Original Article

Association Between Body Mass Index and Response to Duloxetine for Aromatase Inhibitor-Associated Musculoskeletal Symptoms in SWOG S1202

N. Lynn Henry, MD, PhD [1]; Joseph M. Unger, PhD[2,3]; Cathee Till, MS[2,3]; Anne F. Schott, MD[4]; Katherine D. Crew, MD, MS[5]; Danika L. Lew, MA[2,3]; Michael J. Fisch, MD, MPH[6]; Carol M. Moinpour, PhD[7]; James L. Wade III, MD[8]; and Dawn L. Hershman, MD, MS[5]

BACKGROUND: Aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) negatively impact adherence to and persistence with therapy. In SWOG S1202, patients with AIMSS who were treated with duloxetine, a serotonin norepinephrine reuptake inhibitor, reported improvement in pain by 12 weeks compared with placebo. Based on the authors' prior observation that responses to pain interventions differ between obese and nonobese patients, the current study examined whether response to duloxetine therapy differed by obesity status. **METHODS:** In SWOG S1202, a total of 299 AI-treated postmenopausal women with stage I to III (AJCC 7th Edition) breast cancer who developed new or worsening average pain were enrolled, randomized to duloxetine or placebo, and treated for 12 weeks. Patient-reported outcomes were obtained at baseline and through 12 weeks. Patients were categorized into nonobese (body mass index [BMI] <30 kg/m^2) or obese (BMI ≥30 kg/m^2). The authors tested the interaction between intervention and obesity with respect to average pain at 12 weeks in the 289 eligible patients, using a *P* value of .05 to indicate statistical significance. **RESULTS:** In approximately 54% of evaluable patients with a BMI ≥30 kg/m^2, the reduction in the mean average pain score between baseline and 12 weeks was statistically significantly greater for patients treated with duloxetine compared with those receiving placebo (-2.73 vs -1.64 points; *P* = .003). Conversely, in the nonobese patients, the reduction in the mean average pain score was similar in the 2 cohorts (-2.46 vs -2.34 points; *P* = .75). The *P* value for interaction was .02, thereby meeting the threshold criteria of the current study. Similar findings were evident for other pain-related patient-reported outcomes. **CONCLUSIONS:** In this trial, obese patients with AIMSS obtained more analgesic benefit from duloxetine compared with nonobese patients. Additional studies are warranted to determine the biologic basis for these findings. ***Cancer* 2019;125:2123-2129**. © *2019 American Cancer Society*.

KEYWORDS: arthralgias, breast cancer, duloxetine, obesity, placebo.

INTRODUCTION

Although aromatase inhibitors (AIs) have been shown to reduce the risk of disease recurrence and mortality in postmenopausal women with early-stage, hormone receptor-positive breast cancer,[1] adherence to and persistence with therapy is limited by treatment-emergent toxicity.[2,3] In particular, AI-associated musculoskeletal symptoms (AIMSS) occur in a substantial percentage of women undergoing AI therapy and contribute to the discontinuation of therapy in as much as 25% of treated patients.[3]

To the best of our knowledge, the mechanism underlying the development of AIMSS remains undefined. Several predictors of developing treatment-emergent symptoms have been identified, including age closer to menopause, higher body mass index (BMI), prior treatment with chemotherapy, and preexisting joint pain, although not all have been validated.[3-5] Management options for AIMSS remain limited. However, randomized trials of a variety of interventions, including exercise, acupuncture, and duloxetine, have been conducted that have demonstrated modest improvements in AIMSS; substantial placebo effects also have been noted.[6-8]

Duloxetine is a serotonin-norepinephrine reuptake inhibitor that is used to treat mood disorders and chronic pain conditions. A large, double-blind, placebo-controlled trial of duloxetine for postmenopausal women with AIMSS examined change in average pain with 12 weeks of therapy (SWOG S1202).[7] Average joint pain on a scale of 0 to 10

Corresponding author: N. Lynn Henry, MD, PhD, University of Utah Huntsman Cancer Institute, 2000 Circle of Hope Dr, Salt Lake City, UT 84112; lynn.henry@hci.utah.edu

[1]Department of Internal Medicine, University of Utah Huntsman Cancer Institute, Salt Lake City, Utah; [2]SWOG Statistics and Data Management Center, Seattle, Washington; [3]Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, Washington; [4]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; [5]Department of Medicine, Columbia University, New York, New York; [6]AIM Specialty Health, Chicago, Illinois; [7]Cancer Prevention Program, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [8]Heartland National Cancer Institute Community Oncology Research Program, Decatur, Illinois.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32024, **Received:** November 14, 2018; **Revised:** January 18, 2019; **Accepted:** January 25, 2019, **Published online** March 12, 2019 in Wiley Online Library (wileyonlinelibrary.com)

was found to be 0.82 points lower for those patients treated with duloxetine compared with those treated with placebo (95% confidence interval, -1.24 to -0.40; $P = .0002$).

