Comparative safety and efficacy of tibolone and escitalopram in postmenopausal women

ABSTRACT

Background: A high prevalence of psychiatric disorders, particularly depressive and anxiety disorders among women is observed through the postmenopausal stage.

Aim: The aim of this study is to compare the safety and efficacy of tibolone (TIB) and escitalopram (ESCIT) in postmenopausal women (PMW).

Materials and Methods: It was an interventional, open-label, hospital-based, follow-up study conducted on 60 PMW with the diagnosis of depression as per the Diagnostic and Statistical Manual of Mental Disorder-5 criteria. Patients were divided into two groups of 30 each, i.e. Group I (TIB-2.5 mg/day) and Group II (ESCIT-10–20 mg/day). The primary outcome was assessed for change in climacteric symptom scores on Greene’s Climacteric Scale (GCS), severity of depression and anxiety on Hamilton Rating Scale for Depression (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A), and sexual functioning on Arizona Sexual Experience Scale (ASEX). The secondary outcome of well-being was assessed on World Health Organization Quality of life (QOL)-BREF. All the observations were carried out from baseline and at 2, 4, 8, and 12 weeks.

Results: Both the groups showed significant improvement in climacteric and depressive symptoms. However, at the 8th and 12th weeks, mean ± standard deviation scores were significantly lower in Group I (GCS score - 24.80 ± 4.92, 20.30 ± 3.56; HAM-D score - 16.57 ± 5.83, 10.2 ± 5.67) compared to Group II (GCS score - 27.27 ± 5.83 and 23.33 ± 5.70, HAM-D score - 19.97 ± 7.98 and 16.17 ± 10.11). No significant difference between the groups was seen for anxiety on HAM-A scores. Only in Group I, there was significant improvement in ASEX scores. QoL in Group I had shown significant improvement in physical and psychological domain compared to Group II at different time interval, i.e. 4th and 8th week onward. In Group I, Alternative Dispute Resolution was reported to be 23.3%, whereas it was 56.7% in Group II. However, none were serious to warrant discontinuation. Conclusion: TIB was better than ESCIT in improving depression, climacteric symptoms, and physical and psychological domain of QoL with an additional benefit of restoring sexual functioning.

Keywords: Anxiety, postmenopausal depression, tibolone
Decreased hormone levels can lead to vaginal dryness and tightness, which can cause pain during sex. A global study of 13,882 women ages 40–80, reported that 26%–48% of women had a lack of interest in sex, and the prevalence of sexual dysfunction in PMW varied from 68% to 86.5%. SSRIs can be used successfully to control the depressive and anxiety symptoms in PMW. However, they have low acceptability in view of their possible side effects including sexual dysfunction. Escitalopram (ESCIT) is a widely used SSRI. It is often used to treat depression and is sometimes used for anxiety, obsessive compulsive disorder, or panic attacks.

It is believed that estrogen has some modulating effect on serotonin, titrated imipramine binding in platelets, serotonin presynaptic reuptake, norepinephrine levels, monoamine oxidase levels, dopamine turnover, brain excitability, endorphin levels, and a possible interaction with gamma amino butyric acid. All these changes have an impact on functioning of the brain and thus could result in psychological changes in PMW. In recent years, hormone therapy (HT) has been projected as a possible strategy that is capable in reducing the physical symptoms and thus make the process of transition to menopause smooth with added benefits of improving the psychological well-being of the affected women. Compounds such as Tibolone (TIB) which directly target the disrupted hormonal systems (in particular estrogen) have shown significant potential to treat depression, anxiety, estrogen-withdrawal symptoms such as hot flushes, sweating, insomnia, headache, and vaginal dryness, and with the additional property of a progestogenic activity on the endometrium. Besides these, it has also positive effects on sexual well-being and mood, and improves dyspareunia and libido. These effects may depend on both estrogenic and androgenic actions exerted at the genital level and in the central nervous system, and on a reduction of sex-hormone-binding globulin and an increase of free testosterone, without affecting Δ-5 androgens levels. However, in spite of having potential, TIB has never been studied for depression, anxiety, sexual dysfunction, and QoL in India. Meagre literature available from elsewhere has shown that TIB is effective for depression, anxiety, sexual dysfunction, and in improving QOL in PMW. However, those findings cannot be generalized to Indian women because of sociocultural differences. Thus present study was planned to assess the efficacy and safety of TIB in PMW and compare it with ESCIT.

