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CLINICAL ARTICLE

Ethinyl estradiol 20 μg/drospirenone 3 mg 24/4 oral contraceptive for the treatment of functional impairment in women with premenstrual dysphoric disorder

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ABSTRACT

Objective: To determine the effects of ethinyl estradiol (EE)/drospirenone in a 24/4 regimen (24 days of active and 4 days of inactive pills) on functional impairment (affecting work, partnership, and social activities) in women with premenstrual dysphoric disorder (PMDD). *Methods:* The present study was a secondary analysis of a double-blind, randomized, parallel-design multicenter trial. Women received EE 20 μg/drospirenone 3 mg (n = 232) or placebo (n = 218) and completed the Daily Record of Severity of Problems (DRSP) scale daily. *Results:* The decrease in mean scores for all 3 DRSP functional impairment items (work, partnership, and social activities) from baseline to cycle 3 mirrored changes in the total DRSP symptom score; the greatest decreases were observed in cycle 1 with further small reductions through to cycle 3. The proportional mean decreases from baseline to cycle 1 for the 3 functional items ranged from 47% to 48%. For all 3 functional items, the mean reductions from baseline to cycle 1 (but not from cycle 1 to cycles 2 and 3) were significantly greater with EE/drospirenone than with placebo ($P<0.05$). *Conclusion:* Ethinyl estradiol 20 μg/drospirenone 3 mg in a 24/4 regimen significantly improved functional impairment in women with PMDD. Symptoms improved in parallel.

1. Introduction

The majority (50–80%) of women of reproductive age experience premenstrual symptoms of at least mild intensity [1]. These symptoms typically occur during the late luteal phase of the menstrual cycle and remit by the end of menstruation [1,2]. Premenstrual syndrome (PMS) is associated with symptoms such as headache, breast tenderness, bloating, and mood changes. In the majority of women, these symptoms do not require medical or psychiatric treatment [3].

Premenstrual dysphoric disorder (PMDD) is a severe form of PMS that usually comprises more distressing affective symptoms such as irritability, mood lability, tension, and dysphoria [3]. The diagnosis of PMDD is made on the basis of strict criteria defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [4]. To receive a diagnosis of PMDD, symptoms—particularly core mood symptoms—must have a marked negative impact on the woman's lifestyle [3].

It is estimated that 3–8% of women of reproductive age are diagnosed with PMDD, but as many as 89% of women with PMDD may go undiagnosed [5]. In addition, there may be another group of women (an estimated 13–18% of those of reproductive age) who experience dysphoric symptoms that result in distress and impairment but do not meet the strict DSM-IV criteria for PMDD [5,6]. The negative effects of PMDD on quality of life, productivity, relationships, and social activities have been documented, and the level of impairment associated with PMDD is similar to that experienced by patients with other major dysphoric disorders [5].

Premenstrual disorders are linked with ovulation and seem to be triggered by the effect of progesterone produced during ovulation. The etiology of premenstrual disorders is unknown, although there is evidence to suggest that the condition is heritable and biologic (as opposed to psychologic) in origin [3]. In addition, women who experience PMS or PMDD seem to have an altered central nervous system response to fluctuations in ovarian sex steroid levels, especially those of progesterone or progesterone metabolites [2,7].

Symptoms of PMDD do not occur during menstrual cycles without ovulation, prior to the onset of menstruation or after menopause [8]. In addition, resolution of PMS symptoms occurs when the hormonal cycle associated with ovulation is interrupted by oopherectomy or hormonal ablation [9,10]. Combined oral contraceptives prevent ovulation and it has been hypothesized that these agents represent a feasible option for the treatment of premenstrual symptoms [11]. However, the affective symptoms of PMS do not seem to respond to treatment with traditional formulations or dosage regimens of oral contraceptives [2,12], and the results of placebo-controlled clinical trials have been disappointing [13,14].