A randomized trial of omega-3 fatty acid (O3-FA) supplementation versus placebo was conducted by SWOG (SWOG S0927) that demonstrated significant improvements in worst pain, although the benefit was similar in both treatment arms.[9] Recently, because of previously reported associations between obesity and inflammation as well as the anti-inflammatory effects of O3-FA supplementation,[10-12] an exploratory analysis was conducted to examine the association between obesity and response to O3-FA supplementation.[13] O3-FA use was found to be associated with a significantly lower Brief Pain Inventory (BPI) worst pain score (range, 0-10) at 24 weeks in patients with a BMI $\geq$30 kg/m^2 who were treated with O3-FA compared with placebo (4.36 vs 5.70; $P = .02$). In contrast, no such association was identified among patients with a BMI <30 kg/m^2 (5.27 vs 4.58; $P = .28$ [P for interaction, .05).

Based on the findings of this exploratory analysis in SWOG S0927, we hypothesized that this BMI effect was due to systemic inflammation, because inflammation is higher in the setting of obesity and O3-FAs have been shown to be anti-inflammatory. We were unsure whether a similar intervention effect would be observed in a trial of the treatment of patients with AIMSS using a drug with a different mechanism of action. Therefore, we analyzed response to duloxetine versus placebo by BMI in patients enrolled on SWOG clinical trial S1202, hypothesizing that patterns of response would differ between obese and nonobese patients.

MATERIALS AND METHODS

Eligibility

SWOG trial S1202 (ClinicalTrials.gov identifier NCT01598298) was approved by the institutional review boards of the participating institutions and enrolled patients between May 2013 and October 2015. All patients provided written informed consent prior to protocol-directed procedures. A description of SWOG S1202, including study design and inclusion and exclusion criteria (including a Consolidated Standards Of Reporting Trials [CONSORT] diagram), was published previously.[7] In brief, postmenopausal women with stage I to III (AJCC 7th Edition) hormone receptor-positive breast cancer who had been receiving AI therapy for at least 3 weeks and for $\leq$24 months and who developed new or worsened average joint pain measuring at least 4 on a scale of 0 to 10 on the BPI were enrolled.

Study Design

Patients were randomized 1:1 to duloxetine at a dose of 30 mg orally daily for 1 week followed by 60 mg orally daily for 11 weeks, or to matching placebo containing Nu-Pareli sugar spheres. Patients were stratified based on prior taxane chemotherapy and baseline average pain score (4-6 vs 7-10). Demographic and clinical information was collected at baseline, including height and weight to calculate BMI. Patients were categorized as those with a BMI <30 kg/m^2 (nonobese) or $\geq$30 kg/m^2 (obese). Validated questionnaires were used to assess patient symptoms. The BPI-Short Form was used to rate average and worst pain over the prior week as well as interference of pain with daily activities on a scale from 0 to 10, and was collected at baseline and after 2, 6, and 12 weeks of treatment.[14] Three other scales also were used to assess patients' symptoms at the same time points, including: 1) the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH); 2) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); and 3) the Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) Trial Outcome Index.[15-17] The Global Ratings of Change questionnaire regarding joint pain and stiffness was assessed at 2, 6, and 12 weeks, with scores ranging from -3 for "very much worse" to +3 for "very much better" than the prior assessment.[18]

Statistical Analysis

Participant characteristics at baseline were described by BMI category (obese vs nonobese). Differences by BMI were identified using chi-square tests for categorical measures and Student t tests for continuous measures.

