Treatment of Depression and Menopause-Related Symptoms With the Serotonin-Norepinephrine Reuptake Inhibitor Duloxetine

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Background: Postmenopausal women with depression frequently have co-occurring symptoms of hot flashes (vasomotor symptoms), sleep disturbance, anxiety, and pain. Treatment strategies that target all of these symptoms together have not been investigated to date.

Method: Study participants were postmenopausal women, 40 to 60 years old, with major depressive disorder (DSM-IV criteria) and vasomotor symptoms. The study design included a 2-week, single-blind placebo run-in phase followed by an 8-week open-label flexible-dosing (60–120 mg per day) study of duloxetine for women who did not respond to placebo. The primary outcome measure was change in Montgomery-Asberg Depression Rating Scale (MADRS) score during 8 weeks of duloxetine therapy. Secondary outcome measures included changes in vasomotor symptoms, sleep quality, anxiety, and pain. Analyses were conducted using nonparametric methods. Patients were enrolled in the study from May 31, 2005, through May 22, 2006.

Results: Of 30 women eligible to participate in this study, 20 initiated treatment with open-label duloxetine. Fourteen (70.0%) of these women completed the study. There was a statistically significant decrease in MADRS scores after 8 weeks of treatment ($p < .001$), with scores declining from 19.0 (interquartile range [IQR] = 15.0–21.0) to 5.5 (IQR = 3.0–9.0). There was also a statistically significant improvement in vasomotor symptoms ($p = .003$), anxiety ($p = .002$), sleep quality ($p < .001$), and pain ($p < .05$).

Conclusions: Postmenopausal women with depression and vasomotor symptoms had significant improvement in depression, vasomotor symptoms, sleep, anxiety, and pain after 8 weeks of open-label duloxetine therapy. Given the common co-occurrence of these symptoms in postmenopausal women, duloxetine may offer important therapeutic benefits for postmenopausal women who have depression and menopause-related symptoms.

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The risk of depression increases in the perimenopause,[1,2] and this increased risk may continue in the early postmenopausal period.[3,4] Women who have recently become postmenopausal are most likely to report vasomotor symptoms (i.e., hot flashes, night sweats).[5] Symptoms of disrupted sleep, sexual dysfunction, pain, and anxiety are also common menopausal symptoms.[6,7] As a result, the treatment of depression in this population requires attention to symptoms that frequently co-occur and that can substantially reduce quality of life.

Treatment of depression, vasomotor symptoms, and other menopause-related symptoms in recently postmenopausal women commonly involves the use of antidepressants and hormonal therapy.[8] However, since the publication of the results of the Women's Health Initiative, use of hormonal therapy has reduced significantly,[9,10] and selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are being used widely to treat vasomotor symptoms.[11] Several studies have examined the effect of citalopram, escitalopram, and mirtazapine on depression in this population.[12–15] A subset of these studies has examined the effect of SSRI on vasomotor symptoms in women who are depressed.[13,14] Other studies have examined the effect of SSRI and SNRI on vasomotor symptoms in women who are not depressed.[16–21] However, the effect of SNRI on vasomotor symptoms in women who are also depressed has not yet been examined.

Duloxetine is a new SNRI that is U.S. Food and Drug Administration (FDA)-approved for the treatment of depression[22] and neuropathic pain syndromes.[23] Duloxetine also reduces anxiety and improves sleep quality.[24,25] However, the effect of duloxetine on depression in women who also experience menopause-related symptoms of vasomotor symptoms, sleep disruption, and pain has not yet been investigated. The purpose of this study was to determine whether duloxetine treats depression in postmenopausal women and to examine whether duloxetine is an effective treatment of vasomotor symptoms, sleep disruption, and pain. We hypothesized that treatment with duloxetine would lead to improvement of multiple domains of menopausal symptoms in postmenopausal women with major depressive disorder.

