Paroxetine versus Vortioxetine for Depressive Symptoms in Postmenopausal Transition: A Preliminary Study
By Camilla Callegari, Marta Ielmini, Ivano Caselli, Giulia Lucca, Celeste Isella, Marcello Diurni, Fabiana Pettenon, Nicola Poloni

ABSTRACT

Background: The impact of menopause is a consequence of social, physical and mental changes; hormonal changes play an important role in inducing an increased risk of developing depressive symptoms. It is essential to treat mood and vasomotor symptoms and to prevent their onset to promote an improvement in the quality of life, both in terms of clinical and psychological conditions. Objective: This observational study aims to compare paroxetine and vortioxetine in a sample of patients affected by postmenopausal depression attending the Anxiety and Depression Clinic in terms of: efficacy in determining clinical remission (HDRS ≤ 7) and tolerability; improvement of autonomic and cognitive symptoms. Methods: 39 female outpatients with a diagnosis of Postmenopausal Depression (according to DSM-5 criteria) were evaluated as the routine clinical practice through the following scales: Hamilton Depression Rating Scale (HDRS); Menopause Rating Scale (MRS); Montreal Cognitive Assessment (MoCA); Antidepressant Side-Effect Checklist (ASEC); data from baseline, after 8 weeks and 12 weeks were recorded. Results: Both antidepressants resulted to be effective in clinical remission (HDRS ≤ 7) without statistical differences between the two groups (p = 0.3), although paroxetine showed a faster remission than vortioxetine (p = 0.01). Autonomic symptoms showed a higher improvement in the vortioxetine group (p = 0.002). Paroxetine group referred insomnia and sexual problems while patients taking vortioxetine referred diarrhoea and palpitations. Data show a superiority of cognitive performance in the Paroxetine group (p = 0.005), contrary to what stated in literature. Conclusions: Data are related to a small sample retrospectively assessed through a 6-month observation period. Thus, the preliminary results need further research to be confirmed.

Callegari, MD, PhD, Associate Professor, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Ielmini, MD, PhD Student, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Caselli, MD, PhD Student, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Lucca, MD, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Isella, MD, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Diurni, MD, PhD, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Pettenon, MD, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy. Poloni, MD, PhD, Researcher, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Varese, Italy.

To whom correspondence should be addressed: Camilla Callegari, MD, PhD, Associate Professor, Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Viale Borri 57, 2100 Varese, Italy. Phone: 0332 278727; E-mail: camilla.callegari@uninsubria.it
INTRODUCTION

The impact of menopause in women is a consequence of social, physical and mental changes. Although menopause represents a condition linked to physiological aging, it is evident that the consequent physical and mental alterations produce a radical change in women’s life. About 75% of women manifest typical signs and symptoms, which constitute the “climacteric syndrome”; these symptoms seem to be extremely variable from individual to individual and influenced by social, cultural, environmental and psychological factors.1,2 The most common symptoms of the postmenopausal transitions are autonomic symptoms (hot flashes, sweating, palpitations, vertigo, tachycardia), sexual sphere disorders (reduction of libido and vaginal dryness) and psycho-emotional symptoms, such as insomnia, anxiety, depression, asthenia, emotional lability, irritability and apathy.3–7

The onset of psychological symptoms during the menopause transition seems to be related to psychological factors (as the loss of the procreative role and the transformation of external image) and to neurotransmitter alterations linked to the modification of hormone levels. Several studies8,9 describe the neuro-modulation effects of estrogens on serotonergic and noradrenergic systems as a cause of amines dysregulation. Alongside with these, cognitive symptoms are also highlighted, such as loss of concentration and memory; in fact, estrogens modulate synaptic plasticity and neuroprotection and their chronic deficiency reduces the neuronal repair capacity, the number of dendritic spines and the synthesis, deposit and release of neurotransmitters.10–12

Depression peak incidence is estimated between 55 and 74 years,13 and its prevalence is twice in women than in males.14 In modern society, the increase in life expectancy has meant that about a third of women’s life is spent in menopause. Therefore, studies on correlation between menopause and depression acquire primary importance.15 Numerous evidences show that menopause represents a window of vulnerability for the onset of Major Depressive Disorder, both in women with a previous affective disorder, and in women without psychiatric background.16–18

