapy, and prior tamoxifen therapy, between the responders and the nonresponders did not reveal any statistically significant differences (data not shown).

Table 1. Baseline Demographic and Clinical Characteristics of Eligible, Enrolled Patients (n=29)

Characteristic	Value
Median age, y [range]	56 [36-70]
Race	
White	89.7%
African American	6.9%
Native American	3.4%
BMI, mean ± SD	30.5 ± 6.5
Prior treatments	
Chemotherapy	21 (72.4%)
Taxane	18 (62.1%)
Tamoxifen	10 (34.5%)
AI while on study	
Anastrozole	6 (20.7%)
Exemestane	11 (37.9%)
Letrozole	12 (41.4%)
Median duration of AI therapy	
Current AI treatment, mo [range]	7.9 [0.7-46.1]
Total AI therapy, prior plus current, mo [range]	14.4 [2.3-46.1]

Abbreviations: AI, aromatase inhibitor; BMI, body mass index; SD, standard deviation.

Safety and Tolerability

Safety was assessed in all 34 patients who received at least 1 dose of study medication. Adverse events and treatment discontinuation of duloxetine were similar to safety findings in previously reported duloxetine studies.[9-12] Seven patients (20.6%) discontinued therapy because of adverse events, including 6 evaluable patients and 1 who was subsequently

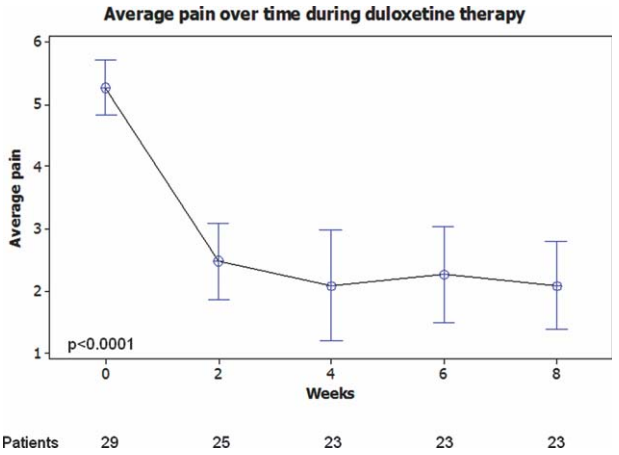

Figure 2. Average pain over time during duloxetine therapy was assessed using the Brief Pain Inventory. Error bars reflect standard deviation at each time point. The number of evaluable patients at each time point is listed below the graph.

Table 2. Change in Outcome Measures With Duloxetine Therapy

Outcome Measure	Baseline, n = 29	2 Weeks, n = 25	4 Weeks, n = 23	6 Weeks, n = 23	8 Weeks, n = 23	P[a]
Average pain, 0-10	5.48[b] (1.09)	2.48 (1.53)	2.09 (2.04)	2.26 (1.79)	2.09 (1.62)	<.0001
Worst pain, 0-10	7.21 (1.40)	3.36 (2.38)	3.13 (2.55)	3.30 (2.01)	2.87 (2.32)	<.0001
Pain interference, 0-10	4.32 (1.96)	1.58 (1.73)	1.33 (1.70)	1.06 (1.04)	0.96 (1.26)	<.0001
HAQ, 0-3	0.484 (0.312)	0.197 (0.260)	0.245 (0.330)	0.212 (0.286)	0.234 (0.283)	.0012
Hot flash interference, 0-100; HFRDIS	17.10 (21.87)		10.09 (14.49)		6.96 (12.48)	.0194
Hot flash interference, 1-8; MENQOL vasomotor subscale	2.86 (1.99)		2.20 (1.38)		2.56 (1.67)	.31
Depression; CESD	10.14 (8.77)		5.83 (4.70)		3.52 (3.19)	.0035
Sleep, 0-21	8.00 (3.25)		7.87 (4.09)		6.91 (4.04)	.025

Abbreviations: CESD, Center for Epidemiologic Studies-Depression Scale; HAQ, Health Assessment Questionnaire; HFRDIS, Hot Flash Related Daily Interference Scale; MENQOL, Menopause-Specific Quality of Life Questionnaire.
[a] The difference between baseline and 8 weeks; 2-tailed paired *t* test.
[b] Mean (standard deviation).

