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ORIGINAL INVESTIGATION

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Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone and placebo

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Abstract *Rationale:* It is well established that serotonin reuptake inhibitors (SRIs) are effective for the treatment of premenstrual dysphoria (PMD), but the receptor subtype(s) mediating this effect of serotonin have yet not been identified. *Objective:* In this trial, the possible efficacy of buspirone, a partial 5HT1A receptor agonist, and nefazodone, a combined SRI and 5HT2 receptor antagonist, was evaluated in women with PMD. *Methods:* After a three-menstrual-cycle screening phase, patients were randomised to buspirone (n=19), nefazodone (n=22) or placebo (n=22). During the first two treatment cycles, patients were taking the drug during the luteal phase only (mean ± SD daily dose of buspirone: 21±6 mg; nefazodone: 228±54 mg). During the subsequent two cycles, the medication was taken each day of the menstrual cycle (mean daily dose of buspirone: 27±10 mg; nefazodone: 304±95 mg). *Results:* With respect to self-rated global improvement, buspirone (P<0.001) but not nefazodone was significantly superior to placebo. While buspirone appeared to reduce self-rated irritability (visual analogue scale) more effectively than placebo, other self-rated symptoms did not differ markedly between the groups. The side-effects were mild, and sexual dysfunction was not significantly more common in patients given buspirone or nefazodone than in those given placebo. *Conclusion:* It is suggested that buspirone is mildly effective for premenstrual irritability. In patients experiencing sexual dysfunction when treated with an SRI, buspirone may be a useful alternative.

Keywords Premenstrual dysphoria · Placebo-controlled · Nefazodone · Buspirone · Sexual dysfunction

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Introduction

Many studies have shown that serotonin exerts an inhibitory influence on irritability and aggression (for review see Eriksson and Humble 1990). Given that irritability is the cardinal symptom of premenstrual dysphoria (PMD), the assumption that facilitation of serotonergic transmission may be effective in the treatment of this condition is not far-fetched. Supporting this notion, a large number of studies have shown that serotonin reuptake inhibitors (SRIs) are not only much superior to placebo (Steiner et al. 1995; Yonkers et al. 1997; Dimmock et al. 2000), but also superior to non-serotonergic antidepressants for the treatment of PMD (see Eriksson 1999). On the other hand, when serotonergic activity is decreased by means of administration of a tryptophan-depleted diet, women with premenstrual complaints report aggravated irritability (Menkes et al. 1994).

The effect of serotonin in the brain is mediated by a large number of receptor subtypes. Which receptor subtype(s) that are mediating the beneficial effects of SRIs in PMD remains to be established. Clarifying this would be of theoretical interest, and would also facilitate the development of new treatment modalities for PMD. In particular, it would be useful to identify a receptor-specific compound reducing premenstrual complaints without eliciting the sexual side-effects (reduced libido, anorgasmia) that often occur during treatment with SRIs.

The purpose of this study was to investigate the efficacy and tolerability of two drugs displaying affinity for different subtypes of serotonin receptors, nefazodone and buspirone, in women suffering from severe premenstrual irritability and/or depressed mood, and fulfilling slightly modified criteria of premenstrual dysphoric disorder (PMDD). Buspirone is a partial 5HT1A receptor agonist, and nefazodone is a combined SRI and 5HT2 receptor antagonist. According to preliminary studies, both substances may be effective in reducing PMD (Rickels et al. 1989; Brown et al. 1990; Freeman et al. 1994); moreover, both compounds are believed to induce sexual side-effects less often than do the SRIs (Rickels 1990; Feiger et al. 1996; Landén et al. 1999).

The onset of action of SRIs is much faster when used for PMD than when used for depression, hence enabling intermittent administration during luteal phases only (Sundblad et al. 1993; Steiner et al. 1997; Wikander et al. 1998). Prompted by this observation, we administered buspirone and nefazodone intermittently for two cycles before giving the treatment continuously for two additional cycles.

