Efficacy of Citalopram as a Monotherapy or as an Adjunctive Treatment to Estrogen Therapy for Perimenopausal and Postmenopausal Women With Depression and Vasomotor Symptoms

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Background: Women frequently report depressive and vasomotor symptoms during the menopausal transition. Hormone therapy has been shown to improve some of these symptoms, although its safety as a long-term treatment has been questioned. It is still unclear whether the use of antidepressants alone may alleviate menopause-related mood and vasomotor symptoms or enhance the response observed with short-term use of estrogen therapy.

Method: Perimenopausal and postmenopausal women with depressive disorders (DSM-IV criteria) and menopause-related symptoms received treatment with 20 to 60 mg/day of citalopram alone (N = 22) or adjunctive to estrogen therapy (N = 13). Adjunctive treatment was offered to subjects who had failed to show remission of depression after 4 weeks with estrogen therapy (estradiol [E_2]) alone. Depressive symptoms, menopause-related symptoms, and global clinical improvement were assessed at baseline and at endpoint of adjunctive treatment (8 weeks) or citalopram monotherapy (12 weeks). Remission of depression was defined as a score of < 10 on the Montgomery-Asberg Depression Rating Scale and a score of ≤ 2 on the Clinical Global Impressions scale at endpoint. Data were collected from November 2000 to February 2002.

Results: Twelve women (92.3%) concluded the 8-week adjunctive treatment; 11 subjects (91.6%) achieved full remission of depression. Symptoms that had persisted after an initial 4-week treatment with E_2 alone (e.g., tension, anxiousness, tiredness, and difficulty in concentrating) improved significantly ($p < .05$). Fifteen subjects concluded the treatment with citalopram monotherapy; 13 subjects (86.6%) showed full remission of depression. Anxiety and other somatic complaints had significant improvement ($p < .05$), while there was a trend toward improvement in vasomotor symptoms in those receiving monotherapy ($p = .06$).

Conclusion: Citalopram alone is an efficacious treatment for perimenopausal and postmenopausal women with depression. Citalopram also appears to be efficacious as an adjunctive treatment for depressed subjects who remain symptomatic after treatment with E_2 (i.e., E_2 nonremitters). The role of citalopram monotherapy for the management of vasomotor symptoms warrants further investigation.

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In the United States, more than 1,300,000 women are expected to reach menopause every year.[1,2] The menopausal transition—a period of heightened hormonal variability—is associated with morbidity due to the occurrence of severe vasomotor symptoms, increased risk for osteoporosis, increased sexual dysfunction,[3,4] depressive symptoms,[5–9] and significant psychosocial impairment.[10]

Clinical evidence suggests that estrogen therapy may alleviate depressive symptoms in perimenopausal women. Two recent double-blind, placebo-controlled studies demonstrated significant antidepressant benefit associated with the use of transdermal estradiol (E_2) in perimenopausal women with major depressive disorders.[11,12] Existing data, however, suggest increased risk of adverse events, prominently with long-term (greater than 5 years') combined use of estrogen and progesterone.[13,14]

The recent controversy involving hormone therapy will not prevent some women from continuing to opt for estrogen as a short-term strategy to alleviate menopause-related symptoms and to improve quality of life. Although

estrogen appears to be particularly helpful during the perimenopausal and early postmenopausal years, its use may not result in full remission of symptoms.[15,16]

More recently, novel alternatives to hormonal interventions have been sought, including herbal supplements and antidepressants.[17,18] Few studies have attempted to determine the prevalence of antidepressant use and its efficacy for menopausal women suffering from depressive and other menopause-related symptoms.[19] Others have examined retrospectively the antidepressant response to selective serotonin reuptake inhibitors among menopausal women with and without concomitant use of hormone therapy, with mixed results.[20,21] The existing literature on use of antidepressants as an adjunctive strategy for women who failed to achieve a satisfactory response with hormonal treatment is particularly sparse.[22]

In the present study, we examine the efficacy of citalopram for the treatment of depression and menopause-related symptoms in subpopulations of perimenopausal and postmenopausal women. The efficacy of citalopram is examined either as a monotherapy for women without concomitant use of estrogen therapy or as an adjunctive strategy to estrogen therapy in women who failed to achieve remission of depression with estrogen alone.