The primary prespecified aim was to examine whether intervention effects with respect to the main outcome from SWOG S1202 (BPI average pain at 12 weeks) differed between obese (BMI $\geq$30 kg/m^2) and nonobese (BMI <30 kg/m^2) patients. Mean scores of multiple patient-reported outcomes (PROs) were calculated at baseline and through 12 weeks, corresponding to the intervention period, separately by treatment group (duloxetine vs placebo) and BMI group (<30 kg/m^2 vs $\geq$30 kg/m^2). Multiple linear regression was used adjusting for the stratification factors and the baseline score. In the main regression model, we tested whether

TABLE 1. Patient Characteristics at the Time of Study Entry

Characteristic	BMI <30 kg/m^2 N = 133	BMI ≥30 kg/m^2 N = 156	*P*
Age, y			
<55	31 (23%)	36 (23%)	.16
55-59	41 (31%)	31 (20%)	
60-64	26 (20%)	39 (25%)	
≥65	35 (26%)	50 (32%)	
Hispanic ethnicity			
No	128 (97%)	149 (96%)	.52
Yes	4 (3%)	7 (4%)	
Race			
Black	5 (4%)	22 (14%)	.02
Other	2 (2%)	2 (1%)	
Asian	6 (5%)	3 (2%)	
Unknown	1 (<1%)	–	
White	119 (89%)	129 (83%)	
AI			
Anastrozole	73 (55%)	96 (61%)	.42
Letrozole	45 (34%)	48 (31%)	
Exemestane	15 (11%)	12 (8%)	
Mo receiving AI therapy	11.8 (9.0)[a]	12.4 (8.6)[a]	.60
Y since menopause	12.5 (10.4)[a]	13.5 (9.2)[a]	.38
Taxane chemotherapy	65 (49%)	91 (58%)	.11
Baseline BPI average pain score			
4-6	103 (77%)	117 (75%)	.63
7-10	30 (23%)	39 (25%)	
Treatment group			
Duloxetine	67 (50%)	78 (50%)	.95
Placebo	66 (50%)	78 (50%)	

Abbreviations: AI, aromatase inhibitor; BMI, body mass index; BPI, Brief Pain Inventory.
[a]The values shown in parentheses represents the standard deviations.

the interaction of BMI status and the intervention effect (evaluated as the product of indicator terms for intervention [duloxetine (1) vs placebo (0)] and BMI category) was statistically significant at the α level of .05. Secondary outcomes were examined in a similar fashion, including BPI worst pain and BPI pain interference; the Physical Well-Being, Functional Well-Being, and Endocrine Subscales of the FACT-ES; WOMAC; M-SACRAH; and Global Ratings in Change in joint pain and joint stiffness. Race also was included as a covariate in a secondary analysis of the regression models of the primary and secondary outcomes.

RESULTS

Patient Characteristics

Of the 299 patients enrolled in SWOG S1202, a total of 145 patients who were treated with duloxetine and 144 who were treated with placebo were eligible for the primary analysis. All eligible patients had BMI measurements available and therefore were included in this analysis. Of the analyzed patients, 54% were obese, and the median BMI was 31 kg/m^2 (range, 18-76 kg/m^2). Patient characteristics at baseline, by BMI, are provided in Table 1. All factors were well balanced with the exception of race: obese women were more likely to be black.

