Treatment of premenstrual dysphoric disorder (PMDD) with a novel formulation of drospirenone and ethinyl estradiol

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Abstract: Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome (PMS). Pharmacologic options studied for treating severe PMS and PMDD may include selective serotonin reuptake inhibitors, anxiolytic agents, gonadotropin-releasing hormone agonists and the diuretic spironolactone. However, the use of combined oral contraceptives (COC) may be a therapeutic option in treating PMS and PMDD. The combination of drospirenone with ethinylestradiol (EE/drospirenone) was approved for marketing as an oral contraceptive in Europe and the United States. The preparation is characterized by a high contraceptive efficacy in combination with excellent cycle control, good tolerability, and a favourable impact on lipid and glucose metabolism. Recently, some placebo-controlled, randomized studies have tested clinical efficacy and tolerability of this COC in the treatment of PMDD. The aim of the present review was to elucidate the possible benefits or disadvantages of PMDD treatment with this novel formulation of EE/drospirenone. The results of trials evaluating the use of EE/drospirenone combination in the treatment of PMDD are encouraging but further studies are needed. However, the reported clinical efficacy and the relative good tolerability of EE/drospirenone may contribute to widen the therapeutic spectrum of PMDD.

Keywords: Premenstrual dysphoric disorder, oral contraceptives, drospirenone, ethinylestradiol, efficacy, tolerability.

Introduction
Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome (PMS). The essential symptoms are markedly depressed mood, appreciable anxiety, pronounced affective swings, and decreased interest in activities. For a precise definition of the syndrome these symptoms should have regularly occurred during the last week of the luteal phase in most menstrual cycles during the past year. They should also remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses (Endicott et al 1999). A change in symptoms from the follicular to the luteal phase of at least 50% is suggested for the diagnosis of PMDD (Steiner and Born 2000).

While majority of women regularly experience some degree of symptomatology during the premenstrual or late luteal phase of their reproductive cycles some menstruating women meet diagnostic criteria for PMDD (Johnson et al 1988). Early descriptions of premenstrual syndrome by Frank (1931) have now evolved into a diagnostic category that has striking similarities to major depression. The diagnostic criteria for PMDD are found in the appendix of the diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV) (APA 1994) and are also listed in the text as “depressive disorder not otherwise specified.”
Epidemiologically, PMDD seems to be less common than PMS, with 12-month prevalence rates of 3%–8% (Angst et al 2001; Wittchen et al 2002), and differs from PMS in that mood symptoms predominate over somatic complaints, overall symptoms are severe, and functional impairment is pronounced (Steiner and Born 2000). However, the diagnosis (and conversely the differential diagnosis) may be not so simple. As specified, a diagnosis of PMDD requires documentation with prospective charting of mood, behavioural, and physical symptoms for at least two consecutive menstrual cycles in order to establish the cyclic nature of symptoms and to exclude a premenstrual exacerbation of an underlying psychiatric or organic disorder (Frackiewicz and Shiovitz 2001).

Some instruments may help the diagnostic process and are used in clinical trials; these include the daily record of severity of problems (DRSP), the premenstrual record of impact and severity of menstruation (PRISM), the calendar of premenstrual experiences (COPE), the daily symptom report (DSR) and the use of visual analogue scales (VAS) (Futterman and Rapkin 2006). As an alternative to formal rating scales, patients may keep an informal diary of symptoms throughout the month (Steiner et al 1999).

Pharmacologic options studied for treating severe PMS and PMDD may include selective serotonin reuptake inhibitors (SSRIs), anxiolytics, gonadotropin-releasing hormone (GnRH) agonists and the diuretic spironolactone. The US food and drug administration (FDA) (2002) has labelled fluoxetine (Sarafem), sertraline (Zoloft) and paroxetine (Paxil CR) for the treatment of PMDD. The ACOG (2000) recommends SSRIs as initial drug therapy in women with severe PMS and PMDD (Evidence level C, expert/consensus guidelines). To date, SSRI are considered to be the gold-standard in the treatment of this disorder (Freeman 2004).