MATERIALS AND METHOD

Subjects

Thirty postmenopausal women with major depressive disorder were enrolled in an 8-week, open-label clinical trial of duloxetine from May 31, 2005, through May 22, 2006. Participants were recruited through advertisements in the Boston area. Subjects were 40 to 60 years old and postmenopausal, defined clinically as amenorrhea lasting 12 months or longer. Women who were postmenopausal secondary to bilateral oophorectomy were also eligible. Subjects were deemed eligible if they met DSM-IV criteria for major depressive disorder (MDD) on the Mini-International Neuropsychiatric Interview (MINI)[26] and had significant depressive symptoms, defined as a Montgomery-Asberg Depression Rating Scale (MADRS, range 0–63, higher score worse) score of 20 or higher at the screening visit.[27] In addition, participants were required to have significant vasomotor symptoms (≥ 14 hot flashes/week or Greene Climacteric Scale [GCS] vasomotor subscale score > 3) or significant menopausal symptoms overall (GCS total score ≥ 20).[28]

Exclusion criteria included hysterectomy without bilateral oophorectomy, psychotic symptoms, suicidal ideation, or Axis I disorders active within the past 6 months. Women meeting current criteria for comorbid generalized anxiety disorder and social phobia were eligible to enroll. Disallowed medications included current or recent use of hormonal therapy (past 4 weeks), antidepressants (past 8 weeks), or hypnotics (past 2 weeks) or current or recent chronic use of analgesics (past 2 weeks).

The study protocol was approved by the Partners Healthcare System Institutional Review Board. Written informed consent was obtained from all subjects.

Procedures

The primary study design was an 8-week open-label trial of duloxetine that followed a 2-week, single-blind placebo run-in period. After we determined that initial study criteria were met, eligible participants started the run-in phase. At the end of the run-in phase, participants were reevaluated to confirm that they did not respond to the placebo treatment before initiating treatment with duloxetine. Women were considered placebo responders and excluded at the end of the run-in period if they had significant improvement of depression (≥ 50% decrease in MADRS score) or menopausal symptoms (≥ 50% reduction in GCS total score and a GCS vasomotor subscore < 2).

Participants who did not respond to placebo started treatment with duloxetine 30 mg/day for 1 week, followed by 3 weeks of duloxetine 60 mg/day. After 4 weeks of treatment with duloxetine, there was an optional dose adjustment for the remaining 4 weeks of the study. Those who did not have significant improvement of depression (≥ 50% decrease in MADRS score) or menopause-related symptoms (≥ 50% reduction in GCS total score and vasomotor subscore < 2) had their dose of duloxetine increased to 90 or 120 mg/day. Subjects with improvement in depression and/or menopausal symptoms continued to receive treatment with duloxetine 60 mg/day.

For the purpose of this study, the visit at the end of the placebo run-in period is considered the baseline assessment. Upon starting treatment with duloxetine, subjects were reevaluated after 2, 4, and 8 weeks of open-label duloxetine treatment. At each visit, mood was assessed using the clinician-rated MADRS.[27] Changes in overall clinical outcome occurring with treatment were measured with the Clinical Global Impressions (CGI) scale.[29]

Secondary outcome measures were assessed using self-reported instruments to measure menopausal symptoms, including vasomotor symptoms, sleep, anxiety, and pain. The GCS, Hot Flash Related Daily Interference Scale (HFRDIS),[30] and Menopause-Specific Quality of Life Questionnaire (MEN-QOL)[31] were used to assess changes in vasomotor symptoms and other menopause-related symptoms. The GCS is a widely used menopause scale (range, 0–63) that measures 4 components (psychological, somatic, vasomotor symptoms, and sexual) of menopause-related symptoms and quality of life, with each scale ranging from 0 to 33, 0 to 21, 0 to 6, and 0 to 3, respectively (higher score worse).[28] For the GCS vasomotor subscale, scores of 0 to 2 are consistent with none or mild hot flashes and night sweats, while scores of 3 to 6 suggest moderate to severe vasomotor symptoms. The HFRDIS scale (range, 0–100, higher score worse) measures the extent to which vasomotor symptoms have bothered an individual during the previous week.[30] The MEN-QOL evaluates 4 components of menopause-related quality of life over the past month, including vasomotor, psychosocial, physical, and sexual (range per subscale, 1–8, higher score worse).[31]