TABLE 2. BPI Endpoint Results by Intervention Assignment and BMI Status

		BMI <30 kg/m^2			BMI ≥30 kg/m^2			
		Duloxetine N = 67	Placebo N = 66		Duloxetine N = 78	Placebo N = 78		
Patient-Reported Outcomes	Time Point	Mean (SD)	Mean (SD)	*P*[a,b]	Mean (SD)	Mean (SD)	*P*[a,b]	*P*[c]
BPI average pain	Baseline	5.39 (1.32)	5.50 (1.33)	.46	5.65 (1.39)	5.59 (1.43)	.90	.35
	Wk 2	3.67 (2.22)	4.10 (2.00)	.22	3.93 (2.30)	4.96 (1.73)	**.001**	**.0009**
	Wk 6	3.10 (2.13)	3.34 (2.16)	.59	2.94 (2.13)	4.52 (1.91)	**<.0001**	**<.0001**
	Wk 12	2.93 (2.16)	3.16 (2.22)	.75	2.92 (2.10)	3.95 (2.02)	**.003**	**.02**
BPI worst pain	Baseline	6.77 (1.45)	7.11 (1.60)	.14	7.22 (1.56)	7.08 (1.51)	.67	.25
	Wk 2	4.83 (2.59)	5.38 (2.33)	.30	4.64 (2.46)	6.37 (2.11)	**<.0001**	**<.0001**
	Wk 6	4.30 (2.43)	4.84 (2.71)	.31	3.88 (2.77)	5.77 (2.44)	**<.0001**	**.0003**
	Wk 12	4.15 (2.80)	4.66 (2.76)	.40	3.95 (2.86)	5.31 (2.64)	**.003**	**.03**
BPI pain interference	Baseline	4.45 (2.02)	4.92 (1.99)	.12	5.05 (2.11)	4.94 (2.09)	.84	.24
	Wk 2	2.40 (2.16)	3.34 (2.34)	**.03**	2.48 (2.16)	3.67 (1.83)	**<.0001**	**<.0001**
	Wk 6	1.78 (1.87)	2.41 (2.16)	.16	2.08 (2.36)	3.58 (2.20)	**<.0001**	**<.0001**
	Wk 12	1.80 (2.10)	2.31 (2.17)	.38	2.01 (2.18)	3.05 (2.16)	**.002**	**.005**

Abbreviations: BMI, body mass index; BPI, Brief Pain Inventory; SD: standard deviation.
Decrease in score reflects less pain or pain interference.
[a]*P* values used linear regression to compare treatment groups, separately by BMI group, and were adjusted for the stratification factors of baseline pain score (4-6 vs 7-10) and prior taxane therapy (yes vs no). Postbaseline measures also were adjusted for baseline measures.
[b]Bold type indicates statistical significance.
[c]*P* value tested the interaction between the treatment group and BMI group.