Materials and methods

Summary of study design

This was a placebo-controlled, double-blind trial with parallel groups, undertaken at two University clinics in Sweden (Göteborg and Uppsala). In total, three investigators performed the assessments and interviews. A screening visit was followed by daily symptom rating during three menstrual cycles. Eligible patients were given intermittent drug administration (i.e., treatment during luteal phases only) during two cycles, and continuous drug administration for two more cycles. The rationale for switching the regimen after two cycles was that we wanted to explore both the possibility that intermittent administration would be effective, and the possibility that continuous treatment might be effective in patients not responding to luteal dosing.

Participants

The participants were recruited by advertisements in local newspapers. After a structured telephone interview, eligible patients were seen at a screening visit. In order to be preliminarily included in the trial, patients should fulfil the diagnostic criteria A–C of PMDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV; American Psychiatric Association 1994). To fulfil the D criterion for PMDD, prospective daily symptom rating for two cycles should confirm that the patient display menstruation-related cyclicity with respect to at least 5 of 11 relatively heterogeneous symptoms. The primary objective of this trial was to explore the efficacy of buspirone and nefazodone for what we believe to be the core symptoms of PMDD, i.e. irritability and depressed mood. For inclusion in the study, it was hence required that the two cycles of prospective daily symptom rating should confirm cyclicity of at least one of these two symptoms, rather than cyclicity of 5 of the 11 symptoms listed in DSM-IV. In this respect, our inclusion criteria were hence not exactly those of PMDD in DSM-IV, but a slightly modified version of these.

Eligible subjects were asked to perform prospective daily symptom rating during three menstrual cycles using a visual analogue scale (VAS; 0–100 mm) comprising the symptoms 'irritability', 'depressed mood', 'tension', 'affect lability', 'food craving', 'breast tenderness' and 'a sense of bloating'. To be eligible for the treatment phase, the patients should display a 100% increase in irritability and/or depressed mood during the luteal phase (calculated as the mean rating of the 5 days preceding the 1st day of menstruation) as compared to the follicular phase (calculated as the mean rating of days 6–10 of the cycle) for at least two of the three reference cycles. The mean premenstrual rating of the symptom qualifying for inclusion should exceed 30 mm in these cycles.

In addition, participants should be between 18 and 45 years old, and report regular menstrual cycles with a duration of 22–35 days. A structured psychiatric interview was performed (Mini International Neuropsychiatric Interview; Sheehan and Lecrubier 1998). Excluded were patients with a history of any major psychiatric disorder other than depression, patients with an ongoing episode of depression or reporting an episode of depression within the past 2 years, patients with ongoing somatic illness, patients on continuous medication, patients using any hormonal form of contraception, patients in whom a significant suicidal risk was identified, patients previously treated with buspirone or nefazodone, and patients with any other condition or therapy that in the investigators' opinion could pose a risk to the patient if included in the trial, or interfere with the study objectives. In addition to the structured interview, the Montgomery Åsberg Depression Rating Scale (Montgomery and Åsberg 1979) comprising ten items (with a maximum score of 60) was administered at the screening visit to ensure that the included subjects did not suffer from depression. A score higher than 14 was regarded as indicative of depression and thus used as an exclusion criterion.

Intermittent drug administration (treatment cycle 1 and 2)

During the first two treatment cycles, patients were not taking any medication during the follicular phase but only during the luteal phase (=intermittent administration). Drug intake hence started at the estimated day of ovulation, with a daily dose of 10 mg buspirone or 100 mg nefazodone (or placebo). After 3 days, the daily dose was increased to 20 mg buspirone or 200 mg nefazodone (or placebo), and this was also the dose the patients were recommended to take until the 1st day of menstruation, when drug intake should stop. In the second treatment cycle, the medication regimen was the same as in the first cycle. The daily dose was always given as two capsules, one to be taken in the morning, and one to be taken in the evening. Although the patients were recommended to take two capsules per day, they were allowed to reduce the dose to one capsule (=10 mg buspirone or 100 mg nefazodone) if bothered by side-effects, and to increase the dose to three capsules (=30 mg buspirone or 300 mg nefazodone) if the effect on the premenstrual symptoms had been unsatisfactory.