However, the use of combined oral contraceptives (COC), in particular containing a combination of dospirenone and ethinylestradiol, may be a therapeutic option in treating PMS and PMDD. The combination of dospirenone with ethinylestradiol (EE/dospirenone) was recently approved for marketing as an oral contraceptive in Europe and the United States. The preparation is characterized by a high contraceptive efficacy in combination with excellent cycle control, good tolerability, and a favourable impact on lipid and glucose metabolism (Parsey and Pong 2000).

The aim of the present review was to elucidate the possible benefits or disadvantages of PMDD treatment with this novel formulation of EE/dospirenone.

**Pharmacological characteristics of EE/dospirenone combination and its potential benefits in premenstrual symptoms**

The progestin dospirenone is derived from 17α-spirolactone and its pharmacological profile more closely resembles that of natural progesterone compared to other progestins (Oelkers 2004). Dospirenone acts by binding to aldosterone receptors, blocking aldosterone action in the kidneys, resulting in a substantial rise in sodium and water excretion and some retention of potassium. Therefore, dospirenone can counteract estrogen-induced stimulation of the renin-angiotensin-aldosterone system that can lead to sodium and water retention and symptoms such as breast tenderness and oedema: This effect may be useful in the treatment of patients with PMDD (Parsey and Pong 2000). Clinical studies with EE/dospirenone have shown it to have reliable contraceptive effects and a good safety profile (Huber et al 2000; Parsey and Pong 2000). The 3-mg dose of dospirenone has been shown to be equivalent to 25 mg of spironolactone. Other effects include improved acne and other skin-related problems, which are in part related to the anti-androgenic activity of dospirenone (van Vloten et al 1999).

Concerning premenstrual symptoms, Foidart and colleagues (2000) reported that they were lower in women using dospirenone/30EE compared with desogestrel/ethinylestradiol. In addition, Apter and colleagues (2003) conducted an open study of 336 women to evaluate the actions of 30EE/dospirenone on fluid-related symptoms during the luteal phase of the cycle and the effects of these symptoms on overall wellbeing. The use of EE/dospirenone was associated with a significant reduction in the incidence and severity of the abdominal bloating and breast tenderness associated with the menstrual cycle as well as a positive effect on psychological well-being as measured by the Psychological General Well Being Index. These findings were also confirmed later by Sangthawan and Taneepanichskul (2005).

More recently, Schultz-Zehden and Boschitsch (2006) conducted an uncontrolled survey of 10947 women using the EE/dospirenone in 15 European countries and found that the severity of premenstrual symptoms including depressed mood, irritability, breast tenderness or pain, abdominal bloating or swelling, skin and hair problems, and swelling of the extremities all improved during treatment with the 30EE/dospirenone. Moreover, 10441
(95%) respondents were satisfied or very satisfied with the EE/drospirenone and 9016 (82%) would recommend it to a friend.

**Rationale for COCs treatment of PMDD**

The pathophysiology of severe PMS and PMDD is closely linked to an active hypothalamic-pituitary-gonadal (HPG) axis (Lobo and Stanczyk 1994). There is a clear relationship between the presence of PMS/PMDD symptomatology and the levels of sex steroids associated with ovulation (Freeman 2002). The menstrual cyclicity of the ovarian hormones is most likely the trigger for the psychological as well as the somatic premenstrual symptoms. PMS and PMDD do not occur during pregnancy, premenarchally or in post menopausal women who are not receiving hormone replacement therapy, or for the most part during spontaneously anovulatory cycles (Rapkin 2003). Moreover, Casper and Hearn (1990) have showed that symptoms of severe PMS may resolve with oopherectomy. So, researchers’ attention has thereby focused on ovulation suppression with COCs for the treatment of PMS/PMDD.

The decreasing levels of ovarian steroid hormones in the late luteal phase of the menstrual cycle may be accounted as one of probable cause of PMDD as it has been demonstrated that decreases in estrogens levels after ovulation may correlate with depressed mood during the late luteal phase (Watson et al 1990; Michener et al 1999).