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).[32] The PSQI is a widely used questionnaire that measures sleep quality over the past month

(range, 0–21, higher score worse). PSQI scores greater than 5 suggest poor sleep.[32]

Anxiety was measured using the Beck Anxiety Inventory (BAI, range, 0–63, higher score worse), which measures anxiety symptoms over the past week.[33] Pain symptoms were assessed using the Visual Analog Scale (Pain VAS).[34] The Pain VAS measures the severity of 4 types of pain including overall pain, headaches, back pain, and shoulder pain. For each of the pain subscales, the range is 0 to 100 (higher score worse). The scale also quantifies how much overall pain interferes with the ability to complete daily activities and the proportion of the time that pain is experienced while awake. It is used widely to document improvement in pain with treatment.[22]

Serum levels of follicle-stimulating hormone (FSH) and thyroxine (T_4) were obtained at enrollment using radioimmunoassay methods, but an elevated serum FSH level was not required for study eligibility. Hormone assays were all analyzed at the Massachusetts General Hospital Reproductive Endocrine Laboratory.

Statistical Analysis

The primary analyses of the primary and secondary clinical outcomes were conducted on study completers (those finishing 8 weeks of open-label duloxetine therapy) using the Wilcoxon matched-pairs signed rank test. The primary outcome was the change in MADRS scores from baseline (after 2 weeks of single-blind placebo run-in) to study end (after 8 weeks of open-label duloxetine therapy). Differences in MADRS, CGI, BAI, GCS, HFRDIS, MEN-QOL, PSQI, and Pain VAS scale scores from baseline to study end were assessed using the Wilcoxon signed rank test for nonparametric data. For the primary outcome, a last observation carried forward (LOCF) analysis of the median change in MADRS scores from baseline to study end was also performed to include all participants who completed at least 2 weeks of open-label duloxetine therapy, the time point at which the first follow-up assessment after initiating medication was conducted. An LOCF analysis was also carried out for the secondary outcomes of vasomotor symptoms (GCS vasomotor subscore) and sleep quality (PSQI) using the same approach.

Comparisons between completers and noncompleters and between depression remitters (study end MADRS score < 10) and nonremitters were conducted using χ^2 tests (or Fisher exact test in the case of small samples) for categorical measures, Student t tests for parametric continuous measures, and the Wilcoxon rank sum test for nonparametric continuous measures.

Spearman rank correlations assessed the associations between symptoms of depression, anxiety, vasomotor symptoms, other menopause-related symptoms, sleep quality, and pain.

Statistical analyses were conducted using SAS statistical software version 9.1 (SAS Institute Inc., Cary, N.C.), and statistical significance was set at the $\alpha = .05$ level.

RESULTS

Subjects

Forty-four women consented to participate in the study and 30 were eligible to initiate treatment with single-blind placebo after the initial evaluation. Of these 30 subjects, 20 (66.7%) continued on to the open-label duloxetine treatment phase of the study, while 8 (26.7%) were excluded because they responded to placebo and 2 withdrew during the placebo run-in phase because of inability to make the time commitment to the study. Of 20 women initiating treatment with duloxetine, 14 (70.0%) completed the study. Participants who initiated duloxetine treatment but did not complete the study were withdrawn because of side effects (N = 3) or because they initiated a disallowed medication when they enrolled in another clinical trial for depression (using escitalopram or quetiapine) (N = 3).

The demographic, psychiatric, and menopause characteristics of the 30 women who enrolled in the study are listed on Table 1. The mean ± SD age of the subjects was 52.3 ± 4.1 years. The majority was naturally postmenopausal, with a median interval since the final menstrual period of 30.0 months (interquartile range [IQR] = 15.0–57.0 months). Serum FSH levels (mean ± SD = 76.9 ± 44.1 IU/L) were consistent with postmenopausal status in most subjects. However, 2 study completers were found to have a serum FSH level less than 25 IU/L. Analysis of the data after excluding these 2 subjects did not alter study results (data not shown). No subject had hypothyroidism. There were no differences in the subject characteristics between those who did and did not complete the study except that noncompleters had a higher HFRDIS score at study entry (p = .019).