Risk factors for menopausal depression are represented by previous episodes of depression, history of premenstrual syndrome and iatrogenic menopause, but also psychological and social factors such as: negative attitude towards menopause, reduction of social relationships and changes in lifestyle.19–21 Moreover, the presence of major menopausal symptoms, as hot flashes, night sweats and insomnia, represent a confounding factor since they could overlap depression symptoms themselves.22–26
For these reasons, it is widely shared that treating postmenopausal symptoms is essential to gain an improvement in women’s life quality, prevent the onset of Major Depressive Disorder and reduce the related financial and social costs.\textsuperscript{27,28}

The efficacy of antidepressants, particularly Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), on anxiety and depressive symptoms, but also on vasomotor and cognitive symptoms, is widely documented in professional literature.\textsuperscript{29–31} Among antidepressants, Paroxetine has proven to be the most effective drug to treat vasomotor and cognitive symptoms in postmenopausal transition, as well as the first non-hormone therapy for vasomotor symptoms approved by the Food and Drug Administration in 2013.\textsuperscript{32–36}

Also in 2013, FDA approved the use of Vortioxetine in the treatment of depressive disorders. Vortioxetine is a so-called serotonin modulator and stimulator with a proven effectiveness both on mood and cognitive symptoms. Compared to the other SSRIs, Vortioxetine seems to present a better tolerability profile, especially for effects poorly tolerated by menopausal women such as loss of libido, weight gain and withdrawal symptoms.\textsuperscript{37–42}

While many authors agree on the antidepressant efficacy of Vortioxetine, there are few studies in literature dealing with the efficacy on menopausal symptoms; preliminary data showed statistically significant efficacy on hot flashes, anxiety, and cognitive complaints\textsuperscript{43} but the topic needs further analysis. In light of these considerations, this study aims to compare Paroxetine and Vortioxetine in terms of efficacy in: determining clinical remission of affective symptoms (HDRS $\leq$ 7) and tolerability; improving autonomic symptoms and cognitive impairment.

**MATERIALS AND METHODS**

*Study Design and Population*

In this preliminary observational naturalistic study, 39 female patients in menopausal transition attending the Anxiety and Depression Clinic of the Psychiatry Unit of Varese between April 2017 and January 2018 have been evaluated. Outpatients had to fulfil the following inclusion criteria: age between 45 and 65 years; history of amenorrhea for at least 12 months; presence of depressive symptomatology clinically verified by psychiatric specialist examination; score at the *Hamilton Depression Rating Scale* (HDRS) $\geq$ 12; have a prescription of paroxetine or vortioxetine, as a switch from other antidepressants or as a new therapy. Patients’ data were made anonymous obscuring sensitive data in the
research to protect the recognizability of the patients. As data were made anonymous and unidentifiable, the Provincial Health Ethical Review Board (Ethics Committee of Insubria – Azienda Socio Sanitaria Territoriale Sette Laghi, Varese, Italy) consulted prior to the beginning of the study, has confirmed that, as it was a retrospective study, it did not need authorization from the Board.

Data collected referred at three evaluation times defined: baseline, $T_0$ (before the start of the treatment), $T_1$ (after 8 weeks), $T_2$ (after 12 weeks). At baseline socio-demographic and clinical data of patients were collected. Socio-demographic variables considered were: age; nationality; current residence; education; working condition; marital status and cohabitation; number of children. Physiological data as age of onset of menopause, any hormone replacement therapy in progress, smoking and alcohol habits, were also collected. Psycho-pathological anamnesis included: investigation of current and previous medical illnesses and therapies; familiarity for depressive disorders or previous depressive episodes; current or previous pharmacological or psychotherapeutic interventions, with particular attention to antidepressant and anxiolytic drugs. The date of antidepressant introduction was considered as baseline. During the therapy the clinicians routinely administer different assessment scales at the time of new therapy introduction and after 8 and 12 weeks of treatment, considering those visits as follow-up. The assessment scales considered are the following: Hamilton Depression Rating Scale (HDRS or HAM-D) for the evaluation of depressive and anxious symptoms; Menopause Rating Scale (MRS) to analyse the typical symptomology of menopause, with particular reference to autonomic symptoms; Montreal Cognitive Assessment (MoCA) to evaluate cognitive performance; Antidepressant Side-Effect Checklist (ASEC), in order to define the tolerability profile of the drug used. The last one was considered for $T_1$ and $T_2$, whereas the others were considered also for the baseline.

