The efficacy and the tolerability of escitalopram in the treatment of premenstrual dysphoric disorder

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Abstract

Objective: *The primary objective of this study was to assess the efficacy and the tolerability of daily treatment throughout the menstrual cycle with escitalopram (20 mg/day) after 3 cycles of treatment in premenstrual dysphoric disorder.*
Method: *This naturalistic study included 18 women aged 21–44 years with regular menstrual cycles and confirmed premenstrual dysphoric disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). The primary efficacy measurement was the visual analogue scale (VAS)-Mood score, which is the mean of 4 core symptoms: irritability, tension, depressed mood, and affective lability.*
Results: *Fifteen (83.33%) of the eighteen patients enrolled were responders, and five (27.77%) patients respectively were remitters. Adverse events were mild to moderate.*
Conclusions: *Escitalopram is well tolerated and efficacious in reducing symptoms of premenstrual dysphoric disorder. More studies are needed for this category of patients.*
Keywords: *premenstrual dysphoric disorder, escitalopram, visual analogue scale*

Introduction

Premenstrual dysphoric disorder (PMDD) (previously known as late luteal phase dysphoric disorder) is characterized in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[1] as a cluster of psychological, behavioural, and somatic symptoms that appear regularly during the 3 to 10 days prior to menstrual bleeding (luteal phase) and remit completely after the onset of menstruation (follicular phase). A symptom-free period during the follicular phase of the menstrual cycle is essential in differentiating PMDD from preexisting anxiety and mood disorders. Because of the absence of generally agreed-on criteria (in DSM-IV-TR there are only research criteria), the epidemiology of premenstrual dysphoric disorder is not known with certainty. Some studies reported that about 40 to 80 percent of women have at least mild symptoms of the disorder. It is estimated that the full diagnostic criteria for PMDD are present in 3-10 percent of women of childbearing age[2-6].

According to DSM-IV-TR premenstrual dysphoric disorder is classified as a depressive disorder, emphasizing emotional and cognitive-behavioural symptoms. These symptoms are present in most menstrual cycles during one year and cause a significant impact on family, work, and social functioning. They are more severe and debilitating than those seen in women with premenstrual syndrome (PMS) and are not merely an exacerbation of the symptoms of another psychiatric disorder. These criteria must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. The diagnosis may be made provisionally prior to this confirmation1. In PMS, the patient reports at least one of the affective

or somatic symptoms during the 5 days before menses in each of the three prior menstrual cycles. In PMDD there must be at least five symptoms for most of the menstrual cycles during the past year[7].

The diagnostic criteria for PMDD proposed in DSM-IV-TR request that five or more of the following symptoms must be present:

- depressed mood;
- anxiety, tension;
- anger or irritability;
- difficulty in concentrating;
- lack of interest in activities once enjoyed;
- lethargy, easy fatigability;
- moodiness;
- increased appetite;
- insomnia or hypersomnia;
- feeling overwhelmed or out of control;
- other physical symptoms.

Somatic symptoms may include edema, breast tenderness or swelling, bloating, joint or muscle pain, weight gain, syncope and headaches[1].

Some authors consider that PMDD symptoms may be of comparable severity to those of major depressive disorder (MDD) and cause a marked impairment in functioning in the week prior to menstruation[8]. The difference between PMDD and MDD is that PMDD symptoms are subsiding with onset of menses. There is also an important overlap between the symptoms of anxiety disorders and PMDD, which is reported in certain studies and raises questions as if there are shared underlying biological abnormalities[9-10]. Premenstrual dysphoric disorder is considered a somatopsychic illness triggered by the changing levels of sex steroids that accompany an ovulatory menstrual cycle[7]. Current research implicates mechanisms of serotonin as relevant to etiology and treatment[11-17].

Patients with mild to moderate symptoms of premenstrual syndrome (PMS) may benefit from nonpharmacologic interventions such as education about the disorder, lifestyle changes and nutritional adjustments[18-20], but patients with premenstrual dysphoric disorder (PMDD) and those who fail to respond to more conservative measures may also require pharmacologic management. *Selective serotonin reuptake inhibitors* (*SSRIs*) are the first-line treatment for PMDD[11-17]. This drug class reduce emotional, cognitive-behavioural, and physical symptoms, and improve psychosocial functioning. As SSRIs, sertraline, fluoxetine and paroxetine (as an extended-release formulation) are approved by the Food and Drug Administration (FDA), for luteal phase, as well as continuous administration[11,13-17]. Escitalopram is a more recent SSRI (closely related with citalopram) and is approved in Romania for the treatment of depressive and anxiety disorders. It is used off-label for other disorders, including premenstrual dysphoric disorder[21], which is included, as discussed, in depressive disorders.

