

Key Words: *paroxetine, women, premenstrual dysphoric disorder, menopause, breast cancer, hot flashes*

Paroxetine Treatment of Mood Disorders in Women: Premenstrual Dysphoric Disorder and Hot Flashes

By *Kimberly A. Yonkers, MD*

ABSTRACT ~ With the relatively recent introduction of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants, increased attention has been focused on the use of antidepressants in the treatment of mood disorders across the female life cycle. Evidence for the efficacy of antidepressants in the treatment of premenstrual dysphoric disorder (PMDD) and hot flashes associated with menopause and breast cancer has emerged. The clinical trials experience with paroxetine and the controlled-release (CR) formulation of paroxetine is reviewed. Psychopharmacology Bulletin. 2003;37(Suppl 1): 135-147

INTRODUCTION

Depression is one of the most significant and disabling illnesses in women. Findings from the World Health Organization's Global Burden of Disease study illustrate the relative ranking of depression as a source of death and disability worldwide and in the United States. Based on 1996 estimates, the leading cause of disability among both men and women in the United States was ischemic heart disease. Motor vehicle accidents were the second most common source of death and disability in men. In sharp contrast, the second largest contributor to disability in women was major depression, which in women was ranked higher than cerebrovascular disease, respiratory tract cancers, osteoarthritis, and breast cancer.¹

For reasons that are not completely understood, women are at increased risk for mood disorders compared with men. Gender differences in the rates of major depression are not apparent in prepubertal children. However, beginning with puberty and continuing through the end of a woman's childbearing years in midlife, the ratio of major depression in females to males is 2:1.^{2,3} There are particular times during a woman's reproductive life, such as pregnancy, the postpartum period, the

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luteal phase of the menstrual cycle, and the perimenopause and menopause, which seem to represent increased periods of vulnerability to depression and other mood disorders.

Recognition of the gender difference in the prevalence of mood disorders has enabled better diagnosis of depression in women. Coincident with these advances was the increasing availability in the past 10 years of safe and effective antidepressants, including the selective serotonin reuptake inhibitors (SSRIs). In keeping with the theme of this supplement, the clinical experience with paroxetine and the controlled-release formulation of paroxetine (ie, paroxetine CR) in the treatment of premenstrual dysphoric disorder (PMDD) and in the treatment of hot flashes is reviewed.

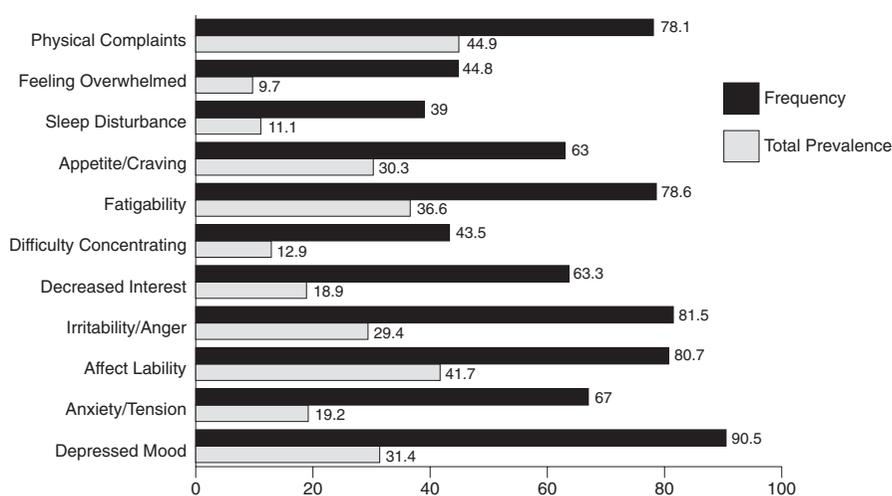
PREMENSTRUAL DYSPHORIC DISORDER

It has been estimated that as many as 25% of women of reproductive age experience untoward mood, anxiety, and physical symptoms prior to the onset of their monthly menstrual cycle.^{4,5} Premenstrual syndrome (PMS) is characterized by mood and somatic symptoms of bloating, weight gain, breast tenderness, and swelling of the extremities. In contrast, PMDD is significantly more debilitating than PMS (Figure 1).