Moreover, it has been demonstrated that estrogens has also been found to increase serotonergic activity by increasing the number of serotonergic receptors, transport, and uptake (Halbreich et al 1995). As it is well known that serotonin levels may influence the mood, low estrogens levels may further explain the depressed mood seen in women with PMDD.

Concerning progesterone, although decreased levels were a long-standing hypotheses in PMDD (Dalton 1964), the majority of controlled trials have failed to find that progesterone is superior to placebo in reducing premenstrual symptoms (Freeman et al 1995). In fact, the rationale for progesterone therapy in PMDD is not supported by studies of gonadal hormone levels in this disorder because they have showed a relative lack of consistency in results. In fact, whereas it has been reported that low progesterone levels may be present during the luteal phase (Wang et al 1996), some studies showed instead increased progesterone in this phase (Redei and Freeman 1994; Watts et al 1985) or no differences in PMDD women versus controls (Parry et al 1991; Girdler et al 1993). Thus, despite the overwhelming evidence for an obligatory role of the gonadal hormones in the pathophysiology of PMDD, it is generally agreed that neither a deficiency nor excess in progesterone levels is etiologically relevant to the disorder (Rubinow and Schmidt 2006).

Conversely, it has been reported that progesterone-derived neuroactive steroid allopregnanolone may be involved in the pathogenesis of PMDD (Wang et al 1996). Allopregnanolone is a metabolite of progesterone and is produced not only by ovary and adrenals but also de novo in brain (Paul and Purdy 1992). Girdler and colleagues (2001) observed a relationship between premenstrual symptom severity and allopregnanolone levels in the PMDD women. The results of this study showed a dysregulation of allopregnanolone in PMDD and suggested that allopregnanolone may negatively modulate the HPG-axis in human female subjects as it does in animals, and that allopregnanolone levels in PMDD women may influence severity of premenstrual symptoms also through GABA-A brain receptors. Moreover, has been reported that the allopregnanolone has the ability to cause augmentation of allopregnanolone in PMDD (Wang et al 1996). As COCs may regulate allopregnanolone levels (Rapkin et al 2006), these compounds may be useful to treat psychic symptoms associated with PMDD (Sangthawan and Taneepanichskul 2005). However, COCs may act also on other neuroactive steroids such as pregnenolone sulphate (PS) and dehydroepiandrosterone sulphate (DHEAS) that are in general GABA-A receptor antagonists (Paoletti et al 2004; Dubrovsky 2005).

Taken together, these findings may suggest that a possible mechanism involved in the pathogenesis of PMDD may be rather related to a hormonal ratio imbalance, and not to hormone fluctuation (Halbreich et al 1986). In fact, a relative higher level of estrogens compared to relative low levels of progesterone may account for triggering PMDD symptomatology. Halbreich and colleagues (1986) found a significant association between the rate of change of progesterone (increase and decrease) and to a lesser degree, rate of change of estrogens, and severity of symptoms. When progesterone and estrogens fluctuated in different rates there was a significant correlation between the difference of rate and severity of symptoms.

So, the use of COCs in the treatment of PMDD may restore balanced hormone levels leading to the therapeutic success (Rapkin et al 2006).
Treatment of PMDD with EE/drospirenone combination

In the recent years, only few placebo-controlled studies have examined the efficacy of the OC formulation containing EE/drospirenone in the treatment of PMDD. Freeman and colleagues (2001) conducted a double-blind placebo-controlled trial that included 82 women with PMDD who were randomized to EE 30 µg/drospirenone 3 mg (Yasmin®) (n = 42) or placebo (n = 40). Diagnoses were made according with DSM-IV criteria and the primary end point was change from baseline in luteal phase symptom scores as assessed on the COPE scale. The EE/drospirenone combination was observed to have a positive effect on symptoms of PMDD, with the between-group differences reaching statistical significance in appetite, food cravings, and acne (P = 0.03). Moreover, the secondary end points, Beck Depression Inventory and Profile of Mood States, were consistent with the primary end point in that patients treated with the oral contraceptive and showed a numerically greater improvement from baseline compared with those treated with placebo.