METHOD

This report describes 2 studies conducted on a population of women with depressive disorders and other menopause-related symptoms. Thirty-five perimenopausal and postmenopausal women were consecutively recruited to examine (1) the efficacy of citalopram as an adjunctive treatment for those who remained depressed following a 4-week treatment with transdermal E_2 alone (N = 13) and (2) the efficacy of citalopram as a monotherapy (N = 22). Study procedures were fully explained to all participants, who then signed a written consent form. The study protocols were reviewed and approved by the Internal Review Board at Massachusetts General Hospital. Data were collected from November 2000 to February 2002.

Perimenopausal status was defined as having irregular cycles or amenorrhea for less than 12 months; postmenopausal status was defined as having amenorrhea for 12 or more months. All study subjects presented with serum levels of follicle-stimulating hormone > 20 IU/L, suggestive of declining ovarian function.

The Structured Clinical Interview for DSM-IV (SCID) was administered to all participants for the diagnosis of depressive disorders.[23] A semistructured interview was used to collect demographic data regarding menstrual and reproductive history (age at menarche, history of premenstrual symptoms, previous use of oral contraceptives or hormone therapy). Severity of depressive symptoms was assessed with the Montgomery-Asberg Depression Rating Scale (MADRS)[24] and the Beck Depression Inventory (BDI)[25] at study entry and at each study visit (every 4 weeks). A diagnosis of depressive disorder (SCID) and MADRS total score > 13 were required prior to enrollment to study 2 (citalopram monotherapy), and for the short-term treatment with E_2 that preceded study 1. Menopause-related symptoms were assessed at each study visit with the Greene Climacteric Scale (GCS).[26] This scale provides both total scores and subscores of psychological (anxiety, depression), physical (e.g., muscle and joint pains, headaches), and vasomotor symptoms (hot flashes, night sweats). Its predict and construct validity have been tested and established in several research studies.[27,28] The Clinical Global Impressions-Global Improvement scale (both the investigator [I-CGI] and patient [P-CGI] versions)[29] was administered at each study visit. Subjects also completed hot flash diaries throughout their participation in the study.

Study 1: Citalopram as an Adjunctive Treatment

Subjects were considered eligible for this study if they failed to show full remission of depression (defined as total MADRS score < 10 and CGI score ≤ 2) after a 4-week open treatment with transdermal E_2 alone (100 μg/day of E_2).[30] Those who reported remission of depression after a 4-week treatment with E_2 (35% [7/20]) were not eligible for study 1 and were followed while using estrogen alone until completion of a 12-week therapy (data not shown).

Thirteen subjects aged 40 to 60 years (3 perimenopausal, 10 postmenopausal) who did not achieve full remission of depression with E_2 treatment were accessioned into an 8-week open treatment with citalopram (20–60 mg/day) as an adjunctive treatment. Subjects continued to use transdermal matrix adhesive systems (once-weekly application), containing 7.6 mg of E_2, and designed to release 100 μg/day of 17β-E_2 continuously on application. Citalopram was added to the treatment; initially, 20 mg/day for 4 weeks. Dosing could be adjusted up to 60 mg/day by the study investigator at each study visit for those who did not achieve remission of symptoms or had a CGI score ≥ 3 at lower doses. Depressive symptoms, menopause-related symptoms, and global improvement were reassessed after 4 and 8 weeks of treatment with E_2 and citalopram. Remission of depression was defined as MADRS score < 10 and CGI score ≤ 2 (both patient's [P-CGI] and investigator's [I-CGI] versions) at week 8.

All subjects received unopposed E_2 during study 1. Hence, a 14-day progestogen phase (micronized progesterone; 200 mg/day) was added after treatment completion. Treatment with citalopram was maintained during the progestogen phase. Subjects were then reassessed to examine the impact of adding progesterone on mood symptoms.