Method

Study Objectives

The primary objective of this study was to assess the efficacy of daily treatment throughout the menstrual cycle with escitalopram (20 mg/day) after 3 cycles of treatment. The secondary objective of the study was to assess the tolerability of treatment with escitalopram.

The main scale used was the Visual analogue scale revised (VASs)[22-23]. The primary efficacy variable was the change in the mean luteal phase VAS-Mood scores from baseline to end of treatment cycle 3[22-23]. Secondary outcome measures included change from baseline to treatment in the sum of the 11 VAS symptoms (VAS-Total) and change from baseline in mean luteal phase VAS physical symptoms (last item).

We also evaluated the proportion of patients showing response, the proportion of patients in remission, the mean change from baseline in the Montgomery Åsberg Depression Rating Scale (MADRS)[24], the mean change in the Clinical Global Impressions Severity (CGI-S)[25] and the mean score of Clinical Global Impressions-Improvement scale (CGI-I)[25].

We defined response as a ≥ 50% reduction from baseline VAS-Mood scores and a Clinical Global Impressions-Improvement CGI-I item score of 1-very much improved or 2-much improved. Remission was defined as a VAS-Mood score less than or equal to the baseline mean follicular phase score.

More details about instruments used are given in clinical trial methodology.

Subject Selection

This was a naturalistic fixed-dose, non-placebo controlled study aimed to assess the efficacy and tolerability of escitalopram in women with PMDD. Eligible patients included 18 women aged 21-44 years with regular menstrual cycles (duration between 22-35 days) and confirmed PMDD (DSM-IV-TR)1. Symptoms of the disorder must have been present in at least 9 out of 12 menstrual cycles over the previous year. To confirm the diagnosis of PMDD, subjects were required to prospectively rate their symptoms using daily diaries (using VASs scale) for 2 cycles prior to baseline (requirements of DSM-IV-TR) [1]. Subjects were considered eligible for the study if the onset of severe premenstrual symptoms during the luteal phase was followed by symptom subsidence during the follicular phase based on the 4 core symptoms of PMDD (irritability, tension, affective lability, and depressed mood). During the reference cycles women were required to demonstrate a 200% luteal phase worsening on 1 core PMDD symptom or a 100% worsening on 2 core symptoms, which included irritability, tension, affective lability and depressed mood (the 4 core items of VASs). Patients must also have had a baseline Clinical Global Impressions-Severity of Illness scale (CGI-S) score of ≥ 3 (for the luteal phase)[25].

Patients were considered ineligible if they met DSM-IV-TR criteria for other important psychiatric disorder in the previous 12 months, were diagnosed with gynaecological or other clinically significant disease, presented significant risk for suicide, were already taking medication for PMDD symptoms, or were breastfeeding or pregnant. Use of oral or systemic contraception during the study also precluded participation.

All potential patients provided signed informed consent prior to participation. Escitalopram is approved in Romania for the treatment of depressive and anxiety disorders.

Patients with suicidal risk represent a psychiatric emergency and are not usually included in clinical studies. Patients with suicidal thoughts should be referred for psychiatric evaluation.

Study design

Eighteen subjects were required to prospectively rate their symptoms using daily diaries (using VASs scale) for 2 cycles prior to baseline. Selection criteria were described in the subject selection section.

No medication was administered during the first 2 reference cycles. Patients who successfully completed 2 consecutive reference cycles and met all entry criteria have begun the treatment with escitalopram, once daily in the morning, continuously throughout the menstrual cycle.

Escitalopram was titrated during the first cycle of treatment as follows: 5mg/day for the first 3 days, then 10mg/day for other 7 days and then 20mg/day. We maintained the 20mg/day dose during the 3 cycles of treatment. We have chosen this dose because of the results in other previous studies, which revealed that 20mg/day seems to be more efficient than 10mg/day11. After the initiation of treatment, study visits were scheduled to occur within the first 5 days of the onset of menses for up to 3 treatment cycles.