Recently, the availability of a low-dose oral contraceptive with drospirenone (EE 20 µg/drospirenone 3 mg – Yasminelle®, Yaz®) stimulated researchers to verify its potential efficacy in the treatment of PMDD. In this novel formulation, the active hormones were administered for 24 consecutive days (24/4) rather than the conventional 21 days in a 28-day cycle (21/7). This new treatment platform is associated with greater suppression of follicle development and a more stable hormonal status than the standard 21/7 regimen. Therefore, together with the reported efficacy of spironolactone for premenstrual symptoms, the follicular suppression found with a 24/4 regimen as well as the lower estrogens dose may be effective in the treatment of premenstrual symptoms.

Pearlstein and colleagues (2005), in a small, multicenter, double-blind, placebo-controlled crossover study, administered EE 20 µg/drospirenone 3 mg formulation or placebo for 24 days in a 28-day cycle (24/4), rather than the usual 21-day active treatment, to 64 women who were randomized to either study treatment for three cycles and then after a washout period of one treatment-free cycle switched to the alternate treatment. They observed that the mean decrease from baseline for total DRSP scores while using EE/drospirenone was significantly greater than for placebo with a positive response (ie, a score of 1 or 2 in the Clinical Global Impressions-Improvement scale) occurring in 61.7% and 31.8% of subjects while taking EE/drospirenone and placebo, respectively. They concluded that EE/drospirenone, given in a 24/4 regimen, was superior to placebo for improving symptoms associated with PMDD.

In the same period, Yonkers and colleagues (2005) studied 450 women with symptoms of premenstrual dysphoric disorder randomized to either placebo or COC formulation containing EE 20 µg/drospirenone 3 mg. This multicenter, double-blind, randomized clinical trial consisted of 2 run-in and 3 treatment cycles with daily symptom charting with DRSP. At endpoint, the total DRSP symptom score in subjects receiving EE/drospirenone decreased by 47% compared to 38% of placebo group. Moreover, overall improvement according to the Clinical Global Impression-Improvement observer-rated scale was greater for subjects receiving active treatment than for those in the placebo group. In conclusion, this placebo-controlled, double-blind study showed that the new drospirenone-containing COC formulation administered for 24 of 28 days in a cycle ameliorates symptoms associated with PMDD.

Adverse effects in clinical trials with drospirenone/EE combination in PMDD

The EE/drospirenone combination was generally well tolerated in all studies.

In the Pearlstein and colleagues (2005) trial, 28 (48.2%) subjects using EE/drospirenone experienced adverse effects related to the study drug. The most frequent were nausea, upper respiratory infection, headache, intermenstrual bleeding, breast pain, nervousness and asthenia. The discontinuation rate due to adverse effects in the active treatment group was 13%. One subject discontinued due to an increased serum potassium levels during washout phase but authors classified this event as “not likely to be study related.”

In the trial of Yonkers and colleagues (2005) adverse events considered by investigators possibly related to the study drug occurred in 118 (51.1%) subjects receiving EE/drospirenone. The most frequent were intermenstrual bleeding, headache, nausea and breast pain. There was also one severe adverse event (dysplasia) considered by the investigator to be possibly related to study drug in the active-treatment group. 35 subjects (29.7%) in the active treatment group discontinued due to adverse events, but no significant difference in serum potassium levels between active and placebo groups during the treatment period was reported.
Conclusions
The results of trials evaluating the use of EE/drospirenone combination in the treatment of PMDD are encouraging but further studies are needed. In addition, a burgeoning body of literature has emerged that supports the role of the SSRIs as first-line treatment of PMDD and severe PMS. Moreover, further complicating the issue is the fact that many somatic symptoms of PMDD such as breast tenderness, headache, bloating, and nausea can also be adverse effects of some oral contraceptive pills including EE/drospirenone.