Continuous drug administration (treatment cycle 3 and 4)

During the third and fourth treatment cycles, the medication was taken continuously throughout the menstrual cycle. The recommended dose was higher when the drug was given continuously as compared to when it was given intermittently; during the third and fourth treatment cycles, the participants were hence recommended to take a daily dose of 40 mg buspirone or 400 mg nefazodone, i.e., two capsules in the morning and two in the evening. If bothered by side-effects, they were however allowed to reduce the dose to three, two, or one capsule per day.

Assessments

Throughout the four treatment cycles, symptoms were assessed using the same VAS as during the pretreatment reference cycles (items: irritability, depressed mood, affect lability, tension, food craving, breast tenderness and bloating; see above). The change in symptom score in percent for each treatment cycle was calculated using this formula: (baseline score – treatment score) × 100 / baseline score. The baseline score was defined as the mean rating of the 5 days prior to menses during all three reference cycles. The

score for each treatment cycle was defined as the mean rating during the 5 days prior to menses of that cycle. After the last treatment cycle, or immediately after dropout, the patients were asked to assess the global efficacy of the drug, using a form corresponding to the clinical global improvement (CGI) scale (Guy 1976; 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', 'very much worse'). The CGI data accounted for in the results section refer to improvement/worsening of the premenstrual symptoms, not taking into account possible side-effects.

The patients recorded possible adverse events at 2-week intervals throughout the study, beginning at the end of the first treatment cycle. On the form used for this purpose, the patient was specifically asked (yes/no) whether she had experienced 'increased libido', 'decreased libido', 'increased orgasm function', 'decreased orgasm function', 'light-headedness', 'drowsiness' or 'dry mouth'. After these specific questions, an open question followed in response to which the patient could register any potential side-effects that she had experienced during the previous 2-week period. Appended to this form was a list comprising 25 different side-effects previously reported to occur during treatment with nefazodone or buspirone.

Calculations

Assessment of efficacy was based on an intention-to-treat (ITT) analysis, using the last observation carried forward (LOCF) strategy, comprising all randomised patients who had completed at least one treatment cycle. For the LOCF procedure, the intermittent treatment phase of the trial (i.e. the first two treatment cycles) and the continuous treatment phase (the last two treatment cycles) were regarded as separate trials. Thus, if a patient dropped out after having completed the first treatment cycle, the scores obtained in cycle 1 were carried forward to cycle 2, but not to cycle 4. On the other hand, if a patient dropped out after treatment cycle 3, her scores from that cycle were carried forward to cycle 4.

VAS ratings cannot be expected to be normally distributed; therefore, non-parametric statistics (the Kruskal-Wallis ANOVA by ranks test followed by the Mann-Whitney *U*-test) were used for comparisons of groups with respect to these ratings. For between-group comparisons of categorical variables, the chi-squared two-tailed test was employed. A P value <0.05 was regarded as statistically significant.

Ethical considerations

All patients consented orally and in writing to participate in the study. The study protocol was approved by the Ethics Committees of the Faculty of Medicine at Göteborg and Uppsala Universities. The trial was carried out according to the Helsinki Declaration.

Results

Patients' characteristics and dosage of medication

Of the patients attending the screening visit, 143 fulfilled the DSM-IV criteria A–C for PMDD as well as the other inclusion criteria, without meeting any of the exclusion criteria. After three cycles of daily symptom rating (see Materials and methods), 69 patients were eligible for the treatment phase of the study; the remainder either did not display the fluctuations in irritability and/or depressed mood that was required for inclusion, or withdrew from the study during the reference cycles. Six women dropped out shortly after randomisation and drug dispensation, without completing one cycle of daily symptom rating, and could therefore not be included in the ITT analysis. Of these six early dropouts, one had been randomised to placebo, four to buspirone, and one to nefazodone. Of the 63 patients included in the ITT analysis for the intermittent treatment phase, 19 were randomised to buspirone, 22 were randomised to nefazodone and 22 were randomised to placebo. Due to dropouts during the intermittent treatment phase, the number of subjects eligible for the ITT analysis of the continuous treatment phase was lower than that of the intermittent treatment phase: 16 (buspirone), 20 (nefazodone) and 19 (placebo). The mean ± SD age of these subjects was 37±6 years in the buspirone group, 37±4 years in the nefazodone group and 33±5 years in the placebo group; the duration (mean years ± SD) of premenstrual complaints was 9±3 in the buspirone group, 10±3 in the nefazodone group and 10±3 in the placebo group.