Study 2: Citalopram as a Monotherapy

This study included 22 women (15 perimenopausal, 7 postmenopausal) aged 40 to 60 years who presented with

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Table 1. Characteristics at Study Entry of Subjects Recruited to Receive Citalopram as an Adjunctive Treatment (study 1) or as a Monotherapy (study 2)

Characteristic	Study 1 (N = 13)		Study 2 (N = 22)
Race, N (%)[a]			
White	9 (69.2)		12 (54.5)
Black	2 (15.4)		6 (27.3)
Others (combined)	2 (15.4)		4 (18.2)
Marital status, N (%)[a]			
Never married	2 (15.4)		4 (18.2)
Married	3 (23.0)		9 (40.9)
Divorced/widowed	8 (61.6)		9 (40.9)
Education, N (%)[a]			
≤ High school	3 (23.0)		4 (18.2)
> High school	10 (77.0)		18 (81.8)
Employed outside the home, N (%)[a]	12 (92.3)		18 (81.8)
Prior use of oral contraceptives or hormone replacement therapy, N (%)[a]	7 (53.8)		9 (40.9)
History of premenstrual symptoms, N (%)[a]	4 (30.8)		7 (31.8)
Depressive disorder (DSM-IV), N (%)[a]			
Major depressive disorder	8 (61.6)		12 (54.5)
Minor depressive disorder	3 (23.0)		4 (18.2)
Dysthymic disorder	2 (15.4)		6 (27.3)
Age, median (range), y[b]	51 (45–57)		50 (40–57)
Age at menarche, median (range), y[b]	13 (11–17)		13 (9–19)
	Before E_2	After E_2	
MADRS score, median (range)[b,c]	21 (16–32)	15 (11–31)	23 (14–33)
BDI score, median (range)[b,c]	20 (17–32)	18 (11–23)	20 (12–35)
GCS score, median (range)[b,c]	24 (3–44)	15 (4–39)	20 (3–36)
CGI score, median (range)[b,c]	4 (3–5)	4 (3–4)	4 (3–5)
No. of vasomotor episodes/month, median (range)[b,c]	49 (4–315)	24 (5–269)	54 (0–235)

[a]Nonsignificant differences between populations of studies 1 and 2 ($p > .05$ for all comparisons); chi-square tests (Pearson or Fisher tests).
[b]Nonsignificant differences between populations of studies 1 and 2 ($p > .05$ for all comparisons); Mann-Whitney tests.
[c]Statistical comparisons are between median MADRS, BDI, GCS, CGI scores, and vasomotor episodes at study entry (study 2) and before treatment with E_2 (study 1). "After E_2" indicates the scores recorded after 4 weeks of E_2 treatment, before the beginning of citalopram treatment.
Abbreviations: BDI = Beck Depression Inventory, CGI = Clinical Global Impressions scale, E_2 = estradiol, GCS = Greene Climacteric Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

depressive disorders (diagnosis based on SCID interview; MADRS total score > 13 at study entry) and were not using any form of hormone therapy. Subjects entered into a 12-week open trial with citalopram. All subjects initiated treatment with 20 mg/day for 4 weeks, with dosing adjusted up to 60 mg/day by the study investigator at each study visit on the basis of remission and/or response at lower doses. MADRS, GCS, I-CGI, and P-CGI administration was repeated after 4, 8, and 12 weeks of treatment with citalopram. Remission of depression was defined as MADRS score < 10 and I-CGI/P-CGI score ≤ 2 at week 12.

Analytic Plan

Differences in MADRS, BDI, and GCS scores and total number of hot flashes from baseline to endpoint were assessed with the Wilcoxon signed rank test. Chi-square methods for discrete measures (or Fisher exact test for small samples) and nonparametric procedures (Mann-Whitney tests) for continuous measures were used to examine the relationship between demographic characteristics, menstrual and reproductive history, and psychiatric history in women with and without response to citalopram as an adjunctive treatment (study 1) or as a monotherapy (study 2). Spearman correlation coefficients (r_s) were calculated for changes in MADRS, BDI, and GCS scores and subscores from baseline to endpoint. Statistical significance was established at the $\alpha = .05$ level for all analyses.

RESULTS

Sample Characteristics

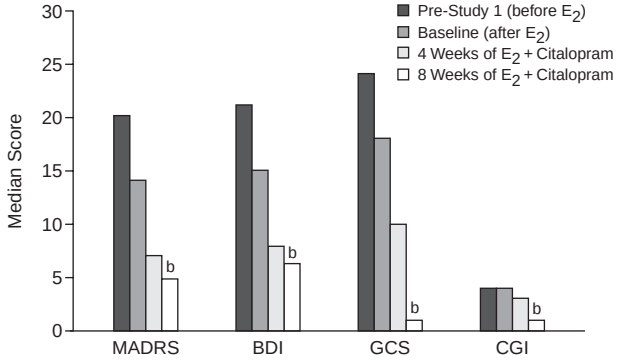
Baseline characteristics of subjects enrolled in studies 1 and 2 are outlined in Table 1. Overall, most women were white, divorced, had a partial or completed college education, worked outside the home, suffered from a major depressive episode, and presented with other menopause-related symptoms, including hot flashes. There were no significant differences between subpopulations enrolled for study 1 and study 2 (see Table 1).