### MATERIALS AND METHODS

This interventional, study was conducted at the Department of Psychiatry of a Tertiary Care Medical College and Hospital. It was an open-label, hospital-based, continuous follow-up study conducted on 60 PMW with clinically confirmed diagnosis of depression as per Diagnostic and Statistical Manual of Mental Disorder (DSM)-5.

#### Inclusion criteria
- Females who have currently achieved natural menopause with amenorrhea for at least 1 year
- Able to give informed consent
- First onset or relapse of major depressive disorder during menopause
- Patients diagnosed as per DSM-5 criteria.

#### Exclusion criteria
- Patients with any history of thyroid dysfunction, active or past history of a venous thrombo-embolic event, breast pathology, undiagnosed vaginal bleeding, or abnormal Pap smear results
- Patients with any significant unstable medical illness such as epilepsy, diabetes, known active cardiac, renal, liver disease; or the presence of any illness causing immobilization
- Patients with psychotic symptoms or past history of severe mental illness
- Use of any form of estrogen, progestin or androgen as HT, or antiandrogen including TIB or use of phyto-estrogen supplements as powder or tablet
- Smoking cigarettes or other nicotine products
- Illicit drug use and alcohol use (however, no participant was excluded because of this).

#### Ethical considerations

The institutional ethics committee gave ethical clearance for the study prior to data collection. The Indian Council of Medical Research guidelines for biomedical research in human subjects were followed. The study was conducted as per the Good Clinical Practice Guidelines and declaration of Helsinki, Geneva. Written informed consent was taken. Patients were informed that they can opt out whenever they wanted and it would not affect the treatment.

#### Sample size

\[
\alpha \text{ error} = \text{Two-tailed 0.05, power } (1-\beta) = 0.8, \text{ standard deviation } = 1.00
\]

The standard normal deviate for \( \alpha = Z\alpha = 1.95996 \)

The standard normal deviate for \( \beta = Z\beta = 0.84162 \)

Standardized effect size = \( (E/S) = 0.75 \)

\( N = 60 \)

\( A = 30, B = 30 \)
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Tools
Sociodemographic and clinical pro forma
It gathers details including name, age, marital status, occupation, educational status, and family type. Clinical parameters such as past history of depression and family history of depression were recorded.

Hamilton Rating Scale for Depression
It consists of 17 items; takes 15–20 min to complete. Interrater reliability for the total score ranges from 0.87 to 0.95. Normal = 0–7 mild depression = 8–13 moderate depression = 14–18 severe depression = 19–22 very severe depression ≥23.[11]

Hamilton Anxiety Rating Scale
It consists of 14 items designed to assess the severity of a patient’s anxiety. A score of 17 or less indicates mild, 18–24 indicates moderate, 25–30 indicates severe anxiety. It has a very good internal consistency with Cronbach’s alphas of 0.79–0.86 and test-retest reliability value of 0.64.[12]

Arizona Sexual Experience Scale
It is a 5-items rating scale that quantifies sex drive, arousal, vaginal lubricationability to reach orgasm, and satisfaction from orgasm. Possible total range from 5 to 30, with the higher scores indicating more sexual dysfunction.[13]

Greene’s Climacteric Scale
It is a validated menopausal symptom scale which is used routinely in clinical practice and as a research tool. The Greene’s Climacteric Scale (GCS) scores the severity of 21 symptoms on a scale of 0–3. Higher scores indicate a greater number of symptoms and/or symptom severity.[14]

World Health Organization Quality of life-BREF
Each item uses a Likert type five-point scale. The items are distributed into four domains (physical, psychological, social, and environmental health). Domain scores are scaled in a positive direction (higher scores denote higher QoL). The scale has good discriminant validity, sound content validity, and good test-retest reliability.[15]

Procedure
Patients were equally divided into two groups of 30 each using computer-generated random numbers, i.e., Group I, TIB (2.5 mg/day) and Group II, ESCIT (10–20 mg/day). The socio-demographic and clinical data were recorded. Primary outcome was assessed for change in climacteric symptom scores on GCS, severity of depression and anxiety on Hamilton Rating Scale for Depression (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A), and sexual functioning on Arizona Sexual Experience Scale (ASEX). The secondary outcome of well-being was assessed on World Health Organization QoL-BREF. All the observations were carried out from baseline and at 2, 4, 8, and 12 weeks [Figure 1].

Statistical analysis
Statistical analysis was performed using the SPSS (version 21) (IBM Inc., Atlanta, USA). The level of statistical significance was set at a $P \leq 0.05$. Student’s $t$-test’ and Mann–Whitney $U$-test were used.