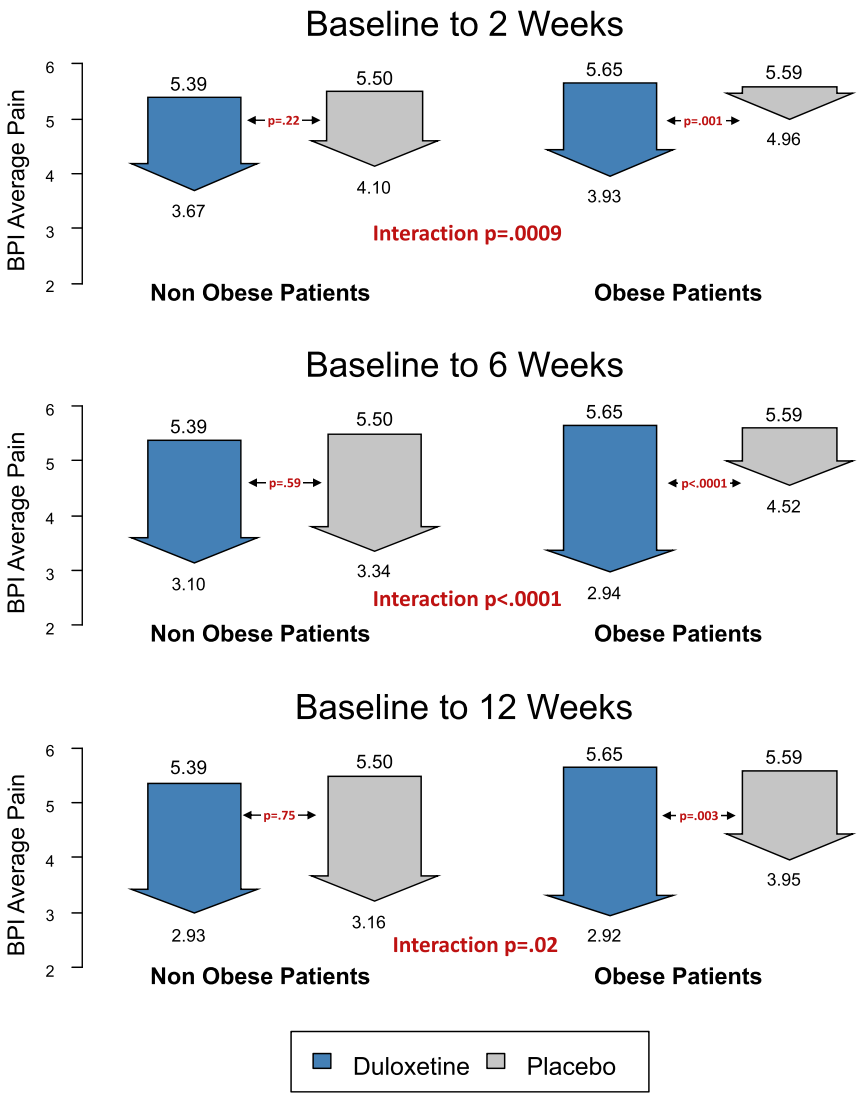

Figure 1. Change in Brief Pain Inventory (BPI) average pain scores from baseline to follow-up by intervention and obesity status. *P* values compared the average pain scores between cohorts treated with duloxetine versus those receiving placebo by body mass index (BMI) cohort at each time point, and *P* values for interaction examined the interaction between BMI and treatment. A decrease in the BPI scores indicates less pain.

Association Between BMI and Response to Therapy

The observed difference between the mean baseline and mean follow-up scores among the patients treated with duloxetine compared with those treated with placebo differed substantially for the obese versus nonobese cohorts (Table 2). In patients with a BMI <30 kg/m^2, the reduction in the mean average pain score was similar between the duloxetine-treated and placebo-treated patients at each time point during treatment. Conversely, among patients with a BMI ≥30 kg/m^2, the reduction in pain score was statistically significantly greater at all postbaseline time points for the patients treated with duloxetine compared with those treated with placebo (Fig. 1). At the 12-week time point in particular, the reduction in the observed mean average pain score was similar by treatment arm for patients with a BMI <30 kg/m^2 (-2.46 points for duloxetine vs -2.34 points for placebo; $P = .75$), but differed between the duloxetine-treated patients and the placebo-treated patients for patients with a BMI ≥30 kg/m^2 (-2.73 points vs -1.64 points; $P = .003$ [P for interaction, .02]). This pattern of different effect sizes between obese and nonobese patients was even more pronounced at 2 weeks (P for interaction,