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The efficacy of a combined oral contraceptive for the treatment of premenstrual symptoms is likely to be greatly affected by the progestin component and the dosing regimen [2]. Therefore, the type of progestin used is very important. Drospirenone, an analog of spirolactone rather than testosterone, is a unique progestin that has antiandrogenic and antimineralocorticoid activity, and a long half-life [15]. In addition, drospirenone has been formulated with ethinyl estradiol (EE) in a new dosing regimen whereby each cycle of treatment comprises 24 days of active pills and 4 days of inactive pills (24/4 regimen). Suppression of folliculogenesis has been shown to be more complete with the 24/4 regimen than with an oral contraceptive regimen with a 7-day hormone-free interval [16]. Together, the long half-life of drospirenone and the 24/4 dosing regimen provide more consistent suppression of endogenous 17β-estradiol and hormonal fluctuations [17].

The new combined oral contraceptive formulation, comprising EE 20 μg/drospirenone 3 mg and administered using a 24/4 regimen, has shown superior efficacy to placebo in reducing symptoms associated with PMDD in 2 clinical trials involving 64 and 450 women, respectively [18,19]. Evaluation of the primary outcome in the 2 studies [19] showed that randomization to EE 20 μg/drospirenone 3 mg in a 24/4 regimen was associated with significant reductions in the mean total Daily Record of Severity of Problems (DRSP) symptom score relative to placebo ($P<0.001$). The DRSP consists of 24 questions that are grouped into 11 symptom domains and 3 functional impairment domains.

The present study was a subanalysis of data from the large clinical trial mentioned previously [19]. The aim was to determine the effects of treatment with EE/drospirenone in a 24/4 regimen on functional impairment in patients with PMDD, and to evaluate the temporal relationship between symptoms and functional impairment.

2. Materials and methods

The present study was a secondary analysis of data obtained from of a multicenter, double-blind, randomized, placebo-controlled parallel-design study. The participants were enrolled from 64 centers in the USA and attended 7 assessment visits between January 2001 and February 2004. All protocols were approved by a local or central Institutional Review Board, and all participants provided verbal and written informed consent. Full details of the study methodology have been published previously [19], and are summarized as follows.

Eligible women were aged 18–40 years and had received a diagnosis of PMDD according to the DSM-IV criteria [4]. Those with a history of anxiety, depression, psychotic disorders, or drug/alcohol use disorders in the past 2 years were excluded. All women used barrier contraception throughout the study and underwent 2 consecutive menstrual cycles to record the severity of their symptoms and functional impairment; the DRSP scale was used to confirm diagnoses of PMDD.

Women with a confirmed diagnosis of PMDD were randomized in a 1:1 ratio to receive EE 20 μg/drospirenone 3 mg (Yaz; Bayer, Berlin, Germany) or placebo for 3 treatment cycles. Treatment was started on day 1 or 2 of the menstrual cycle and was continued until day 24; the last 4 days of the treatment cycle consisted of inert placebo tablets for both groups.

The 7 assessment visits consisted of 1 screening visit, 2 qualification visits (1 during each run-in cycle), 3 treatment visits (1 during each treatment cycle) and an end-of-treatment visit.

The women completed the DRSP scale daily during the study, rating the severity of symptoms or functional impairment on a scale of 1 (not at all) to 6 (extreme); thus, low scores indicate less severe symptoms or less severe functional impairment. For the present subanalysis, the mean total score for the first 21 DRSP items (symptoms) was compared with the mean scores for the last 3 items (functional impairment: specifically, impairment of work productivity [item 22], interference with social activities [item 23], and interference with relationships [item 24]). The average DRSP symptom scores and the individual functional item impairment scores for the last 5 days before menses during each treatment cycle were compared with the average respective scores from both run-in cycles (baseline).

Differences between the 2 treatment arms in the mean total DRSP symptom score and the 3 functional impairment scores were estimated using a 2-sample t test. Within-treatment comparisons with baseline were performed using the paired t test. Data were analyzed with SAS (SAS Institute, Cary, NC, USA).

3. Results

In total, 450 women were randomized to receive EE/drospirenone (n = 232) or placebo (n = 218). One woman from the active treatment group withdrew from the study before taking any medication and was not included in the full-analysis set and, thus, the intent-to-treat analysis included 449 women. The study was completed by 161 (69.4%) women in the EE/drospirenone group and by 167 (76.6%) women in the placebo group; 71 (30.6%) and 51 (23.4%) women in the EE/drospirenone and placebo treatment groups, respectively, withdrew from the study prematurely. The proportion of women who were at least 75% compliant with treatment was 90.9% (n = 210) for EE/drospirenone and 89.9% (n = 196) for placebo. The mean compliance with EE/drospirenone and placebo was 97.6% and 97.9%, respectively.