Assessment of subjects at the initial screening visit revealed moderate levels of depression and menopause-related symptoms. The median MADRS score at study entry for all 30 enrolled subjects was 24.0 (IQR = 21.0–26.0), consistent with moderate depression. The median BAI score was 14.5 (IQR = 12.0–17.0), and 90.0% had a BAI score of 10 or higher, suggesting at least moderate anxiety. The median PSQI score at study entry was 12.5 (IQR = 11.0–14.0), and all participants had a PSQI score greater than 5, indicating poor sleep quality. All participants had moderate-to-severe vasomotor symptoms, defined as a GCS vasomotor symptom score of 3 or higher. Scores on the HFRDIS and MEN-QOL also indicated moderate impairment of quality of life related to the presence of vasomotor symptoms (Table 1).

Although pain was not an eligibility criterion, two thirds of participants reported having joint pain at enrollment and several had been diagnosed with pain syndromes

Table 1. Demographic, Menopause, Psychiatric, Sleep, and Pain Characteristics of Postmenopausal Women With Major Depressive Disorder at Study Enrollment (N = 30)[a]

Subject Characteristics	Value
Demographic characteristics	
Age, mean ± SD, y	52.3 ± 4.1
Race	
White, N (%)	17 (57)
Nonwhite, N (%)[b]	13 (43)
Marital status	
Married/living with partner, N (%)	13 (43)
Separated/divorced/widowed, N (%)	11 (37)
Never married/single, N (%)	6 (20)
Education	
High school degree or less, N (%)	8 (27)
College degree or courses, N (%)	15 (50)
Graduate degree or courses, N (%)	7 (23)
Employment status	
Full- or part-time work, N (%)	20 (67)
Homemaker, N (%)	3 (10)
Unemployed/disabled, N (%)	5 (17)
Retired, N (%)	2 (7)
Menopause characteristics	
Menopausal status: naturally postmenopausal, N (%)	28 (93)
No. of months since final menstrual period, median (IQR)	30.0 (15.0–57.0)
Past hormone therapy use, N (%)	13 (43)
No. of months since hormone therapy use stopped, median (IQR)	9.5 (3.0–24.0)
Serum follicle-stimulating hormone level, mean ± SD, IU/L[c]	76.9 ± 44.1
Greene Climacteric Scale scores	
Total, median (IQR)	28.0 (24.0–33.0)
Psychological, median (IQR)	17.5 (13.0–20.0)
Somatic, median (IQR)	5.0 (3.0–8.0)
Vasomotor, median (IQR)	5.0 (4.0–6.0)
Sexual, median (IQR)	1.0 (1.0–3.0)
Menopause-Specific Quality of Life Questionnaire scores	
Vasomotor, median (IQR)	6.3 (5.3–7.3)
Psychosocial, median (IQR)	5.7 (5.1–6.6)
Physical, median (IQR)	4.5 (3.8–5.9)
Sexual, median (IQR)	5.0 (2.3–7.0)
Hot Flash Related Daily Interference Scale score, median (IQR)	52.5 (38.0–73.0)
Psychiatric, sleep, and pain characteristics	
Beck Anxiety Inventory score, median (IQR)	14.5 (12.0–17.0)
Montgomery-Asberg Depression Rating Scale score, median (IQR)	24.0 (21.0–26.0)
Pittsburgh Sleep Quality Index score, median (IQR)[c]	12.5 (11.0–14.0)
Visual Analog Scale scores	
Back pain, median (IQR)	28.5 (7.0–44.0)
Headaches, median (IQR)	17.5 (8.0–45.0)
Shoulder pain score, median (IQR)	20.5 (3.0–36.0)
Interference, median (IQR)	10.5 (3.0–47.0)
Overall pain, median (IQR)	30.0 (20.0–56.0)
Pain while awake, median (IQR)	37 (15.0–60.0)

