**Differential Time Course Efficacy on Dysphoric & Physical Symptoms of the Intermittent Dosing of Fluoxetine in the Premenstrual Dysphoric Disorder**

Jorge M Tamayo MD, PharmS 1; Gustavo Gómez, MD 2; Rocio Barrios, MD 3; Jorge Holguín, MD 4 & Cecilia Adranzén, MD 5

1 Clinical Research Physician, Caribbean Basin Region, Eli Lilly - Puerto Rico; 2 Gynecologist, Imbanaco Medical Center, Cali, Colombia; 3 Psychiatrist, Colsánitas Medical Center, Santa Fe de Bogotá, Colombia; 4 Psychiatrist, Samen Mental Health Center, Medellín, Colombia; 5 Psychiatrist, Neuroscience Clinical Research Physician, Eli Lilly & Co. Lima, Peru.

**ABSTRACT**

Premenstrual Dysphoric Disorder (PMDD) has been validated by several epidemiological, pharmacological, biochemical and genetic studies. This prospective open-label trial evaluated the efficacy and safety of the intermittent treatment with 20 mg of fluoxetine taken daily during 3 consecutive menstrual cycles in the luteal phase in patients with PMDD according to the diagnostic criteria from DSM-IV. Thirty Latinos patients (Hispanics) with diagnosis of PMDD without depression, were recruited in 2 outpatient specialized centers in Colombia. All patients received 20 mg of fluoxetine taken daily during 3 consecutive menstrual cycles in the luteal phase. The primary efficacy measure was the percentage of change from the initial score in the Calendar of Premenstrual Experiences (COPE) after three consecutive luteal phases. The administration of the COPE showed a significant progressive reduction in the total score of this scale with respect to the initial point of comparison, 37.8% at the end of the first cycle of treatment (p < 0.02), 54.4% after two cycles (p < 0.001) and 77% after three cycles (p < 0.001). A reduction on dysphoric symptoms was observed since the first cycle of treatment (p < 0.01). However, other mood and physical symptoms changes were statistically significant only from the second cycle of treatment. This disparity in response for different symptom categories may suggest a novel mechanism of action of SSRIs in patients with PMDD.

**STUDY DESIGN & METHODOLOGY**

The COPE’s values obtained by the 41 patients (Mean age = 33±8.9) during the first luteal period before to visit 2 were used as a baseline score for the data analysis. Those values were compared with those obtained during the luteal period before visit 3. Other efficacy measures in the treatment with intermittent fluoxetine were obtained with the use of the following instruments: Global Clinical Impression Scale – Illness Severity (CGI-S), Hamilton Depression Scale of 17 items (HAMD17) qualified by clinicians, and Visual Analogue Scale (VAS) qualified by patients. Only those that obtained a total score of VAS > 50 (intensity of symptoms moderate to severe) during the luteal phase (visit 3) with minimal or no symptoms during the follicular phase (visit 2) went on to Visit 4.

**INTRODUCTION & STUDY OBJECTIVE**

Premenstrual Dysphoric Disorder (PMDD) is a well defined and clinically different clinical entity from other well described disorders, such as major depression, panic disorder, etc. PMDD was included in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and is considered a severe form of Premenstrual Syndrome.

The primary objective of this study was to evaluate the efficacy and safety of intermittent treatment with 20 daily mg of fluoxetine administered during 3 consecutive menstrual cycles in the luteal phase in patients diagnosed with PMDD according to the DSM-IV diagnostic criteria and using the Calendar of Premenstrual Experiences (COPE) as a primary efficacy measure.

**MEAN CHANGE IN THE TOTAL COPE SCORE SINCE VISIT 3**

![Graph showing mean change in the total COPE score since visit 3](image)

*p values in comparison to V3: † p < 0.01

**MEAN CHANGE IN THE TOTAL VAS SCORE**

![Graph showing mean change in the total VAS score](image)

*p values in comparison to V3: * p < 0.01

**MEAN CHANGE IN THE GAF-S SCORE**

![Graph showing mean change in the GAF-S score](image)

*p values in comparison to V3: * p < 0.001

**TREATMENT ADVERSE EVENTS**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>6.6</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Bronchial Spasm</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Urinary Infection</td>
<td>1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

**CONCLUSIONS: EFFICACY OF FLX IN PMDD**

- This study corroborates the efficacy and safety findings reported in other ones, and offers the first data about the efficacy and safety of intermittent therapy with fluoxetine in patients of Latin American origin.
- The effect of the intermittent treatment with fluoxetine is faster in the reduction of the dysphoric symptoms, irritability and tension. Other affective and physical symptoms show statistically significant changes only from the second cycle of treatment onwards.
- This observation makes it possible to suggest that the antidysphoric effect depends on the concentration of serotonin in the synaptic space of the hypothalamus, and that symptoms like fatigue, difficulty concentrating, secondary mood changes and physical symptoms, require postsynaptic changes not only in the hypothalamus but also in spiral-hypothalamic pathways and in different areas of the limbic system. These long-term effects could be possible only with a long half-life antidepressant like fluoxetine when an intermittent administration is selected.

**References:**

Sponsored by 

Lilly

Answers That Matter.