Table 1
Demographic and baseline characteristics.[a]

Variable	Placebo (n = 218)	EE/drospirenone (n = 231)
Age, y	32.0 ± 5.48	31.0 ± 5.63 [b]
Body weight, kg	68.43 ± 12.89	70.64 ± 13.20
Height, cm	166.40 ± 7.04	165.95 ± 6.19
BMI [c]	25.11 ± 4.29	26.09 ± 4.56[d]
Regular menstrual cycles	217 (99.5)	229 (99.1)
Cycle length, d	28.8 (25–35)	28.7 (25–37)
Duration of menstrual bleeding, d	5.2 ± 1.4	5.1 ± 1.2
Normal average intensity of bleeding	142 (65.1)	151 (65.4)
Dysmenorrhea	144 (66.1)	155 (67.1)
Current smokers	36 (16.51)	29 (12.55)

Abbreviations: BMI, body mass index; EE, ethinyl estradiol.
[a] Values are given as mean ± SD, mean (range), or number (percentage).
[b] $P<0.048$ versus placebo.
[c] Calculated as weight in kilograms divided by the square of height in meters.
[d] $P<0.015$ versus placebo.

Table 2
Mean reduction from baseline in DRSP scores during treatment with placebo and ethinyl estradiol/drospirenone.[a,b]

Treatment cycle	Placebo (n = 218)	EE/drospirenone (n = 231)	P value[c]
DRSP total score			
1	34.2	44.6	0.001
2	40.5	47.9	0.018
3	41.0	49.7	0.015
Work impairment			
1	36.0	47.3	0.002
2	44.2	49.4	0.119
3	45.2	50.9	0.122
Social impairment			
1	37.6	47.2	0.016
2	44.9	50.1	0.154
3	44.6	51.7	0.099
Partnership impairment			
1	36.5	47.6	0.008
2	44.7	51.4	0.119
3	44.4	51.9	0.112

Abbreviations: DRSP, Daily Record of Severity of Problems.
[a] Values are given as percentage.
[b] Expressed as change in percentage from baseline mean.
[c] Listed for individual percentage changes.

Overall, the baseline characteristics were similar in the EE/drospirenone and placebo treatment groups (Table 1), although the mean age (31.0 years versus 32.0 years; $P=0.048$) and the mean body mass index (calculated as weight in kilograms divided by the square of height in meters; 26.1 versus 25.1; $P=0.015$) were higher in EE/drospirenone recipients than in those receiving placebo. Approximately 80% of women in each treatment group (184 [79.7%] in the EE/drospirenone arm and 167 [76.6%] in the placebo arm) took concomitant medication during the study. Medications or supplements taken by at least 10% of women in either treatment group included ibuprofen, multivitamins, paracetamol, and paracetamol combinations (excluding psycholeptics).

Data pertaining to the mean reductions from baseline in the DRSP scores (total symptom score and individual functional impairment scores) during the 3 treatment cycles are summarized in Table 2. In the EE/drospirenone group, the mean total DRSP symptom score decreased by almost 50% (from 77.4 to 42.9) during treatment cycle 1 ($P<0.0001$), with a further reduction to 37.6 by cycle 3 ($P<0.0001$ versus baseline) (Fig. 1). The changes from baseline to treatment cycle 3 in the mean scores for all 3 functional impairment items (work, social activities, and relationships) mirrored the changes observed in the mean total DRSP score, with the greatest proportional decrease in the mean functional impairment scores seen during cycle 1, followed by further small reductions during cycles 2 and 3. The proportional decreases from baseline to treatment cycle 1 for the 3 functional impairment items ranged from 47% to 48%, whereas corresponding score decreases from treatment cycle 1 to treatment cycle 3 ranged from 9% to 12% (Fig. 1).