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FIGURE 1

TOTAL PREVALENCE AND FREQUENCY OF SYMPTOMS IN WOMEN WITH PMDD



Total prevalence and frequency of premenstrual syndrome symptoms, defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, in women with a diagnosis of premenstrual dysphoric disorder.

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According to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*), diagnosis of PMDD requires that 5 or more of the following symptoms appear cyclically before menstruation and exhibit remission following the onset of menses: depression, anxiety, mood swings, irritability, decreased interest, difficulty concentrating, fatigue, appetite changes, sleep problems, feeling overwhelmed, and physical symptoms.⁶ Unlike PMS, mood and anxiety symptoms predominate over somatic complaints in patients with PMDD.^{7,8}

Roughly 3% to 8% of women of reproductive age are believed to have PMDD. In one prospectively conducted, longitudinal, community survey of more than 1200 women, the approximate lifetime incidence of PMDD was found to be 7.4%.⁵ The age of onset of PMDD is typically in the mid-20s, and most women do not seek treatment until at least 1 decade later.⁷⁻⁹ The mean duration of premenstrual symptoms is 4.8 days per cycle, ranging up to 2 weeks per month.¹⁰ When taken in the aggregate, these observations underscore the significant personal and family burden that is associated with PMDD.^{7,8}

Paroxetine Treatment of PMDD

The SSRIs are considered first-line therapeutic options for PMDD.¹¹⁻¹³ A growing number of studies with the SSRIs have demonstrated efficacy in the treatment of PMDD using either continuous or intermittent treatment.¹⁴⁻¹⁸ As studied, intermittent therapy entails treatment throughout the luteal phase of the cycle. Women begin medication 14 days before menstruation and continue taking it until the first or second day of menstruation. It is important to differentiate luteal-phase (ie, intermittent) dosing from symptom onset dosing. A meta-analysis of randomized, placebo-controlled studies in patients with PMS or PMDD demonstrated the superiority of SSRIs compared with placebo.¹⁹ Several trials have evaluated the use of paroxetine²⁰⁻²³ and paroxetine CR²⁴ in women with PMDD.

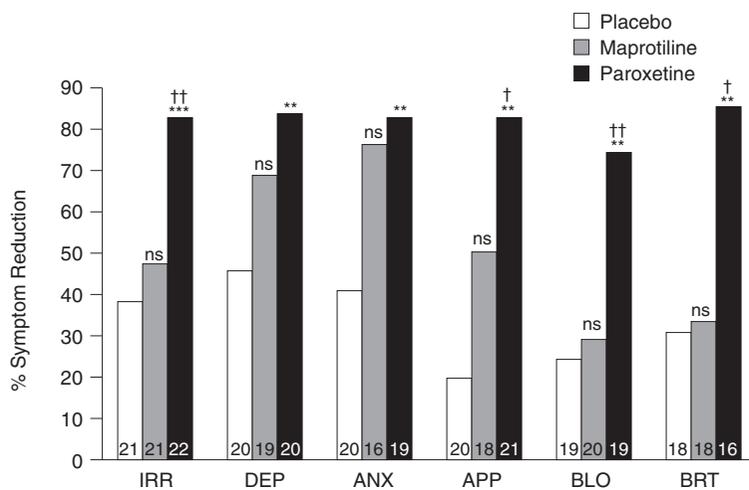
Paroxetine. A double-blind, placebo-controlled trial was conducted in 65 women who fulfilled *DSM-III* criteria for PMDD and exhibited marked irritability and/or depressed mood regularly beginning around ovulation and subsiding shortly after menstruation.²⁰ Before beginning therapy, all patients completed a daily rating score for irritability, depressed mood, tension/anxiety, increased appetite, bloating, and breast tenderness. A visual analogue scale (VAS) was used to record symptom ratings for the next 2 menstrual cycles for use as a baseline. Upon completion of baseline assessments, patients were randomized to receive continuous treatment (ie, daily doses throughout the cycle) with paroxetine 10 to 30 mg, maprotiline 50 to 150 mg, or placebo and continued to rate symptoms daily by VAS for the next 3 menstrual cycles. The 3 study