RESULTS

On comparing the two groups statistically, there was no significant difference with respect to any of the demographic and socioeconomic characteristics [Table 1], and follicle stimulate hormone (FSH) and luteinizing hormone (LH) levels at baseline [Table 2].

Mean scores of HAM-D improved significantly from baseline to all the follow-up intervals in both the groups ($P < 0.001$ **(Highly significant)). However, the scores were significantly lower in the Group I compared to Group II at 8 weeks and 12 weeks [Table 3].

Mean HAM-A scores improved significantly from baseline to all the follow-up intervals in both the groups ($P < 0.001$ **). No statistically significant difference was found between the groups at any follow-up interval [Table 4].

Mean ASEX scores improved significantly from the baseline to all the follow-up intervals in Group I. Between groups, the mean scores were not significantly different at baseline and 2 weeks. However, the scores were significantly
lower in the Group I compared to Group II at 4, 8 and 12 weeks [Table 5].

Statistically, there was no significant difference between groups at baseline, 2 weeks and 4 weeks. However, at 8 week and 12 week intervals, scores in Group I were significantly lower compared to that in Group II. In both the groups, the change in climacteric symptom scores at 12 weeks compared to baseline was significant [Table 6].
Both the groups had shown significant improvement in QOL domains. However, Group I had statistically more significant improvement compared to Group II in psychological domain (from 4th week onward) and in physical domain (from 8th week onward) [Table 7].

None of the patients experienced any serious adverse event in either of the two groups [Table 8].

Table 4: Comparison of Hamilton anxiety score between and within group at baseline and different follow-up intervals

| Variable | Baseline | 2 weeks | 4 weeks | 8 weeks | 12 weeks |
|----------|----------|---------|---------|---------|----------|
| Group I  |          |         |         |         |          |
| Median   | 22       | 18      | 13      | 11      | 8        |
| Mean±SD  | 25.2±14.47 | 21.27±13.4 | 16.67±11.69 | 13.50±10.15 | 11.13±8.1 |
| Group II |          |         |         |         |          |
| Median   | 21       | 18      | 15.5    | 13      | 12       |
| Mean±SD  | 24.77±14.21 | 21.57±14.25 | 19.43±13.73 | 17.10±12.92 | 16.31±12.58 |

The above "P" value is for within group changes from baseline (Wilcoxon signed-rank test)

Table 5: Between and within group comparison of Arizona sexual experience score at baseline and different follow-up intervals

| Group | Baseline | 2 weeks | 4 weeks | 8 weeks | 12 weeks |
|-------|----------|---------|---------|---------|----------|
| I     |          |         |         |         |          |
| Median | 21       | 19      | 16.5    | 14      | 12       |
| Mean±SD | 21.13±3.04 | 19.5±3.08 | 16.8±3.82 | 14.6±3.73 | 12.7±2.61 |
| II    |          |         |         |         |          |
| Median | 19.5     | 19.3±3.52 | 19.3±3.55 | 19.37±3.59 | 19.5    |
| Mean±SD | 19.37±3.56 | 19.03±3.52 | 19.3±3.55 | 19.37±3.59 | 19.5±3.88 |

The above "P" value is for within group changes from baseline (Wilcoxon signed-rank test)

Table 6: Comparison of Greene’s Climacteric Scale total scores between and within group at baseline and different follow-up intervals

| Group | Baseline | 2 weeks | 4 weeks | 8 weeks | 12 weeks |
|-------|----------|---------|---------|---------|----------|
| I     |          |         |         |         |          |
| Median | 37.0     | 33.0    | 30.0    | 25.0    | 20.0     |
| Mean±SD | 37.8±8.34 | 33.13±7.06 | 28.9±6.54 | 24.8±4.92 | 20.3±3.56 |
| II    |          |         |         |         |          |
| Median | 36.0     | 35.0    | 32.0    | 30.0    | 25.0     |
| Mean±SD | 37.9±8.25 | 34.25±6.79 | 30.47±6.89 | 27.27±5.83 | 23.33±5.70 |

The above "P" value is for within group changes from baseline (Wilcoxon signed-rank test)

SD – Standard deviation. **Highly significant

DISCUSSION

This is the first study in India comparing safety and efficacy of TIB with ESCIT. A total of 60 PMW with clinically confirmed diagnosis of depression aged 45–60 years were enrolled in the study. Similarly, in another study the age of PMW with depression was reported to be 41–60 years with majority being in the age group of 46–50 years (60.6%).