**Statistical Analysis**

Socio-demographic data was described by calculating absolute and relative frequencies for dichotomous or categorical variables, and mean and standard deviation for age at recruitment and at menopause. Patients’ characteristics in the two groups were compared using the Chi-square test, for the categorical variables, and the T-test for the comparison between the age averages. All collected scales were described with mean and standard deviation. T-test was applied to highlight any differences between the mean values in the two groups at each visit. A variance analysis for repeated measures was used to evaluate the effect of the two treatments over time and the possible existence of a different effect over...
time. The analyses were made both considering the total score of the scales and the sub-scales, if applicable.

Given the number of the sample, the parametric model appears to be sufficiently robust even in case of deviation from the normal distribution, for this reason no transformation in ranks of the scores of the scales was adopted.

The number of treatment-emergent adverse events (TEAE)\textsuperscript{44} has been evaluated with ASEC; T\textsubscript{1} and T\textsubscript{2} have been described by reporting the absolute and relative distribution of the severity scale. All tests are considered at a significance level of 0.05. Given the pilot nature of the study no adjustment for multiple tests was adopted. The analyses were carried out with the \textit{Statistical Analysis System} (SAS) version 9.4 software.

\section*{Results}

\textbf{Sociodemographic and Clinical Characteristics}

Of the 39 women evaluated, 24 are treated with paroxetine (Par) and 15 with vortioxetine (Vor). All participating women are Italian. Sociodemographic and clinical characteristics of the sample are showed in Table 1. The mean baseline HDRS total score (T\textsubscript{0}) was 15.5 (SD $\pm$ 3.1) in the Par group and 16.2 (SD $\pm$ 3.2) in the Vor group, indicating a mild/moderate severity of depressive disease in both groups. Factors such as working conditions, concomitant medical conditions or care of family members with particular problems, which can in many cases negatively impact on the psychophysical stability, are resulted fully comparable in the two groups. The average age of onset of menopause was 47 years in the Par group and 48 years in Vor; most patients were naturally menopausal women in both groups, as shown in Table 1. Globally, the majority of women have reached menopause in a physiological way and only a minority in the Par group is treated with hormone replacement therapy, a condition that does not lead the two groups to differ significantly. No patient presents alcohol or substance abuse and smoking habits are uniform between the two groups. Concerning the psychopathological anamnesis of the two groups it is shown that 80\% of women in the Vor group presented a familiar predisposition to depression, compared to 62.5\% in the Par group, a difference that appears to be significant ($p = 0.02$). A previous depressive episode has been referred by 50\% of women in the Par group and by 80\% of patients in the Vor group. 100\% of women in the Vor group had taken an antidepressant therapy in the past versus 25\% of patients in the Par group, while the use of benzodiazepines (BDZs), or other psychotropic drugs (as olanzapine and quetiapine) and psychotherapy is homogeneous in the two populations.
### TABLE 1