TABLE 3. PRO Endpoint Results by Intervention Assignment and BMI Status

		BMI <30 kg/m^2			BMI ≥30 kg/m^2			
		Duloxetine N = 67	Placebo N = 66		Duloxetine N = 78	Placebo N = 78		
PRO	Time Point	Mean (SD)	Mean (SD)	$P^{a,b}$	Mean (SD)	Mean (SD)	$P^{a,b}$	P^{c}
FACT-ES Subscales								
Functional Well-Being	Baseline	16.95 (5.58)	16.51 (5.50)	.64	15.79 (5.14)	16.26 (5.77)	.66	.66
(range, 0 to 28)	Wk 2	19.32 (5.42)	17.77 (6.07)	.10	19.00 (5.44)	17.18 (5.45)	**.003**	**.004**
	Wk 6	20.25 (5.90)	19.03 (6.25)	.25	19.37 (6.06)	16.17 (5.63)	**<.0001**	**<.0001**
	Wk 12	19.85 (6.41)	19.57 (5.69)	.93	18.98 (6.28)	17.39 (5.55)	**.01**	**.03**
Physical Well-Being	Baseline	18.00 (5.68)	18.00 (4.87)	.93	17.82 (4.24)	17.63 (4.80)	.70	.98
(range, 0 to 28)	Wk 2	20.49 (5.03)	21.14 (4.98)	.38	20.34 (4.65)	21.20 (3.53)	.13	.37
	Wk 6	22.48 (4.45)	22.00 (5.21)	.49	21.66 (4.75)	20.47 (3.94)	.24	.12
	Wk 12	22.80 (4.48)	22.25 (4.99)	.34	22.10 (4.79)	21.34 (3.74)	.63	.35
Endocrine Subscale	Baseline	57.02 (11.06)	51.63 (12.62)	**.01**	54.37 (10.96)	51.00 (11.38)	.08	**.01**
(range, 0 to 76)	Wk 2	63.25 (9.21)	56.69 (11.30)	**.004**	61.10 (9.99)	57.80 (9.44)	.17	**.02**
	Wk 6	62.24 (10.76)	57.68 (11.69)	.21	62.70 (9.56)	56.52 (9.36)	**.02**	.08
	Wk 12	63.52 (9.26)	58.84 (10.93)	.09	63.00 (9.20)	57.10 (9.21)	**.02**	**.04**
WOMAC	Baseline	52.05 (17.78)	53.15 (18.22)	.62	58.12 (17.21)	55.88 (17.78)	.42	.15
(range, 0 to 240)	Wk 2	29.54 (21.33)	38.75 (23.21)	**.006**	32.10 (21.54)	47.01 (18.95)	**<.0001**	**<.0001**
	Wk 6	25.26 (19.67)	30.60 (23.17)	.13	25.53 (20.12)	43.14 (21.01)	**<.0001**	**<.0001**
	Wk 12	24.20 (19.70)	29.36 (21.31)	.13	24.12 (19.11)	39.19 (21.50)	**<.0001**	**<.0001**
M-SACRAH	Baseline	36.31 (23.27)	38.72 (25.04)	.43	37.42 (24.36)	37.43 (21.51)	.93	.91
(range, 0 to 120)	Wk 2	20.11 (17.90)	28.06 (24.61)	**.02**	17.56 (18.63)	32.62 (20.80)	**<.0001**	**<.0001**
	Wk 6	18.53 (18.26)	23.56 (21.39)	.19	14.70 (17.01)	30.68 (20.72)	**<.0001**	**<.0001**
	Wk 12	18.58 (20.54)	21.37 (21.07)	.51	17.28 (18.42)	27.04 (22.59)	**.005**	**.02**
Global Ratings of Change in joint pain	Wk 2	1.36 (1.23)	0.67 (1.41)	**.004**	1.44 (1.25)	0.61 (1.11)	**<.0001**	**<.0001**
(range, -3 to +3)	Wk 6	1.15 (1.35)	0.93 (1.24)	.32	1.16 (1.42)	0.42 (1.47)	**.003**	**.008**
	Wk 12	0.69 (1.61)	0.69 (1.46)	.99	0.75 (1.60)	0.63 (1.37)	.52	.94
Global Ratings of Change in joint stiffness	Wk 2	1.31 (1.21)	0.49 (1.40)	**.0008**	1.18 (1.36)	0.38 (0.99)	**.0001**	**<.0001**
(range -3 to +3)	Wk 6	0.98 (1.21)	0.77 (1.25)	.28	0.94 (1.20)	0.46 (1.17)	**.02**	.08
	Wk 12	0.59 (1.49)	0.44 (1.48)	.56	0.58 (1.39)	0.59 (1.24)	.96	.93

Abbreviations: BMI, body mass index; FACT-ES TOI, Functional Assessment of Cancer Therapy–Endocrine Symptoms Trial Outcomes Index; M-SACRAH, Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; PRO, patient-reported outcome; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

An increase in FACT-ES subscales scores reflects better well-being. Higher WOMAC scores and higher M-SACRAH scores reflect worse pain, stiffness, and functional limitations.

[a]*P* values used linear regression to compare treatment groups, separately by BMI group, and were adjusted for the stratification factors of baseline pain score (4-6 vs 7-10) and prior taxane therapy (yes vs no). Postbaseline measures (except for Global Ratings of Change measures) also were adjusted for baseline measures.

[b]Bold type indicates statistical significance.

[c]P value tested the interaction between the treatment group and BMI group.

.0009) and 6 weeks (*P* for interaction, <.0001). Given that obese women were more likely to be black, we also included race as a covariate in a secondary analysis; the results were very similar, with *P* values for interaction of .002, <.0001, and .02, respectively, at weeks 2, 6, and 12.

Similar findings were noted for other joint-related PROs assessed (Tables 2 and 3), with the BPI worst pain, BPI pain interference, M-SACRAH, WOMAC, and Functional Well-Being subscale of the FACT-ES all demonstrating statistically significantly more favorable outcomes for obese women in the duloxetine treatment group compared with placebo at all postbaseline time points, but not for nonobese women. No differences between treatment cohorts or by BMI were identified for the Physical Well-Being subscale of the FACT-ES, and only a minimal difference was observed for the FACT-ES Endocrine Subscale. Results were similar if black race also was added as a covariate to the regression models (data not shown).

For the Global Ratings of Change, there was significantly improved joint pain and joint stiffness in patients treated with duloxetine compared with placebo regardless of BMI at the 2-week time point. These differences persisted for obese patients at the 6-week time point, but did not persist for either group during the remainder of treatment.

Results were similar for all measures when the percentage of patients achieving a 2-point improvement in pain scores and other PROs was used (see Supporting Table 1).