Treatment Outcome

Study 1: citalopram as an adjunctive treatment. Twelve women (92.3%) completed the 8-week adjunctive treatment with citalopram. One subject dropped out because of significant dizziness. Study completers had a median MADRS score of 7 (range, 0–12) after 4 weeks of combined treatment and a median MADRS score of 5 (range, 0–12) after completing 8 weeks of treatment. These scores represented significant improvement compared with depressive scores noted at study entry ($z = -3.11$, $p < .01$). Additionally, the improvement was consistent with that reported by the subjects (changes in BDI scores) ($r_s = 0.92$, $p < .01$). Remission of depression (MADRS score < 10 and I-CGI score ≤ 2) was achieved by 11 (91.6%) of 12 of those who completed 8 weeks of combined treatment. Nine subjects had achieved remission of depression after only 4 weeks of treatment with E_2 and citalopram. The overall improvement observed in I-CGI scores and in P-CGI scores was also significant ($p < .01$) **(**Figure 1**)**.

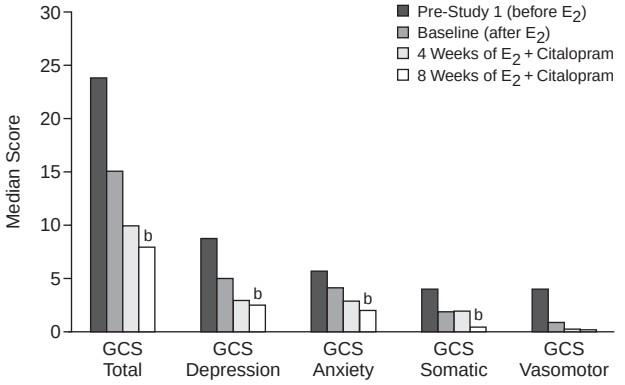
There were no significant differences ($p > .05$ for all comparisons) between women who did and did not achieve remission of depression with respect to demographic characteristics (age, marital status, education, working outside the home), menstrual and reproductive history (age at menarche, menopausal status, history of premenstrual symptoms, prior use of contraceptives or hormone therapy), or subtypes of depressive disorders.

Figure 1. Study 1: Changes in Depressive Symptoms (median MADRS scores, median BDI scores), Menopause-Related Symptoms (median GCS scores), and Median CGI Scores[a]



[a]Baseline scores were obtained after subjects failed to achieve remission of depression with 4 weeks of E_2 alone (pre-study 1); endpoint represents 8 weeks of adjunctive treatment with E_2 plus citalopram (data in figure are those of study completers; N = 12).
[b]$p < .01$ for all changes from baseline to endpoint (Wilcoxon test).
Abbreviations: BDI = Beck Depression Inventory, E_2 = estradiol, CGI = Clinical Global Impressions scale, GCS = Greene Climacteric Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Study 1: Changes in Median GCS Total Scores and Subscores for Depression, Anxiety, Vasomotor, and Somatic Symptoms[a]



[a]Baseline scores were obtained after subjects failed to achieve remission of depression with 4 weeks of E_2 alone (pre-study 1); endpoint represents 8 weeks of adjunctive treatment with E_2 plus citalopram (data in figure are those of study completers; N = 12).
[b]$p < .05$ for all changes from baseline to endpoint (Wilcoxon test), except for vasomotor subscores ($p = .29$).
Abbreviations: E_2 = estradiol, GCS = Greene Climacteric Scale.

Treatment with E_2 and citalopram was well tolerated; the most common adverse events reported were abnormal bleeding (N = 2) and dizziness (N = 2). The mean ± SD weight gain after 8 weeks with citalopram plus E_2 was 0.7 ± 5.7 lb (0.3 ± 2.6 kg) (range, –11 to 15 lb [–5 to 7 kg]), which represented a nonsignificant variation from study entry ($z = –0.66$, $p = .51$).