The mean ± SD dosage of buspirone and nefazodone during the last 7 days of the luteal phase of the second menstrual cycle was 21±6 mg and 228±54 mg, respectively. During the fourth treatment cycle, the mean ± SD dose was 27±10 mg buspirone and 304±95 mg nefazodone.

Outcome

Table 1 shows the results of the ITT analysis of the percent symptom reduction for the four mood symptoms during cycle 2 (intermittent treatment) and cycle 4 (continuous treatment). For each symptom, patients not displaying the symptom in question at baseline (=a mean VAS rating ≤5 mm during the luteal phase of the reference cycles) were excluded from the analysis. In addition to this analysis, we also examined the effect of: (1) calculating an absolute VAS score rather than percent symptom reduction, (2) including only patients completing the trial in the analysis and (3) including also patients not displaying a certain symptom at baseline in the analysis of that symptom. The outcome of these alternative ways of analysing the data did not differ markedly from the results presented in Table 1 and in the text below. Moreover, an analysis of the results obtained in each of the two participating centres did not reveal any major centre-related differences in outcome.

With respect to self-rated global improvement, the Kruskal-Wallis ANOVA by ranks test revealed significant differences between the treatment groups (H=9.8, P=0.008). The outcome of the buspirone group (Mann-Whitney, U=86, P=0.001), but not that of the nefazodone group (Mann-Whitney, U=191, P=0.22), was significantly better than that of the placebo group. The difference between the buspirone group and the nefazodone group was close to statistical significance (Mann-Whitney, U=134, P=0.07). One patient in the buspirone group dropped out due to a traffic accident and failed to fill in the global improvement form, therefore, only 18 patients in the buspirone group completed the CGI.

Regarding the four mood-related symptoms (irritability, depressed mood, tension and affect lability), there

Table 1 Effect of nefazodone, buspirone and placebo on visual analogue scale (VAS)-rated premenstrual dysphoria symptoms. 'Baseline' refers to the median self-rated symptom score during the reference cycles (VAS: 0–100 mm). The effect of treatment is expressed as the median change in percent compared with the baseline rating. Shown in this table is the intention-to-treat population. Between-group comparisons were undertaken employing the Mann-Whitney *U*-test. If a patient was completely devoid of a certain symptom at baseline, she was excluded from the analysis of that particular symptom; consequently, the *n* varies between the different symptoms

	Placebo (*n*)	Nefazodone (*n*)	Buspirone (*n*)	*P* value (nefazodone vs placebo)	*P* value (buspirone vs placebo)
Irritability					
Baseline score	61 (22)	64 (22)	56 (19)		
Intermittent treatment: cycle 2 (% change)	47 (22)	52 (22)	72 (19)	n.s.	n.s.
Continuous treatment: cycle 4 (% change)	54 (19)	47 (20)	83 (16)	n.s.	0.03
Depressed mood					
Baseline score	37 (20)	37 (22)	57 (19)		
Intermittent treatment: cycle 2 (% change)	33 (20)	74 (22)	66 (16)	n.s.	n.s.
Continuous treatment: cycle 4 (% change)	56 (18)	83 (20)	79 (16)	(0.07)	(0.08)
Affect lability					
Baseline score	32 (19)	37 (20)	57 (16)		
Intermittent treatment: cycle 2 (% change)	32 (19)	72 (20)	66 (16)	0.05	n.s.
Continuous treatment: cycle 4 (% change)	52 (17)	82 (18)	87 (14)	(0.08)	(0.1)
Tension					
Baseline score	40 (22)	46 (21)	50 (16)		
Intermittent treatment: cycle 2 (% change)	68 (22)	90 (21)	88 (16)	n.s.	(0.1)
Continuous treatment: cycle 4 (% change)	62 (19)	77 (19)	88 (13)	n.s.	(0.09)