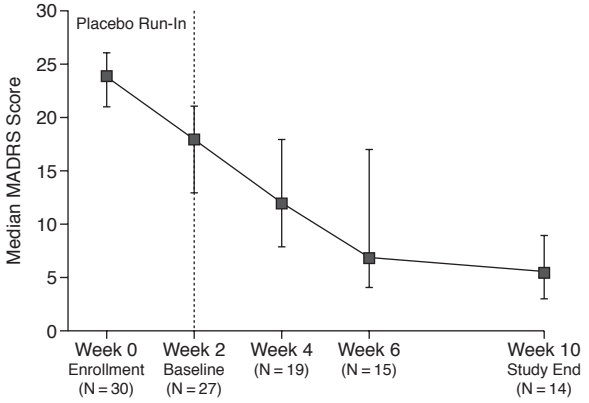
[a]Data presented are N (%) for proportions, mean ± SD for normally distributed data, and median (interquartile range [IQR]) for non-normally distributed data. IQR = 25th percentile–75th percentile.
[b]Other = 10 African American, 1 Asian, 1 Hispanic/Latino, 1 Cape Verdean.
[c]N = 28; data were missing for 2 subjects.

(migraine headaches [N = 2] and fibromyalgia [N = 1]). Table 1 shows the median level of pain for each subscale at enrollment.

Medication Dose and Tolerability

The mean ± SD final dose of duloxetine was 80 ± 18.5 mg/day. On the basis of the assessment of clinical response, the dose of duloxetine was increased above 60 mg/day in 60% of subjects. The study medication was well tolerated. The most common side effects were constipation (N = 8), headache (N = 6), and dry mouth (N = 5). Side effects led to early withdrawal from the study in 3 subjects, who withdrew because of nausea (N = 1), difficulty concentrating (N = 1), and intrusive thoughts (N = 1).

Figure 1. Median MADRS Scores for Study Completers (N = 14) at Enrollment, Baseline (after 2 weeks of placebo run-in), and During 8 Weeks of Open-Label Duloxetine Therapy (60–120 mg/day)[a,b]



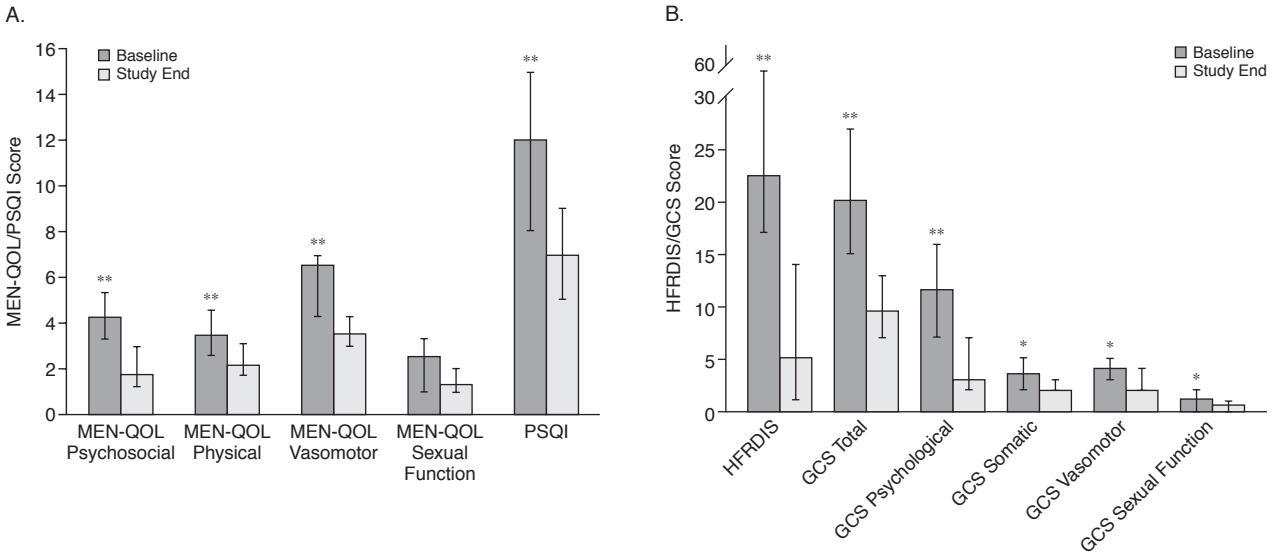
[a]The Y error bars indicate interquartile range (25th percentile–75th percentile) for the median scores.
[b]There was a statistically significant (p < .001) decrease in median MADRS score from baseline to study end (after 8 weeks of open-label duloxetine therapy).
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Outcome

