DR. N. LYNN HENRY (Orcid ID : 0000-0002-4771-5930)

Article type : Original Article

Manuscript Type: Original Article

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

Running Head: Duloxetine for AIMSS and obesity status

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] Dawn L. Hershman, MD, MS[5]

[1]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [2]SWOG Statistics and Data Management Center, Seattle, WA; [3]Fred Hutchinson Cancer Research Center, Seattle, WA; [4]University of Michigan, Ann Arbor, MI; [5]Columbia University, New York, NY; [6]AIM Specialty Health, Chicago, IL; [7]Fred Hutchinson Cancer Research Center, Public Health Sciences Division, Seattle, WA; [8]Heartland NCORP, Decatur, IL

Corresponding Author:

N. Lynn Henry, MD, PhD

University of Utah

Huntsman Cancer Institute

2000 Circle of Hope Dr

Salt Lake City, UT 84112

Tel: 801-585-0255; Fax: 801-585-0160

lynn.henry@hci.utah.edu

Text pages: 14

Tables: 3

Figures: 1

Supplemental Table: 1

Research Support: Research reported in this publication was supported in part by the National Cancer Institute of the National Institutes of Health under Award Number 5UG1CA189974; and in part by Damon Runyon-Lilly Clinical Investigator Award #CI-53-10 [to NLH]; Lilly USA, LLC; and The Hope Foundation [to NLH]. 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: MJF reports employment by AIM Specialty Health, a subsidiary of Anthem. No other authors report any conflicts of interest.

Condensed Abstract

Aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) negatively impact adherence and persistence with therapy. In the SWOG S1202 randomized clinical trial of duloxetine vs placebo for

treatment of AIMSS, obese patients with AIMSS obtained more analgesic benefit from duloxetine compared to non-obese patients.

Keywords: breast cancer, arthralgias, duloxetine, placebo, obesity

Author Contributions:

N.L. Henry: conceptualization, investigation, writing – original draft, writing – review and editing. J.M. Unger: conceptualization, formal analysis, visualization, writing – original draft, writing – review and editing. C. Till: formal analysis, visualization, writing – original draft, writing – review and editing. A.F. Schott: writing – review and editing. K.D. Crew: writing – review and editing. D.L. Lew: visualization, writing – review and editing. M.J. Fisch: writing – review and editing. C.M. Moinpour: writing – review and editing. J.L. Wade, III: writing – review and editing. D.L. Hershman: conceptualization, writing – review and editing.

Abstract

Background: Aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) negatively impact adherence and persistence with therapy. In SWOG S1202, patients with AIMSS treated with duloxetine, a serotonin norepinephrine reuptake inhibitor, reported improvement in pain by 12 weeks compared to placebo. Based on our prior observation that responses to pain interventions differ between obese and non-obese patients, we examined whether response to duloxetine therapy differed by obesity status.

Patients and Methods: In S1202, 299 AI-treated postmenopausal women with stage I-III 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 non-obese (BMI<30 kg/m^2) or obese (BMI≥30 kg/m^2). We tested the interaction between intervention and obesity with respect to average pain at 12 weeks in the 289 eligible patients, using p=0.05.

Results: In 54% of evaluable patients with BMI≥30 kg/m^2 the reduction in mean average pain score between baseline and 12 weeks was statistically significantly greater for duloxetine-treated compared to placebo-treated patients (-2.73 vs. -1.64 points, p=.003). Conversely, in the non-obese patients, the reduction in mean average pain score was similar in the two cohorts (-2.46 vs. -2.34 points, p=.75). The interaction p-value was p=.02, meeting our threshold criteria. 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 to non-obese patients. Additional studies are warranted to determine the biologic basis for these findings.

Introduction

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

The mechanism underlying the development of AIMSS remains undefined. A number of predictors of developing treatment emergent symptoms have been identified, including age closer to menopause, higher body mass index (BMI), prior treatment with chemotherapy, and pre-existing 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 demonstrate modest improvements in AIMSS; substantial placebo effects have also been noted.[6-8]

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) 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 was 0.82 points lower for the patients treated with duloxetine compared with those treated with placebo (95% confidence interval [CI] -1.24 to -0.40, p=0.0002).