was a general trend during both the intermittent and the continuous treatment cycles towards a larger symptom reduction for patients treated with buspirone as compared with those treated with placebo. With respect to the primary effect parameter, irritability, a comparison of the buspirone group with the placebo group reached statistical significance (P=0.03; Mann-Whitney U-test) in the last treatment cycle (continuous treatment); however, a Kruskal-Wallis ANOVA by ranks test comprising all three groups did not reach the level of significance (H=4.1, P=0.13). Nefazodone was no more effective than placebo with respect to reduction in irritability. Regarding depressed mood, tension and affect lability, there was a trend for nefazodone to be somewhat better than placebo; this apparent difference however reached statistical significance only for affect lability and only for treatment cycle 3.

With respect to breast tenderness, bloating and food craving, there were no marked differences between the three treatment groups (data not shown).

Attrition and tolerability

The rate of discontinuation did not differ significantly between the three treatment groups; thus, 8/23 in the buspirone group, 3/23 in the nefazodone group and 4/23 in the placebo group dropped out after drug dispensation (χ^2=3.57, df=2, P=0.17). Reasons for discontinuation were, in the buspirone group, divorce (n=1), nausea (n=1), traffic accident (n=1), amenorrhoea (n=1), pregnancy (n=1), fear of taking medicine (n=1), menstrual disturbance before starting medication (n=1), and light-headedness (n=1); in the nefazodone group, dizziness/light-headedness (n=2), and nausea (n=1); and in the placebo group, 'too much side-effects' (n=1), lack of efficacy in conjunction with light-headedness (n=1), insomnia (n=1) and failure to send in the last diary (n=1).

Overall, both drugs were well tolerated and all reported side-effects were mild, except for those resulting in immediate dropouts (for buspirone light-headedness, for nefazodone nausea). No adverse event required any medical intervention.

The patients were actively inquired regarding the possible occurrence of seven different side-effects ('increased libido', 'decreased libido', 'increased orgasm function', 'decreased orgasm function', 'light-headedness', 'drowsiness' and 'dry mouth'). Of these, light-headedness was more common in patients treated with buspirone than in those treated with placebo (P=0.01), whereas drowsiness appeared more common among those given nefazodone than among those given placebo (P=0.07). Notably, sexual dysfunction was not significantly more common in patients given any of the two active compounds than in those given placebo (Table 2). Spontaneously reported side-effects are shown in Table 3.

Table 2 Sexual side-effects during treatment with buspirone, nefazodone or placebo, reported using an explicit questionnaire. No statistically significant differences were found between the treatment groups (chi-squared test). The total number of subjects responding to each question is displayed in parentheses

	End of treatment cycle 1	Mid-cycle, treatment cycle 2 (no treatment)	End of treatment cycle 2	Mid-cycle, treatment cycle 3	End of treatment cycle 3	Mid-cycle, treatment cycle 4
Decreased libido						
Placebo	2 (16)	4 (16)	6 (19)	5 (18)	4 (19)	5 (18)
Buspirone	2 (16)	2 (12)	2 (17)	2 (17)	1 (13)	2 (14)
Nefazodone	3 (16)	1 (18)	1 (18)	5 (17)	8 (17)	4 (18)
Decreased orgasm function						
Placebo	0 (16)	0 (17)	3 (19)	3 (18)	1 (18)	0 (17)
Buspirone	1 (16)	0 (11)	1 (17)	1 (16)	0 (13)	0 (14)
Nefazodone	1 (16)	0 (18)	2 (19)	1 (16)	4 (18)	2 (17)

Table 3 Most frequently spontaneously reported side-effects. Total number reporting the side-effect at any time of the study. Percentage in parentheses