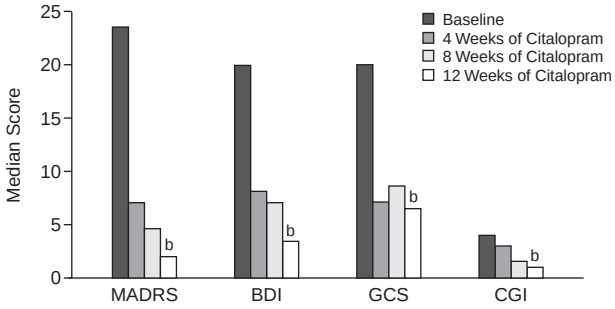
There was a significant improvement in menopause-related symptoms when GCS scores at study entry (after E_2 treatment, median = 15.0; range, 4–39) and after 8 weeks of combined treatment (median = 8.0; range, 2–21) were compared ($z = –2.72$, $p < .01$). Adjunctive treatment with citalopram also resulted in significant improvement of GCS subscores for depression, anxiety (e.g., tension, anxiousness, tiredness, and difficulty in concentrating), and somatic symptoms ($p < .05$). Changes in GCS subscores for vasomotor symptoms, however, were not significant ($z = –1.05$, $p = .29$) (Figure 2). There was no significant correlation of changes in depressive symptoms (MADRS scores) with menopause-related symptoms (GCS scores [$r_s = 0.34$, $p = .24$]) or, more specifically, with decrease in GCS vasomotor subscores ($r_s = –0.02$, $p = .95$).

Seven (77.7%) of 9 subjects who completed the hot flash diaries had a reduction greater than 50% in total number of vasomotor episodes per month after adjunctive treatment with citalopram. Overall, the total number of vasomotor episodes per month decreased substantially (number after treatment with E_2 alone, median = 24; range, 5–269; number after adjunctive treatment with citalopram, median = 5; range, 0–269), although this change did not reach statistical significance ($z = –1.72$, $p = .08$).

Progesterone had no significant effect on mood when added to treatment with E_2 and adjunctive citalopram. Women who completed the progestogen phase (N = 9) did not show significant differences in MADRS scores ($z = –1.123$, $p = .26$)

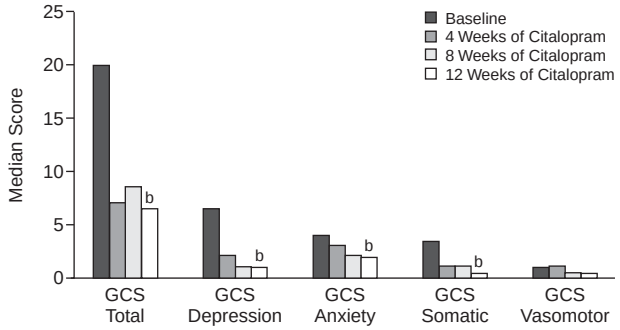
Study 2: citalopram as a monotherapy. Fifteen women (68.2%; 9 perimenopausal, 6 postmenopausal) completed the 12-week treatment with citalopram alone. Subjects who did not complete the study treatment reported "confusion" (N = 2), nausea (N = 2), dizziness (N = 1), lack of efficacy (N = 1), and somnolence (N = 1) as reasons for treatment discontinuation. Analyses of changes in MADRS and GCS scores took into account the last observation carried forward of those who completed at least 1 follow-up visit (N = 17). Median MADRS scores declined from 23.5 (range, 13–33) to 7.0 (range, 2–17) after 4 weeks of treatment with citalopram (20 mg/day) and to a median MADRS score of 4.5 (range, 1–16) after 8 weeks of treatment with citalopram (median dosing = 30 mg/day, SD = 7.7). After 12 weeks of treatment, median MADRS score was 2.0 (range, 0–13; median citalopram dosing = 40 mg/day, SD = 11.4) ($z = –3.11$, $p < .01$) **(**Figure 3**)**. The improvement noted was consistent with that reported by the subjects (changes in BDI scores) ($r_s = 0.86$, $p < .01$). Remission of depression (MADRS score < 10 and I-CGI score ≤ 2) was achieved by 13 (86.6%) of 15 of those who completed 12 weeks of treatment with citalopram. The overall improvement observed in I-CGI scores and in P-CGI scores was significant ($p < .01$). No significant differences were observed between women who did and did not achieve remission of depression with citalopram monotherapy with respect to

Figure 3. Study 2: Changes in Depressive Symptoms (median MADRS scores; median BDI scores), Menopause-Related Symptoms (median GCS scores), and Median CGI Scores[a]