groups were similar at baseline. Significant reduction of the 6 symptoms of PMDD measured in this trial occurred with paroxetine treatment, whereas maprotiline therapy did not result in significant difference in improvement compared with placebo. All treatment arms, including placebo, improved compared to baseline (Figure 2). Improvement associated with paroxetine use was observed in at least 2 of the 3 treatment cycles for each symptom, except for increased appetite. The self-rated global analysis of change further supported the efficacy of paroxetine treatment of symptoms of PMDD compared with placebo ($P=.0004$) and maprotiline ($P=.03$). In general, both medications were well tolerated. This trial was the first to compare the efficacy of an SSRI with a non-serotonergic antidepressant for use in PMDD.

In an open-label, flexible-dose extension of the Eriksson trial, 18 women continued to receive paroxetine and recorded daily symptom ratings for 10 consecutive menstrual cycles.²² Six patients elected to maintain continuous dosing of paroxetine, 5 chose intermittent therapy during the luteal phase only, and 7 chose a semi-intermittent regimen, during which they

FIGURE 2

PERCENT REDUCTION IN SYMPTOMS OF PMDD IN PATIENTS TREATED WITH PLACEBO, MAPROTILINE, OR PAROXETINE



Percent reduction in premenstrual irritability (IRR), depressed mood (DEP), anxiety (ANX), increased appetite (APP), sense of bloating (BLO), and breast tenderness (BRT) in patients treated with placebo, maprotiline, or paroxetine. Bars represent medians. Within each bar is indicated the number of subjects displaying the symptom in question before treatment and included in the calculation.

** $P < .01$ vs placebo; *** $P < .001$ vs placebo; † $P < .05$ vs maprotiline; †† $P < .01$ vs maprotiline; ns=not significant vs placebo.

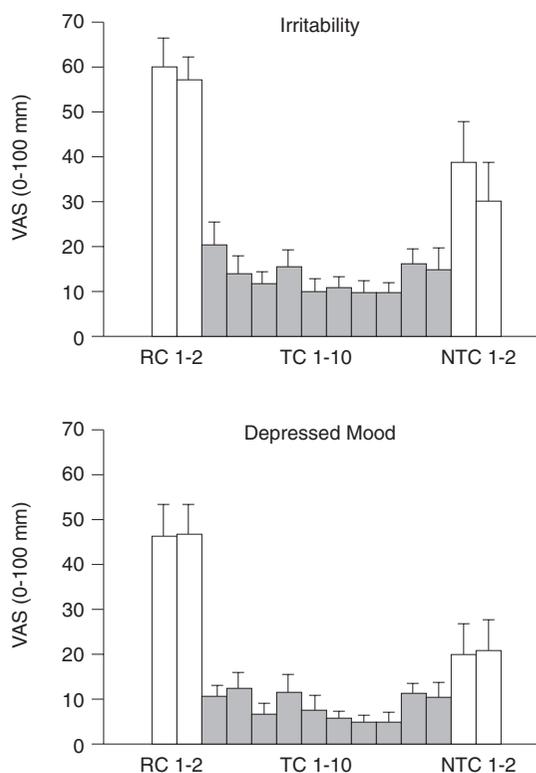
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took medication throughout the cycle, but increased the dose premenstrually relative to the postmenstrual dose. The mean dose of paroxetine during the luteal phase was 17 mg. Regardless of the differences in regimens, paroxetine therapy maintained significant reductions for symptom ratings compared with baseline throughout the 10 menstrual cycles for irritability ($P=.0002$), depressed mood ($P=.0003$) (Figure 3), increased appetite ($P=.0005$), anxiety ($P=.01$), and bloating ($P=.002$). Improvement in breast tenderness was not significantly different than at study entry. Upon discontinuation of paroxetine, patients demonstrated significant relapse for irritability ($P=.04$) and depressed mood ($P=.01$). All patients

FIGURE 3

SELF-RATED IRRITABILITY AND DEPRESSED MOOD DURING THE LUTEAL PHASE OF 2 PRETREATMENT BASELINE REFERENCE CYCLES IN WOMEN WITH PMDD



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Self-rated irritability and depressed mood during the luteal phase of the 2 pretreatment baseline reference cycles (RC 1-2), 10 cycles of paroxetine treatment (TC 1-10), and 2 cycles after medication discontinuation (non-treatment cycles, NTC 1-2).