For the 14 participants who completed the study, depression symptoms improved significantly with treatment, with a change in median MADRS scores from 19.0 (IQR = 15.0–21.0) at baseline to 5.5 (IQR = 3.0–9.0) at study end (Figure 1, p < .001). The median improvement in MADRS scores from baseline to study end was 14.5 (IQR = 11.0–17.0). After 8 weeks of treatment, 11 study completers (78.6%) had a median MADRS score less than 10, consistent with remission of depression. The median CGI scale score improved from 4.0 (IQR = 3.0–4.0) at baseline to 2.0 (IQR = 1.0–3.0) at study end, indicating statistically significant improvement in overall well-being (p = .002).

An LOCF analysis of the primary outcome variable of mood in participants who completed at least 2 weeks of open-label duloxetine treatment (N = 19) found similar results. Depression symptoms improved significantly with treatment, with a change in median MADRS scores from 19.0 (IQR = 15.0–21.0) at baseline to 7.0 (IQR = 3.0–12.0) at study end (p < .001). Using the LOCF analysis,

Figure 2, A and B. Bar Graphs Showing Menopausal Symptom Median Baseline Scores (after 2 weeks of placebo run-in) and Study End Scores (after 8 weeks of open-label duloxetine therapy) for Study Completers (N = 14)[a,b]



[a]The Y error bars indicate interquartile ranges (25th percentile–75th percentile) for the median scores.
[b]There were statistically significant decreases in all MEN-QOL measures (except sexual function) and PSQI from baseline to study end (Figure 2A; $p < .001$) and in HFRDIS and in all GCS measures from baseline to study end (Figure 2B; $p \leq .04$).
*$p \leq .04$.
**$p < .001$.
Abbreviations: GCS = Greene Climacteric Scale, HFRDIS = Hot Flash Related Daily Interference Scale, MEN-QOL = Menopause-Specific Quality of Life Questionnaire, PSQI = Pittsburgh Sleep Quality Index.

the median improvement in MADRS scores from baseline to study end was 13.0 (IQR = 5.0–17.0). Thirteen (68.4%) of participants completing at least 2 weeks of open-label duloxetine treatment had a median MADRS score less than 10 at study end, consistent with remission of depression.

Improvement was also observed in vasomotor symptoms and all other menopause-related symptoms (Figures 2A and 2B). Scores on the total GCS ($p = .0001$), GCS vasomotor subscale ($p = .003$), HFRDIS ($p = .0001$), and MEN-QOL subscales ($p = .0001$ for vasomotor subscale, $p = .0006$ for psychosocial subscale, and $p = .0004$ for physical subscale), with the exception of the MEN-QOL sexual subscale, all improved significantly. At study end, 64.3% of participants (9/14) had a GCS vasomotor subscale score of 2 or less, reflecting no or mild vasomotor symptoms, and 8 (57.1%) of 14 women had greater than a 50% reduction in the GCS total score, consistent with remission of menopausal symptoms. There was a strong correlation among baseline vasomotor symptoms measures ($p < .01$ for all comparisons) and between improvement in vasomotor symptoms as measured by the GCS and the MEN-QOL ($p = .01$). Scores on the PSQI and BAI also improved, reflecting improvement in sleep quality ($p < .002$) and anxiety ($p = .002$), respectively.