Clinical Trial Methodology

Potential study candidates were evaluated based on inclusion criteria at an initial visit and then asked to rate their symptoms, as mentioned in the study design.

VASs is a revised scale made to better reflect the DSM-IV definition of PMDD[23,25], with 4 core mood symptoms (depressed mood, tension, affective lability, and irritability), and with 7 additional clusters of symptoms (decreased interest in usual activities, difficulty with concentration, lack of energy, change in appetite, change in sleep pattern, feeling out of control, and physical symptoms). The use of VASs as a valid and reliable assessment for mood symptoms is well documented. Each VAS item consists of a 100-mm horizontal line with vertical line anchors at each end. The anchors were 0 = "not at all" (that is, "the way you normally feel when you don't have premenstrual symptoms") and 100 = "extreme symptoms" (that is, "the way you feel when your premenstrual symptoms are at their worst"). VAS data of this type is recorded as the number of millimeters from the left of the line in the 0-100 range[23].

Participants completed a self-rating set of 11 VASs daily throughout 5 menstrual cycles (2 pretreatment and 3 treatment cycles). Every score was calculated in the screening (pretreatment) period for diagnostic purposes and inclusion criteria. The scores were also calculated in the 3 cycles of treatment. The VAS scores on the 4 core symptoms were averaged to create a mean score to represent mood symptoms that is, VAS Mood score. This was the primary efficacy variable. We have also calculated the VAS total scores (average of 11 symptom scores) and the mean luteal phase VAS physical symptoms.

Other efficacy assessments used included The Clinical Global Impressions Severity CGI-S, The Clinical Global Impressions-Improvement scale (CGI-I)[25] and The Montgomery Åsberg Depression Rating Scale (MADRS)[24].

The Clinical Global Impressions (CGI) Scale is a standardized assessment tool[25]. The CGI-S assesses the clinician's impression of the patient's current illness state. Scores on the CGI-S range from 1 = not ill at all to 7 = among the most extremely ill. The CGI-I assesses the patient's improvement or worsening from baseline, which here is the beginning of the treatment (the second reference cycle). The CGI-I also goes from 1 = very much improved to 7 = very much worse[25].

The Montgomery Åsberg Depression Rating Scale is a well-known psychiatric scale for depression with 10 items rated from 0 to 6. A score of 10 is used as a *cut-off point* to suspect a depression[24].

Vital signs, laboratory data, and adverse events data were also collected during the study.

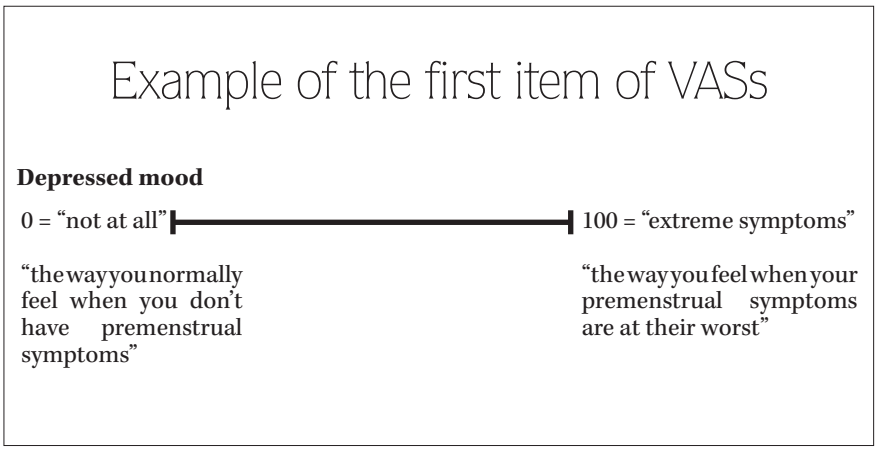
Statistical Methods

For each of the individual VASs items, the patient's mean score was calculated for each luteal phase by averaging the item score over the last 5 days of the luteal phase prior to onset of menstruation. The patient's mean luteal phase VAS-Mood score was then calculated as the mean of the luteal phase core (first 4 items) scores. We calculated also the VAS total scores (total of 11 symptom scores), the mean luteal phase VAS physical symptoms, the mean total MADRS scores and the mean CGI-S and CGI-I scores.