A randomized trial of omega-3 fatty acid (O3-FA) supplementation versus placebo was conducted by 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 associated with a significantly lower Brief Pain Inventory (BPI) worst pain score (range, 0-10) at 24 weeks in patients with BMI ≥30 kg/m^2 treated with O3-FA compared to placebo (4.36 vs. 5.70, *p*=0.02). In contrast, no such association was identified among patients with BMI <30 kg/m^2 (5.27 vs. 4.58, *p*=0.28; interaction *p*=0.05).

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

Methods

Eligibility

SWOG trial S1202 (clinicaltrials.gov NCT01598298) was approved by 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 S1202, including study design and inclusion and exclusion criteria (including Consort Diagram), was previously published.[7] In brief, postmenopausal women with stage I-III hormone receptor-positive breast cancer who had been taking AI therapy for at least 3 weeks and for no more than 24 months and who developed new or worsened average joint pain measuring at least 4 out of 10 on the BPI were enrolled.

Study design

Patients were randomized 1:1 to duloxetine 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 into BMI <30 kg/m^2 (non-obese) or ≥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 0-10 scale, and was collected at baseline and after 2, 6, and 12 weeks of treatment.[14] Three other scales were also used to assess patients' symptoms at the same time points, including the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and 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 Considerations

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

The primary pre-specified aim was to examine whether intervention effects with respect to the main outcome from S1202 (BPI average pain at 12 weeks) differed between obese (BMI ≥30 kg/m^2) vs. non-obese (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 versus placebo) and BMI group (<30 kg/m^2 versus ≥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 the interaction of BMI status and intervention effect (evaluated as the product of indicator terms for intervention, duloxetine (=1) vs. placebo (=0); and BMI category) was statistically significant at the alpha=.05 level. Secondary outcomes were examined in a similar fashion, including BPI worst pain and BPI pain interference; 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 was also 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 S1202, 145 treated with duloxetine and 144 treated with placebo were eligible for the primary analysis. All eligible patients had BMI measures available and were therefore 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.

Association between BMI and response to therapy

The observed difference between mean baseline and mean follow-up scores in the duloxetine- and placebo-treated patients differed substantially for the obese versus non-obese cohorts (Table 2). In patients with BMI <30 kg/m^2, the reduction in mean average pain score was similar in the duloxetine- and placebo-treated patients at each time point during treatment; in contrast, in patients with BMI ≥30 kg/m^2, the reduction in pain score was statistically significantly greater at all post-baseline time points for the duloxetine-treated compared to the placebo-treated patients (Figure 1). At the 12-week time point in particular, the reduction in observed mean average pain score was similar by arm for patients with BMI <30 kg/m^2 (-2.46 points for duloxetine versus -2.34 points for placebo, p=.75), but differed for the duloxetine-treated patients compared to the placebo-treated patients for patients with BMI ≥30 kg/m^2 (-2.73 points versus -1.64 points, p=.003; interaction p-value=.02). This pattern of different effect sizes between obese and non-obese patients was even more pronounced at 2-weeks (interaction p-value=.0009) and 6-weeks (interaction p-value<.0001). Given that obese women were more likely to be black, we also included race as a covariate in a secondary analysis; results were very similar with interaction p-values of p=.002, p<.0001, and p=.02 at weeks 2, 6, and 12, respectively.

Similar findings were noted for other assessed joint-related PROs (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 showing statistically significantly more favorable outcomes for obese women in the duloxetine

treatment group compared to placebo at all post-baseline time points, but not for non-obese 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 was also added as a covariate to the regression models (data not shown).

For the Global Ratings of Change, there was significantly improved joint pain and stiffness in duloxetine-treated patients compared to 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 (Supplemental Table 1).