**Socio-demographic and Clinical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>PAR (N = 24)</th>
<th>VOR (N = 15)</th>
<th>p-VALUE*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Average (SD)</strong></td>
<td>54.8 (5.3)</td>
<td>54.8 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Education n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree</td>
<td>0 (0.0)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>18 (75.0)</td>
<td>12 (80.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Middle School</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Primary School</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maiden</td>
<td>3 (12.5)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>12 (50.0)</td>
<td>12 (80.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Widow</td>
<td>9 (37.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Occupation n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Stable</td>
<td>9 (37.5)</td>
<td>9 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>6 (25.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>3 (12.5)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>3 (12.5)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Cohabitation n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>9 (37.5)</td>
<td>0 (0.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>With other members</td>
<td>15 (62.5)</td>
<td>15 (100.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Descendants n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (50.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (12.5)</td>
<td>9 (60.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>2</td>
<td>6 (25.0)</td>
<td>6 (40.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at menopause Average (SD)</strong></td>
<td>47.9 (2.9)</td>
<td>48.2 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cause of menopause n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td>18 (25.0)</td>
<td>12 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Induced</td>
<td>6 (75.0)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Hormone replacement therapy n (%)</strong></td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Other medical conditions n (%)</strong></td>
<td>12 (50.0)</td>
<td>12 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Medical treatments n (%)</strong></td>
<td>6 (25.0)</td>
<td>6 (40.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Smoke n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (62.5)</td>
<td>9 (60.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>3 (12.5)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Current-smoker</td>
<td>6 (25.0)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Familiarity for depressive disorders n (%)</strong></td>
<td>15 (62.5)</td>
<td>3 (20.0)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Previous depressive episodes n (%)</strong></td>
<td>12 (50.0)</td>
<td>12 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Previous ADs use n (%)</strong></td>
<td>6 (25.0)</td>
<td>15 (100.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Switch from others ADs n (%)</strong></td>
<td>3 (12.5)</td>
<td>15 (100.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Treatment with BDZs n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (62.5)</td>
<td>12 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Introduced</td>
<td>6 (25.0)</td>
<td>3 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Already in place</td>
<td>3 (12.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Regarding the scores of the rating scales at follow-up, a statistically significant difference in the HDRS scores emerged, as shown in Table 2 and in Figure 1. Although both molecules have shown an efficacy in the reduction of both depressive and anxiety symptoms, a statistically significant difference in the control of both symptoms emerged ($p = 0.004$), showing a major improvement in the Par group.

### Menopausal Symptoms

Concerning menopausal symptoms, the average scores, standard deviations and results of the repeated measures analysis, investigated through MRS scale, are illustrated in Table 2. Figure 2 shows that both treatments are effective in reducing menopausal symptoms over the
months, with a significant superiority for vortioxetine even if the Vor group, starts from a higher severity score ($p < 0.001$).

**Tolerability**

The prevalence of TEAEs has been compared through the ASEC scale scores. Both drugs show a good tolerability profile and no patient discontinued therapy due to the onset of serious side effects. Only three patients (out of the total enrolled group) taking paroxetine referred intolerable gastrointestinal disturbances, with a consequent dose reduction by clinicians to 10 mg/die. Regarding the main TEAEs described in literature, nausea was reported as initially very intense in the first week, but gradually attenuating and disappearing in the following months in the Par group; on the contrary nausea was complained as becoming even more severe in the Vor group ($p = 0.002$). In the first 8 weeks of treatment in the Par group are reported somnolence, frequent yawnings and from a moderate to severe increase of appetite. The first two effect were characterized by a significant decrease both in terms of frequency and intensity in the following 4 weeks, while weight gain remained significantly high, more pronounced compared to treatment with vortioxetine ($p = 0.001$). As shown in Figures 3 and 4, a moderate-severe weight gain was referred...
at T2 by the entire population, described by the patient as extremely difficult to tolerate. In the Vor group, during the first treatment period, the reduction of appetite was detected with moderate intensity, further attenuated at T2. A mild-moderate xerostomia was complained with high frequency in both T1 populations; this effect has been reduced in the Par group but has persisted in the Vor population. Insomnia in the Par group and diarrhoea in the Vor group were respectively reported at T1 but they have been reduced at T2. Headache was detected in both group (16.7% in Par group and 25% in Vor group); this effect was resulted as persisting over time. A very common side effect is constipation, also of high intensity (16.7% in Par group and 25% in Vor group).