To determine the proportion of patients in remission (defined as a VAS-Mood score less than or equal to the baseline mean follicular phase score), we calculated the mean baseline VAS-Mood at the baseline visit, and compared it with the mean VAS-Mood at the visit of the third of treatment cycle.

By subtracting a baseline score from the corresponding score at each treatment visit (1, 2 and 3 of treatment period), derived the change score.

This study was a naturalistic one and the number of patients was not sufficient to make other statistical measurements.



Results and discussions

Patients and baseline data

This study was carried out in one outpatient centre. Eighteen patients were selected by symptoms criteria, were then screened for 2 consecutive cycles through daily diaries using VASs, have met all of the inclusion criteria and started the treatment. The mean age at study entry was 34.

Mean baseline VAS-Mood score in the luteal phase was 59.07 mm, while in the folicular phase was 8.42 mm (Table 1). Mean MADRS score at baseline was 26.7 (Table 1). There were no marked differences at baseline between patients

Tabel 1. The mean scores of the 11 items of VAS[a]
(at baseline, during the 3 cycles of treatment and the mean change in each item)

Items	Baseline Luteal	Baseline Folicular	Cycle1 Luteal	Cycle2 Luteal	Cycle3 Luteal	Mean Change	Mean Change (%)
Depressed mood	53.2	8.3	23.3	22.1	21.3	-31.9	-59.96
Tension	61.7	9.1	24.6	23.5	23.3	-38.4	-62.23
Affective lability	57.6	7.5	24.5	23.1	22.8	-34.8	-60.41
Irritability	63.8	8.8	25.6	22.8	23.1	-40.7	-63.79
Decreased interest in usual activities	55.8	8.7	23.1	23.4	22.9	-32.9	-58.96
Difficulty with concentration	56.6	9.5	23.6	22.7	21.4	-35.2	-62.19
Lack of energy	51.6	10.5	21.3	21.2	20.7	-30.9	-59.88
Change in appetite	52.2	10.9	20.4	19.7	18.5	-33.7	-64.55
Change in sleep pattern	59.7	11.1	24.7	23.8	23.9	-35.8	-59.96
Feeling out of control	50.4	6.8	19.6	19.2	17.8	-32.6	-64.68
Physical symptoms	61.4	5.7	53.8	54.6	54.9	-6.5	-10.58

[a] *The mean scores are shown in mm, except for the last column (Mean Change shown in percent); Abbreviation: VASs- Visual Analog Scale revised*

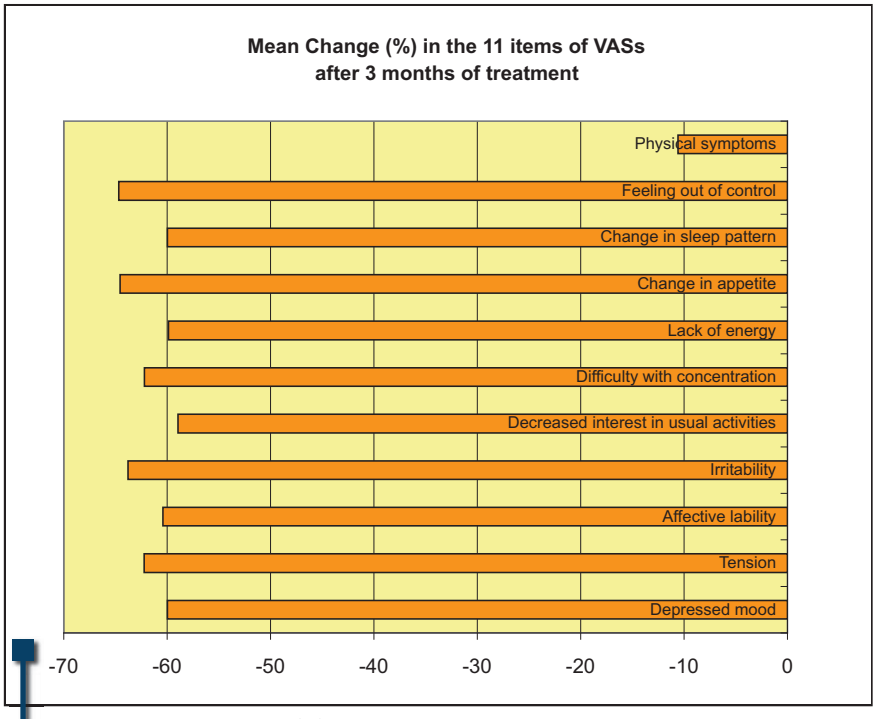


Figure 1. The mean change (%) in the 11 items of VASs after 3 months of treatment[a] ([a] The mean change scores are shown in percentile; Abbreviation: VASs - Visual Analog Scale revised)

with respect to severity of PMDD symptoms as measured by the global assessments. Global assessments of disease severity at baseline in the luteal phase revealed the presence of moderate-to-marked illness, with a mean CGI-S of 4.8 (Table 1).