So, in the authors’ opinion, to date, the EE/drospirenone should be taken into consideration not as a first-line treatment but should be reserved to SSRI-resistant subjects. In particular, future large, double-blind, randomized studies should be evaluate a comparison between SSRI and EE/drospirenone in the treatment of PMDD to verify efficacy and tolerability of these two therapeutic options.

However, the clinical efficacy and the relative good tolerability of EE/drospirenone may be useful to widen the therapeutic spectrum of PMDD.

References
ACOG practice bulletin. 2000. Clinical management guidelines for obstetrician-gynecologists. Premenstrual syndrome. Obstet Gynecol, 95:1–9.
American Psychiatric Association (APA). 1994. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: APA.
Angst J, Sellaro R, Merikangas KR, et al. 2001. The epidemiology of perimenstrual psychological symptoms. Acta Psychiatr Scand, 104:110–6.
Apter D, Borsos A, Baumgartner W, et al. 2003. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. Eur J Contracept Reprod Health Care, 8:37–51.
Casper RF, Hearn MT. 1990. The effect of hysterectomy and bilateral oophorectomy in women with severe premenstrual syndrome. Am J Obstet Gynecol, 162:105–9.
Dalton K. 1964. Premenstrual syndrome. London: Heinemann.
Drug facts and comparisons. 2002. St. Louis: Facts and Comparisons.
Dubrovsky BO. 2005. Steroids, neuroactive steroids and neurosteroids in psychopathology. Prog Neuro-psychopharmacol Biol Psychiatry, 29:169–92.
Endicott J, Amsterdam J, Eriksson E, et al. 1999. Is premenstrual dysphoria a distinct clinical entity? J Womens Health Gen Based Med, 8:662–79.
Foidart JM, Wuttke W, Bouw GM, et al. 2000. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. Eur J Contracept Reprod Health Care, 5:124–34.
Frank RT. 1931. The hormonal causes of premenstrual tension. Arch Neurol Psychiatry, 26:1053–7.
Freeman EW. 2002. Current update of hormonal and psychotropic drug treatment of premenstrual dysphoric disorder. Curr Psychiatry Rep, 4:435–40.
Freeman EW. 2004. Luteal phase administration of agents for the treatment of premenstrual dysphoric disorder. CNS Drugs, 18:453–68.
Freeman EW, Rickels K, Sondheimer SJ, et al. 1995. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. JAMA, 274:51–7.
Freeman EW, Kroll R, Rapkin A, et al. 2001. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. J Womens Health Gen Based Med, 10:561–9.
Futterman LA, Rapkin AJ. 2006. Diagnosis of premenstrual disorders. J Reprod Med, 51(Suppl 4):349–58.
Girdler SS, Pedersen CA, Stern RA, et al. 1993. Menstrual cycle and premenstrual syndrome: Modifiers of cardiovascular reactivity in women. Health Psychol, 12:180–92.
Girdler SS, Straneva PA, Light KC, et al. 2001. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. Biol Psychiatry, 49:788–97.
Halbreich U, Endicott J, Goldstein S, et al. 1986. Premenstrual changes and changes in gonadal hormones. Acta Psychiatr Scand, 74:576–86.
Halbreich U, Rojansky N, Palter S, et al. 1995. Estrogen augments serotonergic activity in postmenopausal women. Biol Psychiatry, 37:434–41.
Huber J, Foidart JM, Wuttke W, et al. 2000. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. Eur J Contracept Reprod Health Care, 5:25–34.
Johnson SR, McChesney C, Bean JA. 1988. Epidemiology of premenstrual symptoms in a non-clinical sample. I. Prevalence, natural history and help-seeking behavior. J Reprod Med, 33:340–46.
Kaura V, Ingram CD, Gartsise SE, et al. 2006. The progesterone metabolite allopregnanolone potentiates GABA(A) receptor-mediated inhibition of 5-HT neuronal activity. Eur Neuropsychopharmacol, in press.
Lobo RA, Stanczyk FZ. 1994. New knowledge in the physiology of hormonal contraceptives. Am J Obstet Gynecol, 170:499–507.
Michener W, Rozin P, Freeman E, et al. 1999. The role of low progesterone and tension as triggers of perimenstrual chocolate and sweets craving: Some negative experimental evidence. Physiol Behav, 67:417–20.
Parry BL, Gerner RH, Wilkins JN, et al. 1991. CSF and endocrine studies of premenstrual syndrome. Neuropsychopharmacology, 5:127–37.
Parsey KS, Pong A. 2000. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. Contraception, 61:105–11.
Oelkers W. 2004. Drospirenone, a progestogen with antimineralcorticoid properties: a short review. Mol Cell Endocrinol, 217:255–61.
Paoletti AM, Lello S, Fratta S, et al. 2004 Psychological effect of the oral contraceptive formulation containing 3 mg of drospirenone plus 30 µg of ethinyl estradiol. Fertil Steril, 81:645–51.
Parsey KS, Pong A. 2000. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. Contraception, 61:105–11.
Paul SM, Purdy RH. 1992. Neuroactive steroids. FASEB J, 6:2311–22.
Pearlstein TB, Bachmann GA, Zucur HA, et al. 2005. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. Contraception, 72:414–21.
Rapkin A. 2003. A review of treatment of premenstrual syndrome and premenstrual dysphoric disorder. Psychoneuroendocrinology, 28(Suppl 3):39–53.
Rapkin AJ, Biggio G, Concas A. 2006. Oral contraceptives and neuroactive steroids. Pharmacol Biochem Behav, in press.
Rapkin AJ, Morgan M, Soglio C, et al. 2006. Decreased neuroactive steroids induced by combined oral contraceptive pills are not associated with mood changes. Fertil Steril, 85:1371–8.
Redei E, Freeman EW. 1993. Preliminary evidence for plasma adrenocorticotropic levels as biological correlates of premenstrual symptoms. Acta Endocrinol, 128:536–42.
Rubinson DR, Schmidt PJ. 2006. Gonadal steroid regulation of mood: the lessons of premenstrual syndrome. Front Neuroendocrinol, 27:210–6.
Sangthawan M, Taneeapanichskul S. 2005. A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 microg on premenstrual symptoms. *Contraception*, 71:1–7.