Discussion

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

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 improvement in pain with O3-FA compared to placebo, whereas non-obese patients obtained similar benefit from both O3-FA and placebo. 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 are ongoing to assess changes in inflammatory markers and response to therapy. Based on pharmacokinetic analyses of duloxetine, patients with higher bodyweight do not have increased exposure to duloxetine, so it does not appear that differential metabolism of the drug accounts for the increased activity in obese patients.[22] Analyses of predictors of placebo effects in studies of treatments

for 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 low BMI, which is the opposite finding from the two AIMSS trials.[24]

Is it possible that there is a difference in etiology of AIMSS between patients with and without obesity? A number of comorbidities are more common in postmenopausal women with obesity, including those associated with chronic pain such as osteoarthritis. Obesity is also associated with low grade chronic inflammation, with abnormal cytokine production and increased activation of inflammatory signaling pathways.[12] There may also be differences in diet and exercise, or other unknown confounders that could contribute to differences in analgesic response. Unfortunately, factors that would allow for 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 starting anastrozole for early stage breast cancer, ECOG-ACRIN E1Z11, is prospectively collecting PROs and samples and could potentially be used to examine these mechanistic questions.

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

This exploratory study had numerous strengths. SWOG 1202 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, so the results are generalizable to many patients with AI arthralgia. Patients were treated uniformly across sites according to the duloxetine package insert. Moreover, our hypothesis for this post-hoc analysis was pre-specified and tested at the alpha=.05 level, limiting the potential for false positive findings. There are also 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 summary, in the placebo-controlled S1202 trial, obese patients with AIMSS obtained more analgesic benefit from duloxetine compared to non-obese patients, and compared to obese patients treated with placebo. In addition, non-obese patients obtained 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 development of AIMSS or pain expression in patients with obesity, or other confounding variables related to analgesic response to duloxetine relative to placebo.

References

1. Burstein HJ, Prestrud AA, Seidenfeld J, et al. 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. 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. 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: 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;epub Aug 29.
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.

Figure Legend

Figure 1. Change from baseline to follow-up in Brief Pain Inventory (BPI) Average Pain scores by intervention and obesity status. P values compare average pain scores between duloxetine- and placebo-treated cohorts by body mass index (BMI) cohort at each timepoint, and interaction p values examine the interaction between BMI and treatment. A decrease in BPI scores reflects less pain.

Table 1. Patient characteristics at study entry. AI: aromatase inhibitor; BMI: body mass index; BPI: Brief Pain Inventory; kg: kilogram; m^2: meter squared

	BMI <30 kg/m^2 N=133	**BMI ≥30 kg/m^2 N=156**	**p-value**
Age			
<55 years	31 (23%)	36 (23%)	0.16
55-59 years	41 (31%)	31 (20%)	
60-64 years	26 (20%)	39 (25%)	
65+ years	35 (26%)	50 (32%)	
Hispanic			
No	128 (97%)	149 (96%)	0.52
Yes	4 (3%)	7 (4%)	
Race			
Black	5 (4%)	22 (14%)	0.02
Other	2 (2%)	2 (1%)	
Asian	6 (5%)	3 (2%)	
Unknown	1 (<1%)	--	

White	119 (89%)	129 (83%)	
Aromatase Inhibitor			
Anastrozole	88 (66%)	115 (74%)	0.16
Letrozole	50 (38%)	57 (37%)	0.85
Exemestane	18 (14%)	17 (11%)	0.49
Months on AI Therapy	11.8 (9.0)	12.4 (8.6)	0.60
Years since menopause	12.5 (10.4)	13.5 (9.2)	0.38
Taxane chemotherapy	65 (49%)	91 (58%)	0.11
Baseline BPI average pain score			
4-6	103 (77%)	117 (75%)	0.63
7-10	30 (23%)	39 (25%)	
Treatment Group			
Duloxetine	67 (50%)	78 (50%)	0.95
Placebo	66 (50%)	78 (50%)	

Table 2: Brief Pain Inventory (BPI) Endpoint Results by Intervention Assignment and Body Mass Index (BMI) Status. Decrease in score reflects less pain or pain interference. SD: standard deviation; N: number.