### Table 7: Between and within group comparison of World Health Organization quality of life at baseline and different follow-up intervals

| Variable | Baseline | 2 weeks | 4 weeks | 8 weeks | 12 weeks |
|----------|----------|---------|---------|---------|----------|
|          | 2 weeks  | 4 weeks | 8 weeks | 12 weeks |
| Z (Mann-Whitney U-test) | 0.287 | 0.504 | 0.997 | 1.252 | 0.72 |
| P        | 0.774 | 0.615 | 0.319 | 0.211 | 0.471 |
|          | 2 weeks  | 4 weeks | 8 weeks | 12 weeks |
| Z (Mann-Whitney U-test) | 0.38  | 0.123 | 0.499 | 0.922 | 0.695 |
| P        | 0.704 | 0.902 | 0.618 | 0.357 | 0.487 |
|          | 2 weeks  | 4 weeks | 8 weeks | 12 weeks |
| Z (Mann-Whitney U-test) | 0.105 | 0.616 | 1.736 | 2.322 | 3.586 |
| P        | 0.916 | 0.538 | 0.083 | 0.02* | <0.001** |
|          | 2 weeks  | 4 weeks | 8 weeks | 12 weeks |
| Z (Mann-Whitney U-test) | 0.075 | 1.281 | 2.463 | 3.09  | 4.238 |
| P        | 0.941 | 0.2  | 0.014* | 0.002** | <0.001** |
|          | 2 weeks  | 4 weeks | 8 weeks | 12 weeks |
| Z (Mann-Whitney U-test) | 0.203 | 0.414 | 1.242 | 1.847 | 1.828 |
| P        | 0.839 | 0.679 | 0.214 | 0.065 | 0.068 |
|          | 2 weeks  | 4 weeks | 8 weeks | 12 weeks |
| Z (Mann-Whitney U-test) | 0.94 | 4.40 | 4.40 | 50.00 | 50.00 |
| P        | 0.001** | <0.001** | <0.001** | <0.001** | <0.001** |

The above *P* value is for within group changes from baseline (Wilcoxon signed rank test).
The mean age of (PMW) in our study was 50 years in Group I and 51.17 years in Group II. An earlier study also reported the mean age of women to be 52.8 and 51 years in TIB versus placebo groups, respectively. Similarly, in India, the age of onset of menopause was reported to be 40–55 years. Thus, the age profile of (PMW) in present study was in accordance with the literature. The study population consisted predominantly of married women (81.7%), well educated (45% graduates and 26.7% higher secondary), living in an extended (45%) or nuclear (41.7%) family and residing in urban areas (60%). Socio-economically, majority (53.3%) was from upper middle class. Statistically, there was no significant difference between study groups with respect to demographic and socio-economic profile. This is expected since both the groups were selected from the same clinic and proper randomization procedure was done. Thus, the demographic and socioeconomic profile did not pose a confounding effect due to random allocation. No significant differences between groups were observed for family history and past history of depression. Out of N = 60; total of 11 (18.3%) patients had a family history of depression and 10 (16.7%) patients reported past history of depression. As far as association of postmenopausal depression with personal and/or family history of depression is concerned, there is divided opinion. One study reported that a personal or family history of major depression is a risk factor for postmenopausal depression. However, another study stated that family history of depression was associated with midlife depression among women rather than postmenopausal depression. Assessment of this relationship was beyond the scope of our work; however, this factor did not emerge as a confounder because of proper randomization. The two groups were also statistically similar for baseline hormonal profile (FSH and LH), climacteric symptoms score, depression and anxiety scores, sexual function scores, and quality of life scores. Thus, the study had an ideal randomization suitable for a randomized comparative non-superiority controlled trial.

The objective of the study was to assess the effectiveness of TIB in postmenopausal depression. At the end of 12 weeks, HAM-D scores showed a decline of 20.63 ± 7.06 (66.92%) in TIB group and 13.83 ± 2.80 (54.25%) in ESCIT group thus, showing a significant improvement among both the groups (P < 0.001**). However, at 8 and 12 weeks, mean scores were significantly lower in TIB compared to ESCIT group (P < 0.05*). This finding suggested that compared to ESCIT, TIB resolved depression not only in a better way but also at a faster rate. In TIB group, the reduction of depression scores was 17%, 30%, 46%, and 67% at 2, 4, 8, and 12 weeks, respectively.