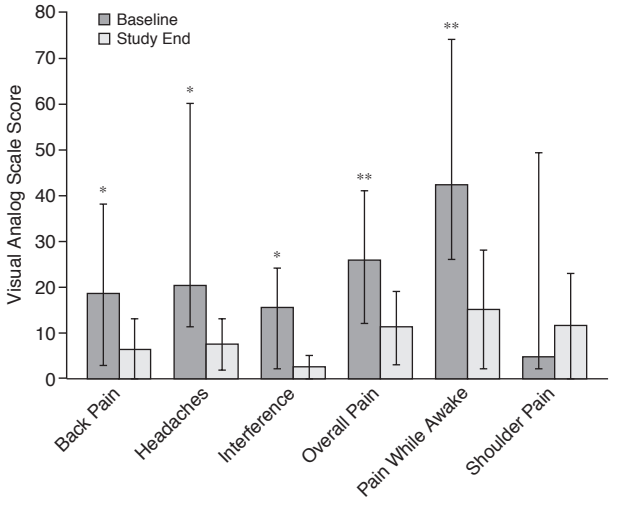
An LOCF analysis of the change in vasomotor symptoms and sleep scores was also conducted in participants who completed at least 2 weeks of open-label duloxetine treatment (N = 19). Results of the LOCF analysis were consistent with those of the completer analysis. There was a statistically significant improvement in vasomotor symptoms on the GCS vasomotor subscore ($p < .001$) and in sleep quality on the PSQI ($p = .002$).

Pain improved in all domains examined ($p < .05$ for all comparisons) except for pain occurring specifically in the shoulder (Figure 3). After 8 weeks of treatment, pain measures (except for shoulder pain) improved by 40.5% to 78.6% from baseline.

Correlations Between Improvement in Menopause-Related Symptoms and Depression, Anxiety, and Pain

Associative analyses were run to examine whether reduction in depression and anxiety symptoms with duloxetine therapy correlated with improvement in other menopause-related symptoms. There was a statistical trend toward a significant correlation between improvement in depression symptoms (MADRS scores) and vasomotor symptoms (HFRDIS, $r_s = 0.50$, $p = .07$). There was also a significant correlation between improvement in anxiety on the BAI and in vasomotor symptoms, as measured by the HFRDIS ($r_s = 0.60$, $p = .02$). However, changes in MADRS and BAI scores did not correlate with improvement in other menopause-related symptoms.

Figure 3. Bar Graphs Showing Median Visual Analog Scale Scores for Pain at Baseline (after 2 weeks of placebo run-in) and at Study End (after 8 weeks of open-label duloxetine therapy) for Study Completers (N = 14)[a,b]



[a]The Y error bars indicate interquartile ranges (25th percentile–75th percentile) for the median scores.
[b]There were statistically significant decreases in all measures of pain, except shoulder pain, from baseline to study end ($p < .05$).
*$p < .05$.
**$p \leq .001$.

DISCUSSION

In the current study, we found that duloxetine therapy improved depression, vasomotor symptoms, and other menopause-related symptoms in postmenopausal women. After excluding women who responded to placebo that was administered as part of a single-blind run-in phase, symptoms of depression, vasomotor symptoms, anxiety, sleep quality, and pain all improved significantly in women who received open-label duloxetine treatment for 8 weeks. Taken together, these data suggest that duloxetine may play an important therapeutic role for postmenopausal women who have major depressive disorder that co-occurs with other symptoms related to the menopause transition.

This study adds to the body of literature that supports the hypothesis that serotonergic antidepressants are effective treatments of depression in postmenopausal women.[12–15] We observed that, like in other studies in this population,[12–15] 80% of women who completed 8 weeks of treatment with duloxetine achieved remission of depression. This response rate is higher than the rate of remission seen in other open-label studies using duloxetine to treat depression in a general population.[35]

To our knowledge, this is the first study to show that an SNRI treats vasomotor symptoms in women with co-occurring depression. Of participants who completed 8 weeks of treatment with duloxetine, 64.3% had no or mild vasomotor symptoms at the end of the study. These data are consistent with SSRI studies in depressed women that also found improvement in vasomotor symptoms.[13,14] Our results are also consistent with trials in nondepressed women showing reduction of vasomotor symptoms with SSRI and SNRI treatment.[8,36] Although studies using estrogen therapy to treat hot flashes have shown a larger therapeutic effect on vasomotor symptoms (78%–96% reduction in symptoms)[37] than SSRI and SNRI, reduced acceptability of hormones since the publication of the results of the Women's Health Initiative has limited their use.[9,10]