Schultz-Zehden B, Boschitsch E. 2006. User experience with an oral contraceptive containing ethinylestradiol 30 mug and drospirenone 3 mg (yasmin®) in clinical practice. *Treat Endocrinol*, 5:251–6.

Steiner M, Born L. 2000. Diagnosis and treatment of premenstrual dysphoric disorder: An update. *Int Clin Psychopharmacol*, 15(suppl 3):S5–S17.

Steiner M, Streiner DL, Steinberg S, et al. 1999. The measurement of premenstrual mood symptoms. *J Affect Disord*, 53:269–73.

Stromberg J, Haage D, Taube M, et al. 2005. Neurosteroid modulation of allopregnanolone and GABA effect on the GABA-A receptor. *Neuroscience*, 143:73–81.

van Vloten WA, van Haselen CW, et al. 2002. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. *Cutis*, 69:2–15.

Wang M, Seippel L, Purdy RH, et al. 1996. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: Study on serum pregnenolone, pregnenolone sulfate, 5α-pregnane-3,20-dione and 3α-hydroxy-5α-pregnan-20-one. *J Clin Endocrinol Metab*, 81:1076–82.

Watson NR, Studd JW, Savvas M, et al. 1990. The long-term effects of estradiol implant therapy for the treatment of premenstrual syndrome. *Gynecol Endocrinol*, 4:99–107.

Wittchen HU, Becker E, Lieb R, et al. 2002. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychol Med*, 32:119–32.

Yonkers KA, Brown C, Pearlstein TB, et al. 2005. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstet Gynecol*, 106:492–501.