VAS=visual analogue scale.

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reported improvement in the self-rated global analysis of change and similar side effects were seen as in the previous trial. Half of the 18 patients returned to paroxetine therapy following the study. Of the 9 who did not, 4 believed they had achieved full or partial remission, 4 endorsed side effects, and 1 was pregnant. Although these findings are preliminary given the small cohort size, they suggest efficacy for intermittent therapy and lack of tolerance to paroxetine with longer use.

Another relatively small study compared the efficacy of continuously administered paroxetine (63 patients) with intermittently administered paroxetine (61 patients) and placebo (62 patients) in the treatment of PMDD.²¹ Patients who were randomized to the continuous treatment arm received 20 mg paroxetine daily, and patients in the intermittent treatment arm received 20 mg paroxetine for the last 14 days of the menstrual cycle. Patients were treated for 3 consecutive menstrual cycles and all completed daily symptom diaries. At end point, both continuous and intermittent groups achieved statistically significantly greater improvement on the composite VAS mood score and irritability item compared with the placebo group ($P < .001$). The percentages of responders on the Clinical Global Impressions (CGI) improvement item (defined as very much or much improved) at end point were 84.8% for continuous paroxetine ($P < .001$ vs placebo), 68.1% for intermittent paroxetine ($P < .001$ vs placebo), and 29.8% for placebo.

Further support for use of paroxetine for PMDD is provided by another open-label study conducted in 14 women diagnosed with PMDD based on *DSM-IV* criteria.²³ Qualifying patients underwent a single-blind, placebo treatment cycle and were excluded from continuing if they responded with a CGI score of 3 or lower. Remaining patients were enrolled into the 3-cycle study and were openly treated with paroxetine 10 to 30 mg. Response was measured by Hamilton Rating Scale for Depression (HAM-D) and CGI scores during the luteal phase, along with a Daily Record of Severity of Problems (DRSP). Daily ratings for anxiety, irritability, difficulty sleeping, behavioral dyscontrol, breast tenderness, bloating, and headache during the luteal phase were significantly improved from baseline by the end of the study ($P < .0001$ to $P < .05$). Luteal measurements of HAM-D ($P < .0001$) and CGI ($P < .0002$) scores also improved significantly from baseline. Nine patients achieved a luteal phase HAM-D score of 8 or less, and 8 patients had a CGI score of 2 or less by study completion.

Paroxetine CR. The efficacy of paroxetine CR was evaluated in a randomized, double-blind, placebo-controlled study of 359 women with PMDD.²⁴ Patients were considered eligible for this study if they fulfilled the *DSM-IV* criteria for PMDD and prospectively completed daily rating scales for 2 consecutive menstrual cycles. Eligible patients were