		BMI <30 kg/m^2			BMI ≥30 kg/m^2			
Patient-reported outcomes	**Time-point**	**Duloxetine N=67**	**Placebo N=66**	**p-value[1]**	**Duloxetine N=78**	**Placebo N=78**	**p-value[1]**	**p-value[2]**
		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		
BPI Average Pain	Baseline	5.39 (1.32)	5.50 (1.33)	0.46	5.65 (1.39)	5.59 (1.43)	0.90	0.35
	Week 2	3.67 (2.22)	4.10 (2.00)	0.22	3.93 (2.30)	4.96 (1.73)	**0.001**	**0.0009**
	Week 6	3.10 (2.13)	3.34 (2.16)	0.59	2.94 (2.13)	4.52 (1.91)	**<0.0001**	**<0.0001**
	Week 12	2.93 (2.16)	3.16 (2.22)	0.75	2.92 (2.10)	3.95 (2.02)	**0.003**	**0.02**
BPI Worst Pain	Baseline	6.77 (1.45)	7.11 (1.60)	0.14	7.22 (1.56)	7.08 (1.51)	0.67	0.25
	Week 2	4.83 (2.59)	5.38 (2.33)	0.30	4.64 (2.46)	6.37 (2.11)	**<0.0001**	**<0.0001**
	Week 6	4.30 (2.43)	4.84 (2.71)	0.31	3.88 (2.77)	5.77 (2.44)	**<0.0001**	**0.0003**
	Week 12	4.15 (2.80)	4.66 (2.76)	0.40	3.95 (2.86)	5.31 (2.64)	**0.003**	**0.03**
BPI Pain Interference	Baseline	4.45 (2.02)	4.92 (1.99)	0.12	5.05 (2.11)	4.94 (2.09)	0.84	0.24
	Week 2	2.40 (2.16)	3.34 (2.34)	**0.03**	2.48 (2.16)	3.67 (1.83)	**<0.0001**	**<0.0001**
	Week 6	1.78 (1.87)	2.41 (2.16)	0.16	2.08 (2.36)	3.58 (2.20)	**<0.0001**	**<0.0001**
	Week 12	1.80 (2.10)	2.31 (2.17)	0.38	2.01 (2.18)	3.05 (2.16)	**0.002**	**0.005**

[1] P-value uses linear regression to compare treatment groups, separately by BMI group, and are adjusted for stratification factors baseline pain score (4-6 vs 7-10) and prior taxane therapy (yes vs no). Post-baseline measures are also adjusted for baseline measures.

[2] P-value tests interaction between treatment group and BMI group.

Table 3. Patient-Reported Outcomes (PRO) Endpoint Results by Intervention Assignment and Body Mass Index (BMI) Status. Increase in Functional Assessment of Cancer Therapy – Endocrine Symptoms (FACT-ES) Trial Outcomes Index (TOI) scores reflects better well-being. Higher Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and higher Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) scores reflect worse pain, stiffness, and functional limitations. N: number; SD: standard deviation.