In the placebo group, the mean total DRSP symptom score was reduced from 78.1 at baseline to 47.3 by treatment cycle 3 ($P<0.0001$). Reductions from baseline to treatment cycle 3 with placebo were also observed in the functional impairment scores relating to work productivity (from 3.94 to 2.25), social activities (from 3.83 to 2.21), and relationships (from 4.14 to 2.35). The mean reductions from

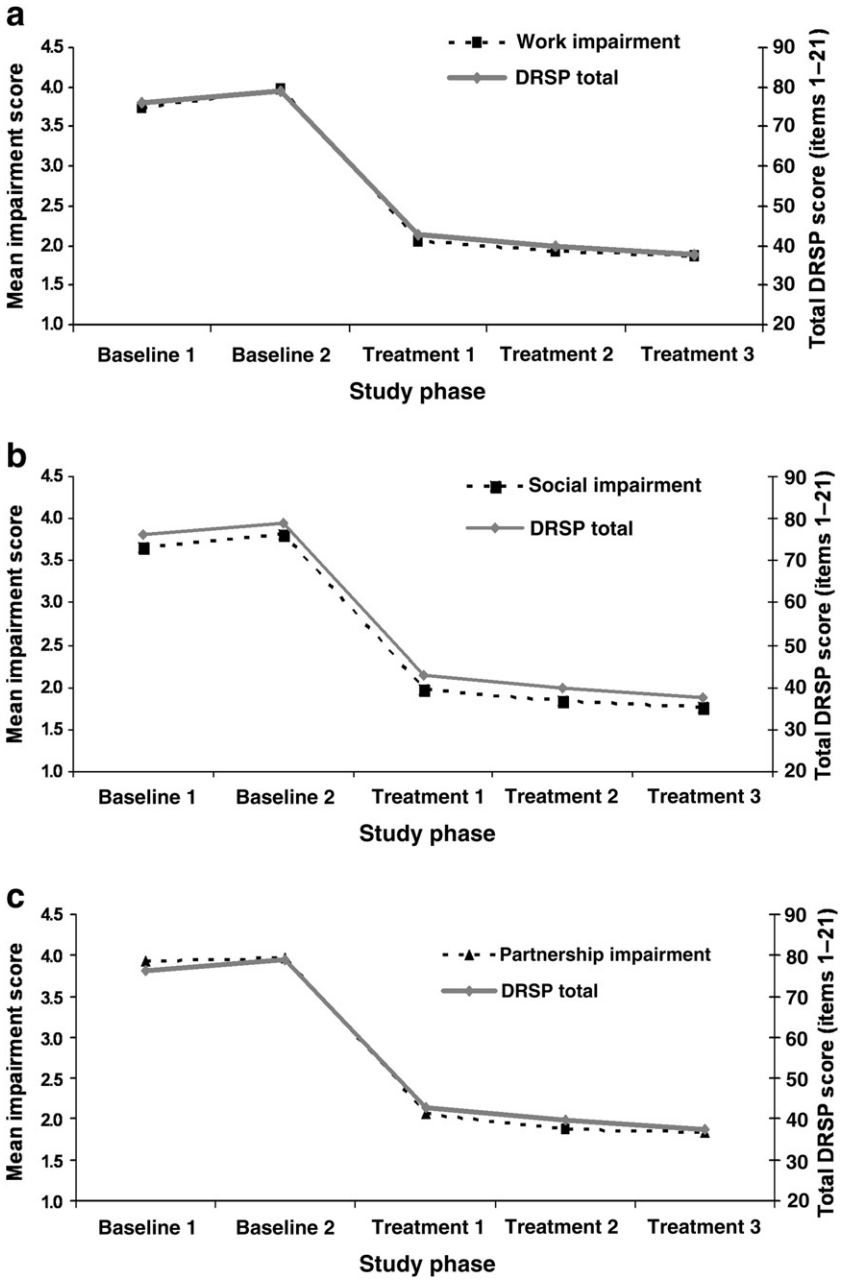

Fig. 1. Association of changes in premenstrual dysphoric disorder symptoms (DRSP items 1–21) with (a) work impairment (DRSP item 22); (b) social impairment (DRSP item 23); (c) partnership impairment (DRSP item 24) in women receiving ethinyl estradiol/drospirenone (n = 231). Abbreviation: DRSP, Daily Record of Severity of Problems.

baseline to cycle 1 were significantly greater in the EE/drospirenone group than in the placebo group for all 3 functional impairment items ($P<0.05$); the subsequent decreases from baseline to cycles 2 and 3 were not significantly different between the 2 groups ($P>0.05$). Nonetheless, the adjusted mean differences over 3 treatment cycles between the 2 treatments were statistically significant in favor of EE/drospirenone ($P\leq 0.003$ versus placebo for all comparisons).