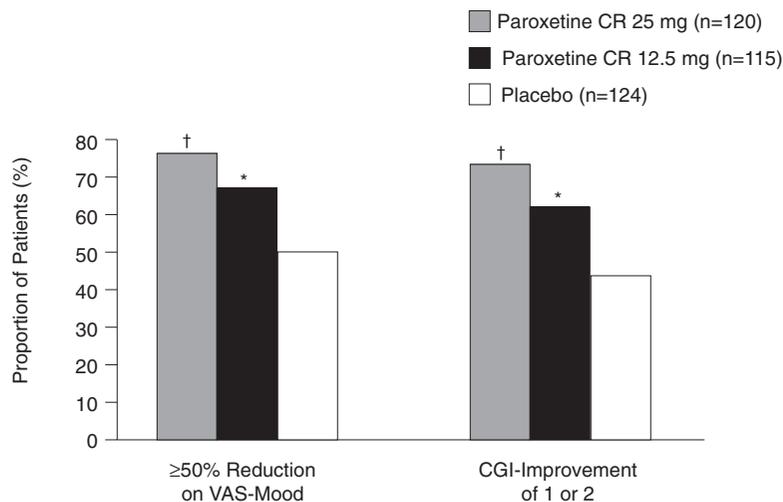
randomized to receive paroxetine CR 12.5 mg (N=115), paroxetine CR 25 mg (N=120), or placebo (N=124) daily for 3 consecutive menstrual cycles. Baseline VAS scores, including depressed mood, irritability, tension, affective lability, and other symptom scores, reflected the severity of PMDD in this population and were similar across treatment groups. Both doses of paroxetine CR resulted in significantly greater improvement in the core VAS mood symptoms compared with placebo. Response, which was defined as a 50% or greater reduction from baseline levels in the VAS mood score, was significantly greater in both active treatment groups, with 76% of patients in the 25-mg paroxetine CR group ($P<.001$ vs placebo) and 67% ($P<.05$ vs placebo) in the 12.5-mg paroxetine CR group responding compared with 50% of patients in the placebo group. Similar improvements over placebo were noted on the CGI Improvement scores of 1 (very much improved) or 2 (much improved) (Figure 4).

MENOPAUSE

Menopause and perimenopause are associated with a wide spectrum of clinical symptoms, including mood instability, hot flashes, night sweats,

FIGURE 4

CONTINUOUS TREATMENT OF PMDD WITH PAROXETINE CR 25 MG OR 12.5 MG OR PLACEBO



Continuous treatment of premenstrual dysphoric disorder (PMDD) with paroxetine controlled-release (CR) 25 mg or 12.5 mg or placebo.

* $P<.05$; † $P<.001$.

CGI=Clinical Global Impressions; VAS=visual analogue scale.²⁴

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vaginal dryness, insomnia, depression, and mood swings. As many as 50% to 80% of women experience one or more of these symptoms as they enter the perimenopausal period.²⁵⁻²⁷ The mean age at onset of menopause among women in the US is 51 years, and the perimenopausal period generally begins 2 to 8 years earlier. Menopause and perimenopause are also times of increased vulnerability to recurrent depression in women with histories of mood disorders.³ There is an increased risk of recurrent major depression in women between the ages of 45 and 54 years, and depression rates decrease in postmenopausal women.²⁸

Hot flashes can be a particularly distressful symptom of the perimenopause, beginning 1 or 2 years before menopause and persisting for up to 5 years. The experience of hot flashes can impair a woman's ability to function at work and in social situations, and can disrupt sleep and self-esteem.^{29,30} Women with breast cancer who are treated with estrogen receptor antagonists also can experience hot flashes, which may be as severe as those associated with perimenopause.^{30,31} Hot flashes are believed to be caused by a disturbance in normal thermoregulatory function that is associated with the estrogen deficiency secondary to cessation of menstruation. The serotonergic system is involved in the pathophysiology of hot flashes whereby activation of 5-HT₂ receptors induces hot flashes experimentally, and treatment with the SSRIs and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) alleviates them in clinical studies.^{29,30} The use of serotonergic agents in this population is of great interest because of concerns about the use of estrogen raised by the results of the Women's Health Initiative trial, which suggest that long-term hormone replacement therapy may be associated with increased risk of cardiovascular disease and breast cancer.³²

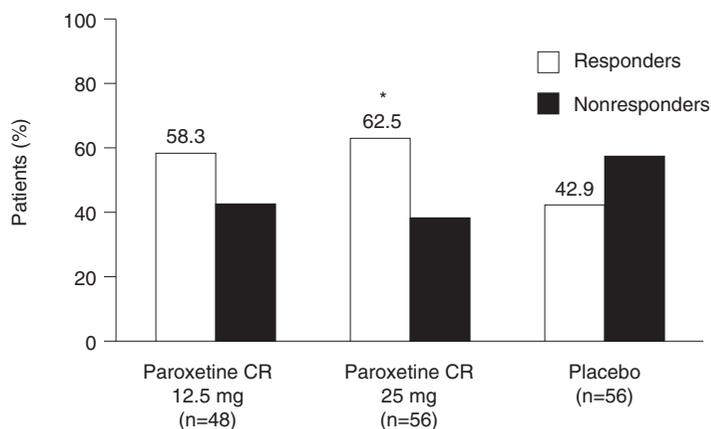
Paroxetine Treatment of Hot Flashes

The use of SSRIs for treatment of menopausal hot flashes or hot flashes in women with breast cancer is relatively new. Two trials have explored the efficacy and safety of paroxetine treatment of hot flashes in women with breast cancer,^{33,34} and a third study assessed the role of paroxetine CR in the treatment of menopausal hot flashes.³⁵

