PHARMACOTHERAPY FOR PREMENSTRUAL DYSPHORIC DISORDER: A META-ANALYSIS OF PHASE 3 TRIALS

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Premenstrual dysphoric disorder (PMDD) is a common condition that temporarily, but repetitively affects patient's global function. Patients and physicians alike are often uncertain whether prescription medication for PMDD is sufficiently effective. The primary objective of this analysis is signal detection in efficacy of pharmacological treatments in PMDD. Secondary objective is to review which symptoms are likely to respond to which medications. The review included otherwise healthy women with clinician confirmed diagnosis of PMDD who participated in phase 3 clinical trials for the treatment of PMDD. Twelve pair-wise comparisons of drug and placebo for 2,420 patients with PMDD were performed. Oral contraceptives and selective serotonin receptor inhibitor were effective in alleviating symptoms of PMDD compared to placebo. Both Intermittent and continuous administration were more effective than placebo. This meta-analysis provides a signal that pharmacological treatment of PMDD is effective.

Keywords: Premenstrual syndrome; Drug therapy; Meta-analysis; Clinical trial, phase 3

Up to 80% of women experience physical and emotional changes that are related to their menstrual cycle. Among the nearly 150 reported cyclically recurrent emotional and somatic symptoms, the most common include irritability, fatigue, depression or mood swings, breast tenderness, bloating, and food cravings [1-3]. Approximately 3%-8% of reproductive-age women experience mood, behavioral and/or physical symptoms during the final week of their menstrual cycle that are severe enough to meet the criteria for premenstrual dysphoric disorder (PMDD) [4-6].

PMDD is thought to result from the complex interaction among ovarian steroid production, endogenous opioid peptides, central neurotransmitters, prostaglandins, and peripheral autonomic and endocrine systems [7-9]. Of the wide range of medications available for this treatment approach, the most commonly used agents are oral contraceptives and antidepressants.

As a clinician faced with patients who complain of premenstrual symptoms, it is difficult to predict which symptoms will benefit from treatment with which drug. In some cases, it is puzzling on the part of both patients and physicians whether premenstrual distress requires medical treatment at all. Often, patients read about alternative remedies advertised in beauty magazines, newspapers, television ads, the internet, and seek advice from friends and family. There is overwhelming amount of information on which under-wear to wear, which foods to eat and avoid, special herbs, drinks, even lucky charms. In the midst of all the available remedies, one wonders what role medications can have in the competition.

This paper aims to summarize and help readers understand the evidence, and ultimately help physicians make practical decisions about pharmacotherapy for PMDD. The primary objective of this review is to search for signals regarding the following questions:

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Does PMDD benefit from pharmacological treatment? If so, how much benefit can be expected? Secondary objective is to review which symptoms are likely to respond to which medications.

**Criteria for Considering Studies for this Review**

1. **Participants**
The review will examine otherwise healthy women with clinician confirmed diagnosis of PMDD according to Diagnostic and Statistical Manual Fourth Edition (DSM-IV) who participated in PMDD phase 3 clinical trials. The reason for selecting only phase 3 studies to compare is mainly because the primary endpoints in PMDD rely mainly on patient’s subjective experience. Unless the studies are well controlled and adequately blinded, there is potentially high risk of bias.

2. **Type of intervention**
The interventions of interest are prescription pharmacological treatments for PMDD. Variations in intervention including dosage, frequency, timing and duration of treatment will be included. Trials including combination with another intervention for PMDD will be excluded. The interventions are to be compared with inactive control intervention (i.e., placebo).

3. **Types of comparisons**
Pair-wise comparisons of each active drug arm and placebo will be performed.

4. **Type of outcomes**
All primary outcome measures that are likely to be meaningful to clinicians will be selected. Outcome measures are not part of the a priori criteria for including studies in this review.

**Search**

Condition search for "premenstrual dysphoric disorder" was performed on http://www.clinicalstudyresults.org. The search yielded ten phase 3 clinical trials. Six out of the ten trials from the initial search output had sufficient information to be included in this analysis. Four studies did not have published trial results. Five trials had sufficient information in the registry, but was linked to a publication [10] which provided the necessary information. Additional PubMed search for (“premenstrual dysphoric disorder” [All Fields] OR PMDD [All Fields] AND Clinical Trial, Phase III [PT]) yielded no result. A total of six trials met the pre-defined patient group, intervention, comparisons, outcomes (PICO) criteria and had sufficient information for analyses. One trial was performed using drospirenone (DR) and ethinyl-estradiol (EE) as the active treatment. The other five trials used paroxetine, a serotonergic antidepressant.

**Review**

The study using DR and EE combination as the active drug was performed by Bayer (study 91001) [11]. This was a double-blind, randomized, placebo-controlled, crossover multicenter trial performed in the US. The study evaluated the efficacy of a monophasic oral contraceptive preparation containing DR 3 mg and EE 20 μg (as beta-cyclodextrin clathrate) in the treatment of PMDD. Otherwise healthy women of reproductive age with a diagnosis of PMDD were enrolled. Sixty-four patients were randomized to either active drug or placebo for three cycles and then after a washout period of one cycle, switched to the other group (crossover). Each subject was observed over three menstrual cycles each on drug and placebo. In the active drug group, subjects received the active tablet for 24 days followed by 4 inert tablets. The primary efficacy measurement was the Daily Record of Severity of Problems (DRSP) score. The measurement used in this meta-analysis is the mean DRSP score over 3 cycles. Two pair-wise drugs vs. placebo comparisons were made from each of the two stages (pre/post crossover).

The five trials using paroxetine were performed by GlaxoSmithKline: 29060/677 [12], 29060/688 [13], 29060/689 [14], 29060/711 [15], 29060/717 [16]. Study 677, 688, and 689 [12-14] had identical study designs: double-blind, placebo-controlled, three-arm fixed-dose studies of two doses of (12.5 mg/day and 25 mg/day) controlled release (CR) paroxetine and placebo continuous treatment. The subjects in these studies were outpatient women of 18 to 45 years of age, with regular menstrual cycles (i.e., duration between 22 and 35 days), with diagnosis of PMDD according to DSM-IV (criteria A-C fulfilled at the screening visit and criterion D in two consecutive reference cycles) and had PMDD in at least 9 out of 12 menstrual cycles during the past year. After screening for historical diagnosis