DISCUSSION

In this secondary analysis of SWOG S1202, we demonstrated clinically and statistically significant improvements in average pain, worst pain, and pain interference with 12 weeks of treatment with duloxetine compared with blinded placebo in obese patients with AIMSS. This is clinically relevant because obesity is a risk factor for the development of AI-associated arthralgias, which can lead to decreased persistence with AI therapy, and to the best of our knowledge, few effective treatment options exist. In contrast, nonobese patients reported a similar improvement in pain regardless of treatment, and the improvement was numerically less than in the obese patients treated with duloxetine.

These findings are consistent with recently published findings from SWOG S0927, in which patients with AIMSS were treated with O3-FA supplementation or placebo.[13] In that exploratory analysis, obese patients also experienced greater improvements in pain with O3-FA treatment compared with placebo, whereas nonobese patients obtained a similar benefit from both O3-FA and placebo. To our knowledge, the mechanism underlying this effect is unclear. Both O3-FA and antidepressants have been shown to have anti-inflammatory properties, although it is not known whether there is a differential anti-inflammatory effect by BMI[19-21]; studies currently are ongoing to assess changes in inflammatory markers and response to therapy. Based on pharmacokinetic analyses of duloxetine, patients with higher body weight do not have increased exposure to duloxetine, and therefore it does not appear that differential metabolism of the drug accounts for the increased activity noted in obese patients.[22] Analyses of predictors of placebo effects in studies of treatments of other conditions generally have not reported effects of BMI.[23] One study examining predictors of placebo response for functional dyspepsia reported a lower placebo response in patients with a low BMI, which is the opposite finding from the 2 AIMSS trials.[24]

Is it possible that there is a difference in the etiology of AIMSS between patients with and without obesity? Several comorbidities are more common in postmenopausal women with obesity, including those associated with chronic pain such as osteoarthritis. Obesity also is associated with low-grade chronic inflammation, with abnormal cytokine production and increased activation of inflammatory signaling pathways.[12] There also may be differences in diet and exercise, or other unknown confounders that could contribute to differences in analgesic response. Unfortunately, factors that would allow for the additional examination of these potential mechanisms, including baseline pain scores at the time of AI initiation, diet composition, and expectations of response to study treatment, were not collected from enrolled patients. A large ongoing observational study of women initiating treatment with anastrozole for early-stage breast cancer, ECOG-ACRIN E1Z11, is prospectively collecting PROs and samples and potentially could be used to examine these mechanistic questions.

The findings of the current study suggest that in studies examining AI toxicity interventions, stratification by BMI should be considered. In addition, given the high rate of placebo response observed in the nonobese patients, this also may need to be accounted for in future management trials, and the identification of predictors of placebo response may be useful.

This exploratory study had numerous strengths. SWOG S1202 was a large multicenter, placebo-controlled randomized trial in which the patient-reported symptoms, including pain scores, were collected prospectively. The inclusion criteria were broad and required moderate to severe average pain at baseline, and therefore the results are generalizable to many patients with AI arthralgia. Patients were treated uniformly across study sites according to the duloxetine package insert. Moreover, the hypothesis for this post hoc analysis was prespecified and tested at the α level of .05, thereby limiting the potential for false-positive findings. There also are a few limitations in addition to those described above, including that the original study was not designed to examine differences in pain scores by BMI, and the intervention was limited to 12 weeks.

In the placebo-controlled SWOG S1202 trial, obese patients with AIMSS derived more analgesic benefit from duloxetine compared with nonobese patients, and compared with obese patients treated with placebo. In addition, nonobese patients experienced similar analgesic benefits from either duloxetine or placebo. Additional studies are warranted to determine the biologic basis for these findings, such as a different mechanism underlying the development of AIMSS or pain expression in patients with obesity, or other confounding variables related to analgesic response to duloxetine compared with placebo.

FUNDING SUPPORT

Supported in part by the National Cancer Institute of the National Institutes of Health (award 5UG1CA189974), in part by Damon Runyon-Lilly Clinical Investigator Award CI-53-10 (to N. Lynn Henry) from Lilly USA LLC, and The Hope Foundation (to N. Lynn Henry). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Lilly USA LLC.