Table 3. Adverse Events That Affected at Least 3 Subjects (n=34)

Toxicity	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Cause of Treatment Discontinuation[a]
Fatigue	7 (20.6%)	6 (17.7%)	1 (2.9%)	0	0	0
Constipation	6 (17.7%)	6 (17.7%)	0	0	0	0
Nausea	6 (17.7%)	4 (11.8%)	2 (5.9%)	0	0	3 (8.8%)
Headache	5 (14.7%)	4 (11.8%)	1 (2.9%)	0	0	3 (8.8%)
Dry mouth	5 (14.7%)	5 (14.7%)	0	0	0	1 (2.9%)
Drowsiness	4 (11.8%)	0	4 (11.8%)	0	0	2 (2.9%)
Heartburn	3 (8.8%)	1 (2.9%)	2 (5.9%)	0	0	1 (2.9%)
Anxiety	3 (8.8%)	2 (5.9%)	1 (2.9%)	0	0	1 (2.9%)

[a] Some subjects reported >1 adverse event, leading to treatment discontinuation.

found to be ineligible. The majority of subjects who discontinued therapy because of adverse events did so within a few days of starting treatment. Reasons for treatment discontinuation included grade 1 and/or 2 drowsiness, headache, and nausea. The majority of reported adverse events were grade 1 and/or 2 fatigue and drowsiness, nausea, xerostomia, constipation, and headache, consistent with prior studies of duloxetine (Table 3), and 76.5% of patients reported at least 1 adverse event. The single reported grade 3 adverse event was tachycardia, categorized as unlikely to be related to therapy by the treating physician. The affected patient completed study-directed therapy, but then discontinued duloxetine because of lack of benefit.

Patient-Reported Nonpain Outcomes

Because other SSRIs and SNRIs have been reported to improve symptoms such as hot flashes, the effect of 8 weeks of duloxetine therapy on hot flashes, depression, sleep, and functional status was assessed. Twenty-nine evaluable patients completed the battery of questionnaires at baseline, and 23 completed them at the 8-week time point. Intrapatient reduction in hot flash interference with daily life, as assessed with the 10-item Hot Flash Related Daily Interference Scale questionnaire, revealed an improvement (baseline, 17.1; 8 weeks, 7.0; $P = .019$), but no change was observed when using the Menopause-Specific Quality of Life Questionnaire vasomotor subscale (Table 2). Assessment of intrapatient change in depression (as assessed using the Center for Epidemiologic Studies-Depression Scale), sleep (as assessed using the PSQI), and functional status (as assessed using the HAQ) with 8 weeks of duloxetine therapy revealed statistically significant improvements in all 3 measures (Table 2).

DISCUSSION

AIs have been shown to cause arthralgias in up to 50% of patients, can be difficult to treat, and can negatively impact quality of life and potentially persistence with therapy. In this pilot clinical trial of duloxetine, we demonstrated that 93% of patients with AI-associated joint aches and pains who completed 8 weeks of therapy experienced at least a 2-point decrease in patient-reported average pain, an improvement that has been shown to be clinically meaningful in studies of other chronic pain conditions and that is the cutoff recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials consensus committee.[22] This response rate compares favorably with that observed in studies of duloxetine in other chronic pain conditions, including fibromyalgia and chronic low back pain.[11,12] Likewise, the improvement in pain was rapid, occurring primarily within the first 2 weeks of study treatment, and sustained through the 8 weeks of protocol-directed therapy in the majority of patients. These findings suggest that duloxetine may be effective for treatment of AI-associated musculoskeletal pain, and are particularly striking in this patient cohort, the majority of whom had already switched from 1 AI to another because of intolerable medication-associated musculoskeletal pain.

In addition to the impact of duloxetine on pain, we also explored potential changes in other symptoms frequently experienced by women treated with aromatase inhibitors. Duloxetine appeared to cause clinically significant improvements in both functional status and depression, although only 4 patients were classified as possibly or probably depressed based on Center for Epidemiologic Studies-Depression Scale scores at baseline. In a published study of patients with major depressive disorder and painful physical symptoms, the improvement in pain was independent of the decrease in depression.[23] These results suggest that the analgesic effect of duloxetine is separate from its antidepressant activity.