Side-effect	Placebo (*n*=22)	Buspirone (*n*=19)	Nefazodone (*n*=22)	*P* value (buspirone vs placebo)	*P* value (nefazodone vs placebo)
Dizziness	4 (18)	11 (58)	12 (55)	0.008	0.01
Disturbance of balance	1 (5)	5 (26)	5 (23)	0.05	0.08
Blurred vision	0 (0)	4 (21)	5 (23)	0.02	0.02
Nausea	9 (41)	10 (53)	15 (68)	n.s.	0.07
Constipation	4 (18)	2 (11)	7 (32)	n.s.	n.s.
Memory disturbance	1 (5)	2 (11)	8 (36)	n.s.	0.009
Headache	8 (36)	6 (32)	8 (36)	n.s.	n.s.
Insomnia	10 (45)	9 (47)	3 (14)	n.s.	0.02
Abnormal dreams	1 (5)	5 (26)	6 (27)	0.05	0.04
Formications	0 (0)	6 (32)	1 (5)	0.004	n.s.
Fatigue	6 (27)	4 (21)	7 (32)	n.s.	n.s.
Somnolence	8 (36)	11 (58)	15 (68)	n.s.	0.04
Sweating	6 (27)	5 (26)	2 (9)	n.s.	n.s.
Flu-like symptoms	6 (27)	0 (0)	1 (5)	0.01	0.04

Discussion

The outcome with respect to patient-rated global improvement suggests that the 5HT1A receptor agonist, buspirone, is superior to placebo for the treatment of PMD. This observation is in line with two previous small but placebo-controlled trials by Rickels and coworkers (1989) and by Brown and coworkers (1990). With respect to the daily symptom ratings (VAS), the comparison of buspirone and placebo was however less clear-cut. Non-mood symptoms, bloating, breast tenderness and food craving, were not substantially reduced by buspirone, which is in line with the report by Brown and coworkers (1990), but in contrast to the study by Rickels and collaborators (1989). The four mood symptoms, irritability, affect lability, depressed mood and tension, generally improved more in patients treated with buspirone than in those given placebo, but this difference between buspirone and placebo reached statistical significance only with regard to irritability.

When interpreting the fact that the difference between buspirone and placebo failed to reach statistical significance for all VAS-rated symptoms except irritability, the small sample size should be taken into consideration. A retrospectively performed power analysis based on the differences between placebo and buspirone obtained with respect to self-rated irritability during cycle 2 (intermittent treatment; mean difference 26, SD 46, alpha 0.05) revealed that a group size of 50 would have been necessary to obtain 80% power in a two-armed study. A three-armed study would need even larger groups. That the superiority of buspirone over placebo reached significance with respect to CGI and irritability only, and not with respect to other VAS-rated symptoms, could hence probably be explained by insufficient statistical power due to the small sample size.

It should however be underlined that group sizes of about the same size as in this study have sufficed to yield highly significant differences between active compound and placebo in previous similarly designed studies evalu-

ating the efficacy of SRIs in PMD (Sundblad et al. 1992, 1993; Eriksson et al. 1995; Wikander et al. 1998). The placebo response in these studies has been of approximately the same magnitude as in the present trial, suggesting that the efficacy of SRIs is probably somewhat more robust and uniform than that of buspirone. In order to confirm this, a head-to-head comparison of buspirone and an SRI is, however, warranted.

Severe irritability is the cardinal symptom of PMD, and it has been suggested that the efficacy of SRIs for PMD is largely due to an anti-irritability effect of these drugs (Eriksson 1999). The partial efficacy of a 5HT1A receptor agonist such as buspirone for PMD is well in line with this notion, since animal experiments suggest that the anti-aggressive effect of serotonin is indeed partly mediated by 5HT1A receptors (Kavoussi et al. 1997). Of interest in this context is also the fact that buspirone has been reported to reduce irritability and aggression associated with pervasive developmental disorder (Ratey et al. 1991), smoking cessation (Hilleman et al. 1992), dementia (Holzer et al. 1995) and traumatic brain injury (Stanislav et al. 1994), as well as in cardiac patients (Littman et al. 1993). If 5HT1A receptor activation is indeed beneficial in conditions characterised by irritability, anger and affect lability, a full agonist at this receptor subtype may be more effective than buspirone, which is a partial agonist only. Notably, buspirone is, however, not only a partial 5HT1A receptor agonist, but it also interacts with dopaminergic receptors (Eison and Temple 1986); moreover, a metabolite of buspirone is a potent alpha-2 receptor antagonist (Blier et al. 1991).