[a]Baseline scores were obtained before subjects initiated treatment with citalopram alone. Data provided include subjects who had at least 1 follow-up visit (LOCF; N = 17).
[b]$p < .05$ for all changes from baseline to endpoint (Wilcoxon test).
Abbreviations: BDI = Beck Depression Inventory, CGI = Clinical Global Impressions scale, GCS = Greene Climacteric Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 4. Study 2: Changes in Median GCS Total Scores and Subscores for Depression, Anxiety, Somatic, and Vasomotor Symptoms[a]



[a]Baseline scores were obtained before subjects initiated treatment with citalopram alone. Data provided include subjects who had at least 1 follow-up visit (LOCF; N = 17).
[b]$p < .05$ for all changes from baseline to endpoint (Wilcoxon test), except for vasomotor subscores ($p = .06$).
Abbreviations: GCS = Greene Climacteric Scale, LOCF = last observation carried forward.

demographic characteristics, menstrual and reproductive history, or subtype of depressive disorder ($p > .05$ for all comparisons).

The mean ± SD weight gain observed after 12 weeks with citalopram was 1.8 ± 2.7 lb (0.8 ± 1.2 kg) (range, –3 to 6 lb [–1 to 3 kg]), which did not represent a significant variation when compared with weight observed at study entry ($z = –2.02$, $p = .08$). With respect to other menopause-related symptoms, there was a significant reduction in median GCS scores from study entry (20.0; range, 3–36) to the endpoint (6.5; range, 0–18) ($z = –2.92$, $p < .01$). For example, GCS subscores for anxiety (e.g., fast heartbeat, tension, anxiousness, panic-like symptoms, difficulty in concentrating) and somatic symptoms (e.g., faintness, joint pains, headaches, breathing difficulties) showed significant improvement ($p < .05$) after 12 weeks of treatment with citalopram. There was a trend toward significance in changes of GCS subscores for vasomotor symptoms ($z = –1.84$, $p = .06$) **(**Figure 4**)**.

Among those subjects who completed the hot flash diaries, 9/15 (60%) showed a reduction greater than 50% in the total number of vasomotor episodes per month. Overall, there was a reduction in the total number of episodes per month from baseline (median = 54; range, 0–235) to study completion (median = 19; range, 0–275), although this reduction was not statistically significant ($z = –0.98$, $p = .32$).

DISCUSSION

Our findings from these 2 open clinical trials demonstrated improvement of depression and other menopause-related symptoms with the use of citalopram as a monotherapy or as an adjunctive treatment for "E_2 nonremitters." In a preliminary study, the use of an antidepressant (mirtazapine) demonstrated efficacy for women who presented with major depression despite the previous use of hormone therapy.[22] However, in that study, women reported different durations of hormone therapy, with various hormone preparations included in the cohort studied. In our study, depressed women who were eligible to receive adjunctive treatment with citalopram had failed to achieve full remission of depression, despite the use of a specific type of estrogen preparation (transdermal E_2) known to be efficacious for menopausal depression.[11,12]

Our findings demonstrate that the addition of citalopram in the treatment of E_2 nonremitters promoted a prompt antidepressant response with relatively low dosages of antidepressant—almost 70% of subjects achieved remission of depression after 4 weeks of adjunctive treatment with citalopram (median dose of 20 mg/day). One could consider that, without a control group with a longer course of E_2 alone, we could not conclude that the improvement noted was due to adjunctive citalopram. However, a previous study suggested that the antidepressant effect with E_2 occurs rapidly (within 4 weeks of therapy) and there is no additional improvement with continuing treatment.[11]

Existing data support the hypothesis that antidepressant response resulting from use of estrogen or antidepressants may be mediated by different mechanisms, rather than a simple down-regulation of postsynaptic receptors.[31,32] These mechanisms include the interaction with nuclear and membrane receptors, ultimately regulating the expression of targeted genes and exerting an effect

in synthesis, release, and metabolism of central nervous system monoaminergic substances.[33] The effect of ovarian hormones on mood in higher primates may be intrinsically related to the serotonin neural system; spayed macaques treated with estrogen and/or progesterone showed a significant increase in citalopram binding to sites of genes that code for the serotonin reuptake transporter (SERT), located in the discrete hypothalamic nuclei.[34]

In study 1, adjunctive citalopram not only promoted a significant improvement in depressive symptoms (assessed by changes in MADRS scores and GCS subscores for depression), but also led to an improvement in GCS subscores of somatic complaints and anxiety. Of note, symptoms of anxiety had not been successfully treated with E_2 alone (data not shown). This finding suggests that a combination of citalopram and E_2 in depressed menopausal women could lead to a greater improvement of well-being across different domains, without promoting significant side effects.