CONFLICT OF INTEREST DISCLOSURES

Michael J. Fisch was employed by AIM Specialty Health, a subsidiary of Anthem Inc. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

N. Lynn Henry: Conceptualization, investigation, writing–original draft, and writing–review and editing. **Joseph M. Unger:** Conceptualization, formal analysis, visualization, writing–original draft, and writing–review and editing. **Cathee Till:** Formal analysis, visualization, writing–original draft, and writing–review and editing. **Anne F. Schott:** Writing–review and editing. **Katherine D. Crew:** Writing–review and editing. **Danika L. Lew:** Visualization and writing–review and editing. **Michael J. Fisch:** Writing–review and editing. **Carol M. Moinpour:** Writing–review and editing. **James L. Wade III:** Writing–review and editing. **Dawn L. Hershman:** Conceptualization and writing–review and editing.

REFERENCES

1. Burstein HJ, Prestrud AA, Seidenfeld J, et al; American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. *J Clin Oncol*. 2010;28:3784-3796.
2. Chirgwin JH, Giobbie-Hurder A, Coates AS, et al. Treatment adherence and its impact on disease-free survival in the Breast International Group 1–98 trial of tamoxifen and letrozole, alone and in sequence. *J Clin Oncol*. 2016;34:2452-2459.
3. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation due to treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol*. 2012;30:936-942.
4. Sestak I, Cuzick J, Sapunar F, et al; ATAC Trialists' Group. Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. *Lancet Oncol*. 2008;9:866-872.
5. Mieog JS, Morden JP, Bliss JM, Coombes RC, van de Velde CJ;IES Steering Committee. Carpal tunnel syndrome and musculoskeletal symptoms in postmenopausal women with early breast cancer treated with exemestane or tamoxifen after 2-3 years of tamoxifen: a retrospective analysis of the Intergroup Exemestane Study. *Lancet Oncol*. 2012;13:420-432.
6. Irwin ML, Cartmel B, Gross CP, et al. Randomized exercise trial of aromatase inhibitor–induced arthralgia in breast cancer survivors. *J Clin Oncol*. 2015;33:1104-1111.
7. Henry NL, Unger JM, Schott AF, et al. Randomized, multicenter, placebo-controlled clinical trial of duloxetine versus placebo for aromatase inhibitor–associated arthralgias in early-stage breast cancer: SWOG S1202. *J Clin Oncol*. 2018;36:326-332.
8. Hershman DL, Unger JM, Greenlee H, et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial. *JAMA*. 2018;320:167-176.
9. Hershman DL, Unger JM, Crew KD, et al. Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor–induced musculoskeletal pain: SWOG S0927. *J Clin Oncol*. 2015;33:1910-1917.
10. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*. 2006;83(suppl 6):1505S-1519S.
11. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol*. 2017;13:633-643.
12. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860-867.
13. Shen S, Unger JM, Crew KD, et al. Omega-3 fatty acid use for obese breast cancer patients with aromatase inhibitor–related arthralgia (SWOG S0927). *Breast Cancer Res Treat*. 2018;172:603-610.
14. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*. 1983;17:197-210.
15. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15:1833-1840.
16. Sautner J, Andel I, Rintelen B, Leeb BF. Development of the M-SACRAH, a modified, shortened version of SACRAH (Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands). *Rheumatology (Oxford)*. 2004;43:1409-1413.
17. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. *Breast Cancer Res Treat*. 1999;55:189-199.
18. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther*. 2009;17:163-170.
19. De Berardis D, Conti CM, Serroni N, et al. The effect of newer serotonin-noradrenalin antidepressants on cytokine production: a review of the current literature. *Int J Immunopathol Pharmacol*. 2010;23:417-422.
20. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev*. 2010;68:280-289.
21. Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta*. 2015;1851:469-484.
22. Lobo ED, Quinlan T, O'Brien L, Knadler MP, Heathman M. Population pharmacokinetics of orally administered duloxetine in patients: implications for dosing recommendation. *Clin Pharmacokinet*. 2009;48:189-197.
23. Horing B, Weimer K, Muth ER, Enck P. Prediction of placebo responses: a systematic review of the literature. *Front Psychol*. 2014;5:1079.
24. Talley NJ, Locke GR, Lahr BD, et al. Predictors of the placebo response in functional dyspepsia. *Aliment Pharmacol Ther*. 2006;23:923-936.