In the Vor group was detected as tending to decrease over time (0% at T2), while in the Par group has often been maintained, requiring a pharmacological remedy (16.7%). As regard as sexual sphere disorder, libido decrease was described in the Par group, 16.7% of patient reported light intensity and 16.7% moderate intensity symptoms at T1; 33.3% of patient reported light symptoms at T2 while no one reported more symptoms of moderate intensity. In the Vor group, instead, no sexual disfunction was detected at T1 while 25% of patients reported light intensity symptoms at T2. A moderate-severe dizziness and a mild-moderate confusion are also described in both groups, but without statistical significance.
FIGURE 3

Side Effects in the Two Groups Compared to T₁ (n = 30)
FIGURE 4

SIDE EFFECTS IN THE TWO GROUPS COMPARED TO T2 (N = 30)
Cognitive Impairment

Regarding cognitive impairment, MoCa scale total score shows a homogeneity of the baseline and T1 scores in the two groups, while a significant difference appeared between the two treatments at T2, with better cognitive performance for the Paroxetine group (p value = 0.005), as shown in Table 2.

Discussion and Conclusions

This preliminary study aimed to compare two antidepressants, paroxetine, a well-known molecule commonly used in clinical practice, and vortioxetine, still little used, especially outside of psychiatric context, in terms of efficacy in remission of depressive and anxiety symptoms and tolerability in a population of post-menopausal women diagnosed with depressive disorder. To this purpose, the scores of four clinical scales (HDRS, MRS, MoCA, ASEC), administered over 12 weeks, to 24 patients taking paroxetine and to 15 patients receiving vortioxetine, have been evaluated.

The two groups were globally resulted uniform for both demographic and clinical characteristics. An exception is represented by the psychopharmacological anamnesis: in the Par population 12.5% of patients had used antidepressants in the past, while in the Vor group, all patients had already used an antidepressant; this datum is unanimous with the literature, since vortioxetine is still little used as a first line treatment.45–48 Treatment efficacy was defined on the reduction of the HDRS score over time, considering the remission of the depressive symptoms to the achievement of a score less than or equal to 7. Both treatments were effective in reducing depressive symptomatology over time, showing a significant decrease, although paroxetine showed a more rapid and statistically significant reduction compared to vortioxetine. The efficacy of Paroxetine on anxiety symptoms, both in monotherapy and in combination with benzodiazepines or atypical antipsychotics is widely described in the literature;49–51 conversely data available on vortioxetine are few but seem to be optimistic;52,53 our results support a comparable efficacy of both molecules in reducing these symptoms, although paroxetine reconfirms its superiority over time in getting remission.

Vor group women presented a higher MRS average total score, corresponding to a higher severity of menopausal symptoms. As reported by many authors, both these aspects could have a significant impact on the quality of life’s perception.54,55 Although the final total average scores do not prove a definite remission of menopausal symptoms, the results, in terms of effectiveness in improving symptoms over time, seem to
confirm what is already known for paroxetine and confirm for vortioxetine what emerged from preliminary studies.\textsuperscript{56} Furthermore, vortioxetine seems to demonstrate superior efficacy and a significantly longer time course compared to paroxetine (p value = 0.0007).

With regard to MocA, the results highlighted the effectiveness of both molecules in improving cognitive abilities at the same time. However, vortioxetine seems to present a limitation in this improvement, while paroxetine shows a long-term efficacy over time.

Dealing with TEAEs we could affirm that these are comparable in the two treatments and are likely to depend on individual susceptibility. This data is consistent to the literature confirming that antidepressants tolerability is very variable, and patient’s response depends on individual variability for at least 40%. It can take several months (even years) of clinical trial and error before an effective tolerable antidepressant is found for an individual patient.\textsuperscript{57}

\textit{Strengths and Limitations}

The study presents some limitations, as the small sample size due to the short period of observation, and the study design. A larger sample would widen the inclusion and exclusion criteria in order to reduce the variables’ number. It would also be appropriate to re-evaluate some of the tools used, choosing a questionnaire for anxiety. The choice of an adequate scale is, in fact, important in terms of using it as a screening tool or even in common clinical practice.\textsuperscript{58–60} It could be interesting to investigate the patient’s resilience at T\textsubscript{0}, in order to identify any differences before the treatment start and in subsequent follow-up to highlight a possible role of therapies on individual adaptability.\textsuperscript{61,62} As the Vor group starts from a higher score than the Par group, it would be useful to study a larger sample size in order to see if this difference remains, once the confounding variables have been eliminated.

\textit{Acknowledgments}

None.

\textit{References}


Paroxetine vs Vortioxetine in Postmenopause