Improvements in other aspects of quality of life were less apparent. Although the change in PSQI scores was

statistically significant, treatment with duloxetine did not appear to result in clinically significant improvements in sleep quality. Hot flash diaries were not used during this clinical trial; instead, assessment of change in hot flash interference in daily life was assessed with questionnaires. Analysis of the Menopause-Specific Quality of Life Questionnaire vasomotor subscale revealed no change in symptoms with 8 weeks of duloxetine therapy. However, when the more detailed, 10-item Hot Flash Related Daily Interference Scale questionnaire was used, a significant improvement in hot flashes was observed. Although the Hot Flash Related Daily Interference Scale data are consistent with a previously reported small pilot study of duloxetine for management of vasomotor symptoms,[13] determination of actual benefit from duloxetine for hot flashes will require further evaluation in subsequent studies. Overall, these results suggest that treatment with duloxetine may result in improvements in multiple AI-associated symptoms, rather than simply reduction of pain symptoms, which could lead to more substantial improvements in overall quality of life.

The findings of this study are limited by its small sample size, fairly high treatment discontinuation rate, and lack of a concurrent control group. As in our study, up to 20% of patients have been unable to tolerate duloxetine in multiple clinical trials of various medical conditions.[9-12] However, despite these limitations, for those women who are able to tolerate the medication, duloxetine appears to be effective for treating AI-associated musculoskeletal symptoms. One other potential limitation is the repeated assessment of pain during the 8-week clinical trial, which can be a source of bias. However, we believe this bias had minimal impact in this study, because most patients reported significant improvement at the first on-treatment assessment, and more than $\frac{3}{4}$ of those patients who completed 8 weeks of treatment chose to continue duloxetine therapy at the time of study completion.

Multiple clinical studies have been performed to elucidate the mechanism underlying development of AI-associated musculoskeletal symptoms, but all have been unrevealing.[4] Therefore, in this study we were dependent on patient-reported outcomes to assess efficacy of duloxetine. Regardless, the BPI is a well-validated measure of pain in cancer and noncancer populations that has been used in multiple other published studies of AI-associated musculoskeletal toxicity.[7,15,24]

The most plausible cause of AI-associated musculoskeletal symptoms appears to be local or systemic estrogen deprivation. Estrogen is known to play a role in pain processing in the central nervous system. AI therapy could therefore lead to an abnormality of central pain processing, thereby causing chronic pain such as arthralgias. Duloxetine is believed to act via modulation of central pain processing, and has been shown to be effective for management of other central pain disorders, including fibromyalgia.[12] Although feasible, an estrogen agonistic effect of duloxetine has not been demonstrated in preclinical or clinical studies. In addition, there are no in vitro or in vivo data to suggest that there are any pharmacologic interactions between duloxetine and any of the AIs that could decrease the effectiveness of AI therapy.[25] Taken together, these observations support our preliminary conclusions that duloxetine could be an effective treatment for AI-associated musculoskeletal symptoms via its direct effect on nociceptive pathways.

We exceeded our prestudy, protocol-stipulated criteria for success in this uncontrolled pilot clinical trial. However, many studies testing the efficacy of agents for treatment of symptoms such as pain and hot flashes have had a substantial placebo effect.[26] In this study, the benefit of duloxetine (72%) was substantially higher than the reported response rates for placebo (19%-40%) in other chronic pain conditions, including fibromyalgia, knee osteoarthritis, and diabetic neuropathic pain.[9,10,12] Therefore, we conclude that these preliminary phase 2 data support the efficacy of duloxetine in reducing symptoms related to AI-associated musculoskeletal symptoms, and that this agent deserves study in a larger, definitive, placebo-controlled trial.

In this regard, this pilot trial was too small to provide meaningful subgroup analysis of potential baseline clinical predictors of response to duloxetine therapy or to investigate changes in biomarkers such as inflammatory biomarkers. In addition, longer term studies are necessary to confirm the durability of the response. Such analyses will be integral to design of larger randomized, placebo-controlled clinical trials, which are currently being planned.

In conclusion, these preliminary results strongly suggest that duloxetine was effective in decreasing AI-associated musculoskeletal pain and its interference with daily activities in the majority of women with early stage, hormone receptor-positive breast cancer. Given the high incidence of AI-associated musculoskeletal symptoms, identification of a therapy to ameliorate these treatment-emergent toxicities is important to optimize persistence with therapy and quality of life.

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CONFLICT OF INTEREST DISCLOSURES

N.L.H. receives research funding from Lilly Pharmaceuticals and AstraZeneca. D.F.H. receives research funding from AstraZeneca, Novartis, Pfizer, and Veridex, and has an immediate family member who is employed by Lilly. C.V.P. receives research funding from Novartis and Amgen. J.B.S. received honoraria from Lilly Pharmaceuticals until July 2008. M.W. is a consultant for Pfizer. M.B., A.F.S., and J.J.G. have no disclosures.

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