Table 1 shows the mean scores of all the 11 items of VAS, at baseline (for the luteal and the follicular phase) and also during the 3 cycles of treatment. It also shows the rough mean change and the change (percent) after 3 cycles.

Efficacy Endpoints

The mean scores show improvements in all the 11 items (the difference between the last cycle, the third of the treatment, and baseline) except for the last one, the physical symptoms, which had a minimal improvement (Table 1; Figure 1). The improvements were observed from the first cycle of treatment and this is similar to the results of previous studies[11] which evaluated the response to escitalopram. Previous findings with fluoxetine[10,13,15], sertraline[16,17] and

Table 2. The primary and secondary efficacy variable[a]
(at baseline, during the 3 cycles of treatment and the mean change in each variable)

Itemi	Baseline Luteal	Baseline Folicular	Cycle1 Luteal	Cycle2 Luteal	Cycle3 Luteal	Mean Change	Mean Change (%)
Mean VASs-Mood	59.07	8.42	24.5	22.87	22.62	-36.45	-61.70
Mean VASs-Total	624	96.9	284.5	276.1	270.6	-353.4	-56.63
Mean MADRS	26.7		14.9	15.2	14.6	-12.1	-45.31
Mean CGI-S	4.8		2.2	2.1	1.9	-2.9	-60.41
Mean CGI-I			2.4	2.2	2.2		

[a] The mean scores are shown in mm, except for the last column (Mean Change shown in percent); Abbreviation: VASs - Visual Analog Scale revised; MADRS – The Montgomery Åsberg Depression Rating Scale; CGI-S - The Clinical Global Impressions Severity CGI-S; CGI-I - The Clinical Global Impressions-Improvement scale

paroxetine[14], also showed the improvement in PMDD symptoms as soon as the first treatment cycle.

Figure 1 illustrates the mean change (%) in the 11 items of VASs after 3 months of treatment.

The benefit of escitalopram on VAS-Mood scores was observed in each of the 4 core mood symptoms of PMDD: irritability, tension, affective lability, and depressed mood and in the mean VASs-Total Score (Table 1 and 2; Figure 1, 2 and 3).

Table 2 shows the mean scores of the primary and secondary efficacy variables and the mean change after 3 cycles of treatment.

Figure 2 illustrates the evolution of the mean VASs-Mood Score by Cycle.

Figure 3 illustrates the evolution of the Mean VASs-Total Score by Cycle.

Change in the mean score of the first 10 items was more than 50%, and change in the mean VASs-Mood Score was of 61.70% (Table 2; Figure 1). Only 15 patients (83.33%) of the 18 treated have had a reduction in the VASs-Mood score of >50% and a CGI-I item score of 1-very much improved or 2-much improved, and were qualified as responders. Of those only 5 (27.77%) have had at the last cycle the VASs-Mood Score less than or equal to the baseline mean follicular phase score and were considered as remitters.

The mean MADRS score improved by 45.31% and the mean CGI-S score improved from 4.8 at baseline to 1.9 at the third cycle. The mean CGI-I score was 2.2 (Table 2).

Tolerability

Escitalopram was generally well tolerated during this 3-month study. None of the 18 patients were withdrawn from the study due to adverse events. Most adverse events were mild to moderate and included nausea, asthenia, decreased libido, somnolence, dizziness, sweating, impaired concentration, diarrhea, constipation.

Conclusions

This study has demonstrated that escitalopram, at doses of 20 mg/day is effective in treating the core mood symptoms of PMDD as measured by the primary measure of efficacy, the VASs-Mood. This primary outcome parameter is comprised of measurements of irritability, tension, depressed mood, and affective lability. Significant improvement was demonstrated in all of these symptoms individually, as well as on the composite VAS-Mood scale.