Adjunctive treatment with citalopram did not change significantly the presence or severity of vasomotor symptoms assessed by changes in GCS subscores. However, more than 75% of subjects who completed the hot flash diaries noted a reduction greater than 50% in their frequency of vasomotor episodes. We hypothesize that the small sample size studied and the initial improvement of vasomotor symptoms obtained with E_2 alone (Table 1) reduced the likelihood of observing further benefits of adjunctive citalopram on residual vasomotor symptoms.

Patients treated with citalopram monotherapy (study 2) showed a robust and rapid antidepressant response that was slightly greater than that observed in other open clinical trials for depression with citalopram.[35] We hypothesize that some of the characteristics of the population enrolled in study 2 (e.g., women with various subtypes of depression, mostly of mild-to-moderate severity, who presented with menopause-related somatic symptoms) contributed to such a response. The use of citalopram monotherapy promoted a substantial improvement not only in depressive symptoms, but also in menopause-related symptoms (assessed with GCS scores), which certainly contributed to improvement of overall well-being among these patients. In addition, there was a significant reduction in GCS subscores of anxiety. This finding is noteworthy, given the high prevalence of comorbid anxiety in depressed patients, with serious implications for patients' quality of life and functioning.[36]

Improvement in vasomotor complaints was documented by changes in GCS subscores, although these changes did not reach statistical significance ($p = .06$). The small number of subjects who completed the hot flash diaries (9/15 women) may have limited the value of these findings. Vasomotor symptoms are frequently experienced by menopausal women[37] and can significantly affect their quality of life.[38] It has been postulated that the serotonergic system is intrinsically involved in the thermoregulatory system, and therefore agents with serotonin reuptake–blocking properties could promote a symptomatic relief of such symptoms.[17] Preliminary but promising data suggest that antidepressants may improve hot flashes.[39–41] If further confirmed by well-controlled studies, the improvement of vasomotor symptoms with citalopram may constitute an interesting alternative for those women who opt to not use estrogen or for whom estrogen therapy has been contraindicated.

Although most subjects in studies 1 and 2 showed satisfactory response to treatment and good tolerance, those receiving citalopram alone experienced a slightly greater number of adverse events resulting in study termination compared with those receiving adjunctive citalopram. Further studies should examine the extent to which the concomitant use of E_2 may alleviate some other menopause-related symptoms (e.g., sexual dysfunction due to hypoestrogenism), which could lead to better tolerability of treatment with antidepressants.

These 2 studies have several limitations, including small sample sizes with mixed menopausal status and various depressive subtypes. Subjects were not randomly assigned a priori to receive either E_2 monotherapy (pre-study 1) or citalopram alone (study 2), and there were no placebo-controlled arms. However, the subjects enrolled in both studies were consecutively recruited at the same institution, with the same study procedures and instruments used and with the same research staff involved. In addition, no significant differences were found at baseline between the 2 study populations (Table 1).

The present study was not designed to explore the relative impact of menopausal status on response to treatment with citalopram; perimenopausal and postmenopausal women were therefore not equally represented in both studies. For instance, postmenopausal women constituted the majority of subjects in study 1, as they were less likely to respond to E_2 alone (pre-study 1).[30] Further studies should include larger sample sizes of perimenopausal and postmenopausal women to better examine this factor.

In summary, our preliminary findings support antidepressant efficacy and good tolerability of adjunctive citalopram for women receiving estrogen therapy and of citalopram as a monotherapy. Citalopram also promoted alleviation of somatic complaints and improved residual symptoms of anxiety. The recent data addressing the potential risks involving long-term (greater than 5 years') use of estrogens and progestins[13] strengthen the need for novel hormonal and nonhormonal treatment alternatives for the range of symptoms experienced by the growing population of menopausal patients.

Drug names: citalopram (Celexa), estradiol (Climara, Vivelle, and others), mirtazapine (Remeron), progesterone (Prometrium, Crinone, and others).

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