Menopausal Hot Flashes. The efficacy and tolerability of paroxetine CR were evaluated in a 6-week, double-blind, placebo-controlled study of 165 menopausal women.³⁵ Patients were randomized to receive fixed doses of paroxetine CR 12.5 mg or 25 mg or placebo in a 1:1:1 ratio. The primary end point was change from baseline in the hot flash composite score, which is a product of daily hot flash frequency and severity ratings. Mean reductions from baseline in the hot flash composite scores were 62.2% for patients in the paroxetine CR 12.5-mg group ($P=.007$ vs placebo), 64.4% for patients in the paroxetine CR 25-mg group ($P<.03$ vs

FIGURE 5

RESPONSE TO PAROXETINE CR TREATMENT OF MENOPAUSAL HOT FLASHES



Response to paroxetine controlled-release (CR) treatment (12.5 mg or 25 mg) of menopausal hot flashes. Response defined as 50% or greater reduction in mean baseline hot flash score.

* $P=.02$.³⁵

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placebo), and 37% for placebo. Response, which was defined as a 50% or greater reduction in the baseline hot flash composite score, was achieved by 58.3% and 62.5% of patients in the 12.5-mg and 25-mg groups, respectively, compared with 42.9% of patients randomized to receive placebo ($P=.02$ paroxetine CR vs placebo; Figure 5).

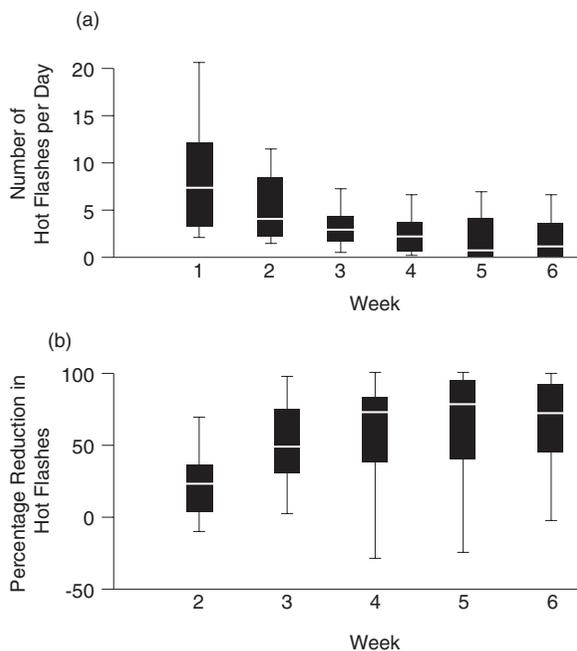
Hot Flashes in Women with Breast Cancer. Stearns and associates³³ enrolled 30 survivors of breast cancer in an open-label trial of paroxetine. Eligible patients experienced hot flashes at least twice daily at screening and were in remission from their breast cancer. Patients completed a daily diary of hot flash frequency and severity for 1 week at baseline prior to initiation of paroxetine therapy. In addition, patients also completed a symptom-assessment questionnaire and quality-of-life rating scale. A 1-week open-label titration of paroxetine 10 mg was conducted to ensure tolerability and assess side effects before beginning daily therapy with a 5-week course of paroxetine 20 mg. Daily diaries were maintained, and symptom assessment and quality of life were measured again at the end of the study. At baseline, patients reported a mean of 8 hot flashes daily, with a mean severity score of 134. At end point, the frequency of hot flashes was reduced by 67% (Figure 6), and 20 patients experienced greater than 50% improvement in hot flash frequency. Mean baseline hot flash severity ratings were reduced by 75% at end point (Figure 7).