4. Discussion

The present subanalysis of a large, randomized clinical trial shows that PMDD symptoms overall and PMDD-related functional impairment (as measured by the DRSP) improved to a similar extent following active treatment with EE 20 μg/drospirenone 3 mg in a 24/4 regimen for 3 treatment cycles. The greatest improvement occurred during cycle 1, with the improvement continuing at a lower rate over the next 2 cycles.

PMDD is a debilitating condition, and to satisfy the strict DSM-IV criteria for a diagnosis of PMDD, symptoms must have a marked negative impact on a woman's lifestyle [3]. This—along with the monthly, unremitting occurrence of symptoms—means that PMDD has a significant adverse effect on daily functioning, lifestyle, and relationships [5]. In many instances, the level of impairment associated with PMDD is similar to that in women with dysthymia or chronic clinical depression [5,20]. Functional impairment has been documented at home, in social settings, at school, and at work [11], and the degree of impairment increases in parallel with symptom severity [11].

There is clearly a need for effective therapies for PMDD to reduce the individual, societal, and economic impact of this condition. Four agents have received approval in the PMDD indication from the US Food and Drug Administration: The selective serotonin reuptake inhibitors (SSRIs) sertraline, fluoxetine, and paroxetine, and the combined oral contraceptive EE/drospirenone in a 24/4 regimen. Both the SSRIs [21] and EE/drospirenone [18,19] are effective for controlling the symptoms of PMDD. Looking beyond symptom control, treatment with SSRIs also improves functioning and social adjustment during the late luteal phase in women with PMDD [20]. Furthermore, in the present analysis, treatment with EE/drospirenone was associated with significant improvements in functional impairment related to work, relationships, and social activities, meaning that women who receive treatment with EE/drospirenone experienced greater productivity, an enhanced enjoyment of social activities, and a better quality of their relationships. These improvements are likely to make an important contribution to the beneficial effect that EE/drospirenone has on the quality of life in women with PMDD [19].

In contrast to SSRIs, EE/drospirenone is an oral contraceptive as well as being an effective treatment for PMDD. This could be an advantage for many women. The desire to achieve good contraceptive efficacy is likely to lead to a high treatment compliance, which has the associated benefit of enhancing the effectiveness of PMDD treatment. However, head-to-head comparisons between SSRIs and EE/drospirenone are currently lacking.

In concordance with previous PMS/PMDD studies [18,22,23], a large placebo effect was observed in the present study. More specifically, the improvements in the total DRSP symptom score and the 3 functional impairment items over 3 treatment cycles were also observed in the placebo group. Nonetheless, both the total symptom score and the individual functional impairment scores after 3 cycles were improved to a significantly greater extent with EE/drospirenone than with placebo ($P\leq 0.003$ for the adjusted mean difference between treatments for all comparisons).

There were some limitations to the current study. Firstly, the 24/4 regimen used for EE/drospirenone may have altered the menstrual cycle and shifted the symptomatic period to the hormone-free interval, as has been previously documented [14]. However, such an effect does not seem to have occurred in the present study [19]. Secondly, the present results were obtained from a subanalysis of data from a previously performed randomized, controlled clinical trial, although the determination of functional impairment using the last 3 items of the DRSP scale was a planned secondary endpoint of that trial. On a positive note, the participants completed the DRSP scale daily during the study, which meant that temporal changes in symptoms could be accurately and thoroughly assessed.

In conclusion, PMDD is a chronic and debilitating condition, which highlights the importance of having effective treatments that reduce symptoms, improve daily functioning, and enhance the quality of life. The results of the present study show that treatment with a combined oral contraceptive agent containing EE 20 μg and drospirenone 3 mg in a 24/4 regimen significantly improves functional impairment in women with PMDD. This occurs in parallel with an improvement in symptoms. The beneficial effects of EE/drospirenone therapy are seen quickly, with the greatest improvement occurring during the first treatment cycle.

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Conflict of interest

Joachim Marr and Michael Kunz are current employees of Bayer—the sponsors of the present study. Klaas Heinemann is a former employee of Bayer. Andrea Rapkin has been a consultant for Bayer.

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