The present trial was designed to evaluate the possible efficacy of the two active compounds, both when given intermittently and when given continuously. Although buspirone did not differ significantly from placebo on VAS-rated irritability (or any other symptom) during the intermittent treatment phase, inspection of the data suggests that there was indeed a reduction in mood symptoms also during the first two cycles, that was of approximately the same magnitude as that seen during the continuous treatment phase. This observation is in line with the previous study by Rickels and colleagues (1989) in which buspirone was administered during the luteal phase only.

Nefazodone is a combined SRI and 5HT2 receptor antagonist (Ellingrod and Perry 1995). A previous open-labelled study suggested that nefazodone may be effective for PMD (Freeman et al. 1994); the present trial lends, however, no strong support for this assumption. Nefazodone was hence not significantly better than placebo with respect to global improvement, and also did not reduce the cardinal symptom of PMD, irritability, more effectively than did placebo. Concerning the other mood symptoms, there was a trend for nefazodone to reduce these more than placebo, but, with the exception of affect lability in cycle 3, these differences did not reach statistical significance. Given the small size of this trial, a mild beneficial effect of nefazodone in PMD should not be excluded, but the efficacy seems less impressive than that of buspirone, and the apparent lack of effect on irritability is noteworthy.

The poor efficacy of nefazodone in PMD is somewhat unexpected, given the fact that the compound does inhibit the reuptake of serotonin. If the beneficial effects of SRIs in PMD is to some extent mediated by 5-HT2 receptors, the apparent lack of effect of nefazodone could be attributed to the 5-HT2-antagonizing effect of the drug. This notion is however challenged by the fact that the tricyclic SRI clomipramine is very effective for PMD, in spite of marked 5HT2 receptor-antagonistic effects (Sundblad et al. 1992). An alternative explanation to the lack of effect of nefazodone in PMD could be that it is relatively weak as an inhibitor of serotonin reuptake.

One purpose of this trial was to investigate the effect of nefazodone and buspirone on sexual function. To this end, all patients were regularly asked to report any possible effect of the treatment on the two aspects of sexual function that are most commonly influenced by SRIs, i.e. libido and orgasm function. To our knowledge, this is the first placebo-controlled trial inquiring the effect of nefazodone on sexual function in a group of patients suffering from a condition that, in contrast to depression, is not per se associated with reduced libido (at least not during the follicular phase of the cycle). The observation that neither reduced libido nor anorgasmia was reported significantly more often in the group given nefazodone than in the group given placebo to some extent supports previous claims (Feiger et al. 1996) that nefazodone does not induce these side-effects as often as do the SRIs. It should, however, be underlined that reduced libido (but not anorgasmia) was reported frequently by subjects given placebo, and that the small sample size necessitates cautious interpretation of the results.

As expected, sexual side-effects were not more common in the group given buspirone than in the group given placebo. This observation is well in line with previous studies, suggesting that buspirone enhances rather than inhibits sexual function (Othmer and Othmer 1987; Norden 1994; Landén et al. 1999).

Although not statistically significant, more patients dropped out in the buspirone group than in the nefazodone group (8/23 vs 3/23, χ^2=3.0, *df*=1, *P*=0.08). However, only 2 out of 8 dropouts in the buspirone group could be attributed to the pharmacodynamic effects of the drug. The dropout rate in the placebo group was 4 out of 23.

In conclusion, this trial suggests that buspirone is superior to placebo for the treatment of PMD. For patients with PMD not tolerating the SRIs because of sexual side-effects, buspirone may be an alternative worth testing, since this compound seems devoid of negative effects on sexual function.

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