Significant improvement also occurred for self-rated depression ($P=.02$), sleep ($P=.0002$), anxiety ($P=.0005$), and quality of life ($P=.04$) by week 6 compared with baseline. Following study completion, 25 women elected to continue paroxetine therapy.

Another open-label study investigated the use of paroxetine for hot flashes in 13 patients with breast cancer.³⁴ Patients underwent a structured diagnostic interview and completed self-report questionnaires on emotional distress, fatigue, and hot flashes. Patients were treated with paroxetine 10 mg daily in the evening for 3 days followed by 20 mg daily in the evening for the remainder of the month. At study completion, patients demonstrated significant improvement in hot flash severity ($P=.002$). All patients had experienced “quite a bit” or “extremely severe” hot flashes at baseline on the Hot Flashes Questionnaire, and only 38% continued to experience that degree of hot flashes at study end point. Sleep quality also improved significantly from baseline, changing from a rating of “fairly bad” to “very good” ($P=.0003$). Although improvement

FIGURE 6

HOT FLASH FREQUENCY DURING PAROXETINE TREATMENT IN WOMEN WITH BREAST CANCER



Weekly summary of hot flash frequency in 27 patients completing the study: (a) average daily number of hot flash episodes; and (b) percent reduction compared to week 1 (baseline).

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in depression scores was not significantly different from baseline at end point, of the 39% of patients meeting criteria for depression at study initiation, only 8% met criteria following paroxetine therapy. The findings of these 2 studies suggest that the use of paroxetine may be of benefit to women with breast cancer and related hot flashes.

CONCLUSION

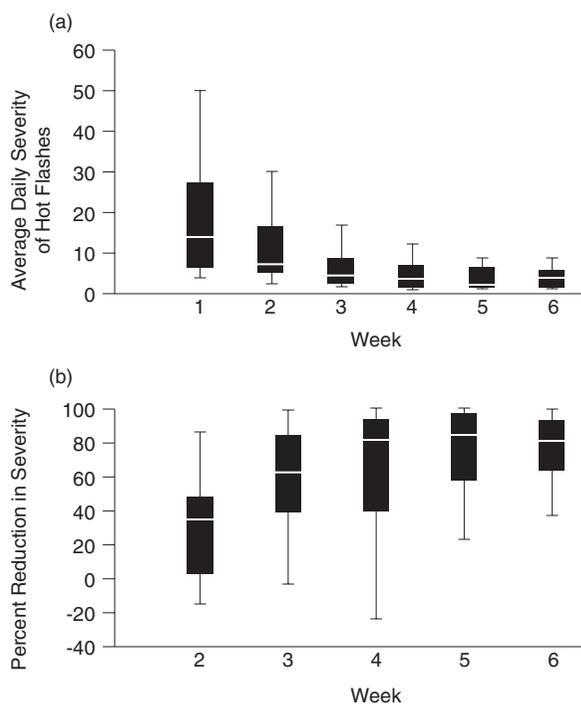
The results of studies of paroxetine and paroxetine CR in the treatment of PMDD and hot flashes associated with menopause and breast cancer represent an advance in women's health care. In women with PMDD, paroxetine and paroxetine CR effectively improve the core symptoms of irritability, depressed mood, and tension during continuous therapy in short-term studies. Longer-term studies are needed to further characterize the utility of this SSRI in the treatment of PMDD. In addition,

FIGURE 7

WEEKLY SUMMARY OF HOT FLASH SEVERITY SCORE IN 26 PATIENTS WITH NONMISSING SEVERITY DATA

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Weekly summary of hot flash severity score in 26 patients with nonmissing severity data: (a) average daily score; and (b) percent reduction compared with week 1 (baseline).

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direct comparative studies are warranted to better identify candidates for continuous vs intermittent SSRI treatment.

Findings from pilot studies also suggest that paroxetine and paroxetine CR reduce the frequency and severity of hot flashes in perimenopausal women and women with breast cancer. Again, additional studies are needed to assess the optimal duration of treatment of hot flashes, particularly in menopausal women. ❀

DISCLOSURE

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