Results also showed that escitalopram improved the VASs-Total Score, the sum of all 11 symptoms that compose the DSM-IV-TR criteria for PMDD. There was not a significant improvement of the physical symptoms of PMDD, as shown in the evolution of the last item of VAS.

Response to treatment with escitalopram can be expected within the first treatment cycle, and most patients have demonstrated a significant improvement at endpoint in the key symptoms as illustrated by the primary outcome parameter. More studies are

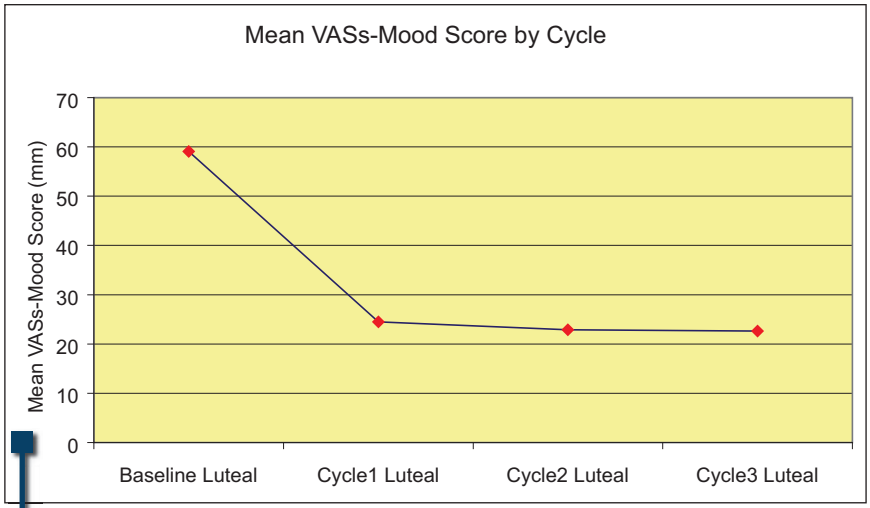


Figure 2. Mean VASs-Mood Score by Cycle[a] ([a] The mean scores are shown in mm; Abbreviation: VASs - Visual Analog Scale revised)

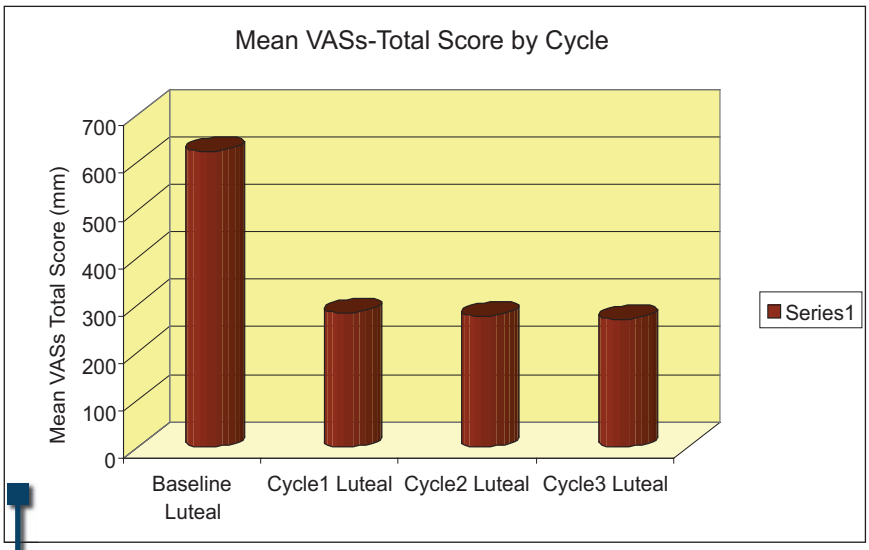


Figure 3. Mean VASs-Total Score by Cycle[a] ([a] The mean scores are shown in mm; Abbreviation: VASs - Visual Analog Scale revised)

needed for this category of patients.

It is also of clinical importance to establish the recommended dose (10mg/day or 20mg/day) as well as the type of administration, intermittent or continuous.

As an SSRI, escitalopram may be recommended for these patients as a first line treatment option. Considering that it does not have the FDA approval at this moment, and based on the existing literature, we may recommend it as a second line option, until more studies will confirm these results. ■

Conflict of interest

I and my colleagues have no financial interest with any organization that could be perceived as a real or apparent conflict of interest in the context of the subject of this activity.

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