		BMI <30 kg/m^2			**BMI ≥30 kg/m^2**			
PRO	**Time-point**	**Duloxetine N=67**	**Placebo N=66**	**p-value[1]**	**Duloxetine N=78**	**Placebo N=78**	**p-value[1]**	**p-value[2]**
FACT-ES TOI		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		
- Functional Well-Being	Baseline	16.95 (5.58)	16.51 (5.50)	0.64	15.79 (5.14)	16.26 (5.77)	0.66	0.66
(range 0-28)	Week 2	19.32 (5.42)	17.77 (6.07)	0.10	19.00 (5.44)	17.18 (5.45)	**0.003**	**0.004**
	Week 6	20.25 (5.90)	19.03 (6.25)	0.25	19.37 (6.06)	16.17 (5.63)	**<0.0001**	**<0.0001**
	Week 12	19.85 (6.41)	19.57 (5.69)	0.93	18.98 (6.28)	17.39 (5.55)	**0.01**	**0.03**
- Physical Well-Being	Baseline	18.00 (5.68)	18.00 (4.87)	0.93	17.82 (4.24)	17.63 (4.80)	0.70	0.98
(range 0-28)	Week 2	20.49 (5.03)	21.14 (4.98)	0.38	20.34 (4.65)	21.20 (3.53)	0.13	0.37
	Week 6	22.48 (4.45)	22.00 (5.21)	0.49	21.66 (4.75)	20.47 (3.94)	0.24	0.12
	Week 12	22.80 (4.48)	22.25 (4.99)	0.34	22.10 (4.79)	21.34 (3.74)	0.63	0.35
- Endocrine Subscale	Baseline	57.02 (11.06)	51.63 (12.62)	**0.01**	54.37 (10.96)	51.00 (11.38)	0.08	**0.01**
(range 0-76)	Week 2	63.25 (9.21)	56.69 (11.30)	**0.004**	61.10 (9.99)	57.80 (9.44)	0.17	**0.02**
	Week 6	62.24 (10.76)	57.68 (11.69)	0.21	62.70 (9.56)	56.52 (9.36)	**0.02**	0.08
	Week 12	63.52 (9.26)	58.84 (10.93)	0.09	63.00 (9.20)	57.10 (9.21)	**0.02**	**0.04**

WOMAC	Baseline	52.05 (17.78)	53.15 (18.22)	0.62	58.12 (17.21)	55.88 (17.78)	0.42	0.15
(range 0-240)	Week 2	29.54 (21.33)	38.75 (23.21)	**0.006**	32.10 (21.54)	47.01 (18.95)	**<0.0001**	**<0.0001**
	Week 6	25.26 (19.67)	30.60 (23.17)	0.13	25.53 (20.12)	43.14 (21.01)	**<0.0001**	**<0.0001**
	Week 12	24.20 (19.70)	29.36 (21.31)	0.13	24.12 (19.11)	39.19 (21.50)	**<0.0001**	**<0.0001**
M-SACRAH	Baseline	36.31 (23.27)	38.72 (25.04)	0.43	37.42 (24.36)	37.43 (21.51)	0.93	0.91
(range 0-120)	Week 2	20.11 (17.90)	28.06 (24.61)	**0.02**	17.56 (18.63)	32.62 (20.80)	**<0.0001**	**<0.0001**
	Week 6	18.53 (18.26)	23.56 (21.39)	0.19	14.70 (17.01)	30.68 (20.72)	**<0.0001**	**<0.0001**
	Week 12	18.58 (20.54)	21.37 (21.07)	0.51	17.28 (18.42)	27.04 (22.59)	**0.005**	**0.02**
Global Ratings of Change in Joint Pain	Week 2	1.36 (1.23)	0.67 (1.41)	**0.004**	1.44 (1.25)	0.61 (1.11)	**<0.0001**	**<0.0001**
(range -3 to +3)	Week 6	1.15 (1.35)	0.93 (1.24)	0.32	1.16 (1.42)	0.42 (1.47)	**0.003**	**0.008**
	Week 12	0.69 (1.61)	0.69 (1.46)	0.99	0.75 (1.60)	0.63 (1.37)	0.52	0.94
Global Ratings of Change in Joint Stiffness	Week 2	1.31 (1.21)	0.49 (1.40)	**0.0008**	1.18 (1.36)	0.38 (0.99)	**0.0001**	**<0.0001**
(range -3 to +3)	Week 6	0.98 (1.21)	0.77 (1.25)	0.28	0.94 (1.20)	0.46 (1.17)	**0.02**	0.08
	Week 12	0.59 (1.49)	0.44 (1.48)	0.56	0.58 (1.39)	0.59 (1.24)	0.96	0.93

[1] P-value uses linear regression to compare treatment groups, separately by BMI group, and are adjusted for stratification factors baseline pain score (4-6 vs 7-10) and prior taxane therapy (yes vs no). Post-baseline measures (except for Global Ratings of Change measures) are also adjusted for baseline measures.

[2] P-value tests interaction between treatment group and BMI group.