In the current study, we observed a trend toward a significant correlation between improvement in mood and in the extent to which hot flashes interfere with daily life. This correlation suggests that women who experience the greatest relief from vasomotor symptoms with treatment may be likely to experience the greatest improvement in mood. Future studies enrolling a larger number of women are required to delineate whether improvement in hot flashes mediates the improvement in mood seen with antidepressants in this population.

We observed that sleep quality improved with duloxetine therapy in a population of postmenopausal depressed women with vasomotor symptoms and significantly reduced sleep quality at baseline. Sleep disturbance is a core symptom of the menopause transition. Poor sleep quality is strongly associated with vasomotor symptoms[38] and with depression.[39] Sleep disturbance has also been hypothesized to mediate the relationship between hot flashes and depression and improvement of postmenopausal depression with treatment.[40] In the current study, improvement in sleep quality did not correlate with improvement of depression, suggesting that changes in sleep do not modulate the effects of antidepressant in this unique population. However, it is also possible that insomnia resulting from duloxetine confounded and diminished the relationship between improvement in sleep and depression, such that a significant effect was not observed. Larger studies that evaluate sleep with objective as well as subjective measures are needed to further elucidate the role of sleep in treating depression during the menopause transition.

Although anxiety symptoms were not an eligibility criterion, anxiety improved significantly in this population of women with depression and menopause-related symptoms. At the end of the study, all participants had either no or mild symptoms. Limited attention has been paid to anxiety symptoms in menopause studies. However, anxiety may be an important symptom for many symptomatic menopausal women. Anxiety symptoms co-occur frequently with depression and may have a shared neurobiological basis.[41] Anxiety is also strongly associated with hot flashes.[7] Vasomotor-symptom treatment studies have found that SSRIs reduce anxiety in nondepressed women.[24,42] Given the high rates of comorbidity of depression and anxiety, it will be important to better

understand the relationship between anxiety, depression, and menopause-associated symptoms in future studies.

In this study, pain improved significantly with duloxetine therapy in depressed postmenopausal women with vasomotor symptoms, the majority of whom also had joint pain at baseline. Pain complaints are increased in postmenopausal women,[43] and are reported more commonly by menopausal women who also have depression.[44] Menopause-related pain symptoms may result from estrogen withdrawal.[45] Given the association between depression and pain in postmenopausal women, duloxetine may play a unique role in this population since it has proven efficacy for both the treatment of depression[22] and neuropathic pain syndromes.[23]

The primary limitations of this study are that it is an open-label study with a modest sample size. However, the inclusion of a placebo run-in phase conducted to exclude placebo responders strengthens the study design and reduces the likelihood that the response rate is attributable to a placebo effect. The study is also limited because of the number of women who dropped out after initiating duloxetine. Our assessment of vasomotor symptoms and sleep would have been enriched if we had also administered daily vasomotor symptom diaries and objective measures of sleep, respectively. Follow-up studies using a randomized placebo-controlled design conducted in a larger number of postmenopausal women that incorporate more detailed assessments of menopausal symptoms are needed. Such studies will provide stronger evidence for the effect of treatment on symptoms of depression, vasomotor symptoms, sleep, anxiety, and pain, which may co-occur and cause significant distress for women during midlife.

In summary, we found that open-label treatment with duloxetine treats depression, vasomotor symptoms, and other menopause-related symptoms of anxiety, pain, and sleep in postmenopausal women with depression and vasomotor symptoms. These symptoms frequently co-occur in postmenopausal women and all warrant evaluation when treating postmenopausal women. Given the efficacy of duloxetine in the treatment of depression and pain, this SNRI is an important addition to the array of treatments used by postmenopausal women who experience depression and other menopause-related symptoms.

Drug names: citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), mirtazapine (Remeron and others), quetiapine (Seroquel).

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