These findings were similar one study which also showed reduction of 19%, 27%, 42%, and 49% in depression scores using MADRS at 2, 4, 8, and 12 weeks, respectively, after the intervention of TIB in 22 patients. Another nonrandomized study, reported a significant reduction of 21% in HDRS scores in 19 patients following 6 months of TIB therapy in PMW which was lower than our study. It is difficult to assign the reason for this difference, but methodological differences could be the reason and the authors of the above study did not disclose the dose and regimen of TIB. In patients receiving ESCIT, there was a reduction of 54.25% in HAM-D scores at the end of 12 weeks in our study. It was slightly lower than reported in previous studies. One study reported a reduction of 65.8% in depression scores using HDRS after 6 weeks of treatment with ESCIT in 20 patients at a similar dose range. Another study also showed 70% decline in mean

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### Table 7: Contd...

| Variable | Baseline | 2 weeks | 4 weeks | 8 weeks | 12 weeks | Baseline versus 2 weeks | Baseline versus 4 weeks | Baseline versus 8 weeks | Baseline versus 12 weeks |
|----------|----------|---------|---------|---------|----------|----------------------------|----------------------------|----------------------------|----------------------------|
| Median   | 41.00    | 41.00   | 41.00   | 47.00   | 47.00    | 0.157                      | 0.010**                    | <0.001**                   | <0.001**                   |
| Mean±SD  | 41.57±14.48 | 41.97±14.71 | 43.50±15.44 | 46.83±15.06 | 47.70±14.63 |                           |                           |                           |                           |
| Z (Mann-Whitney U-test) | 0.343 | 1.039 | 0.94 | 0.544 | 0.852 | The above "P" value is for within group changes from baseline (Wilcoxon signed rank test) |
| P        | 0.731    | 0.299   | 0.347   | 0.586   | 0.394    |                            |                           |                           |                           |

SD – Standard deviation. **Highly significant

### Table 8: Adverse events/complaints by cases of Group I

| Group | Variable | n (%) |
|-------|----------|-------|
| I     | Patient with any serious adverse event | 0     |
|       | Adverse events reported by patients |       |
|       | Vaginal bleeding | 3 (10.0) |
|       | Breast pain | 2 (6.7) |
|       | Pelvic pain | 1 (3.3) |
|       | Headache | 1 (3.3) |
| II    | Patient with any serious adverse event | 0     |
|       | Adverse events reported by patients |       |
|       | Nausea | 4 (13.3) |
|       | Restlessness | 2 (6.7) |
|       | Sexual dysfunction | 10 (33.3) |
|       | Dry mouth | 1 (3.3) |
depression scores on MADRS after 8 weeks of therapy in 308 patients. The relatively better performance of TIB with respect to management of depression as observed in the present study could be attributed to its strong estrogenic effect. Anxiety symptoms scores using HAM-A showed a significant decline of 56% in TIB group at the end of 12 weeks (P < 0.001**). Some previous studies have reported improvement in anxiety with TIB. There was a significant reduction by 34% in anxiety symptoms in ESCIT group at the end of 12 weeks which is lower than reduction of 62.4% in HAM-A scores in an earlier study. The reason for this difference could be due to the difference in methodology. The present study showed that both TIB and ESCIT are effective in the management of postmenopausal depression. However, TIB was more effective than ESCIT in managing depressive symptoms at the 8th and 12th weeks. Both the drugs improved anxiety symptoms significantly.

During the study period, ASEX showed significant 40.60% improvement (P < 0.001**) in patients receiving TIB but no significant change was reported in the ESCIT Group at 12 weeks. Thus, TIB outperformed ESCIT in improving sexual function. In a study, where TIB was given for 24 weeks, satisfying sexual event rate was found to increase three to four times per 28 days. Furthermore, in another study, there was a significant improvement of sexual function in the TIB group in all domains of Female Sexual Function Index after 6 months of treatment.

TIB has been proven to be more effective than other estrogenic alternatives in improving climacteric symptoms according to various studies. In our study, there was significant improvement of 46% in GCS at 12 weeks of treatment which is higher than 38% improvement in GCS following 12 weeks of TIB treatment in another study.

On the other hand, ESCIT showed an significant improvement of 38.57% in the GCS score at 12 weeks (P < 0.001). However, Defronzo Dobkin et al. reported an average decrease of 55% in frequency of hot flashes with ESCIT.

These findings suggest that TIB's positive influence on the sexual function acted synergistically with its estrogenic and serotonergic effects that has improved depression and anxiety scores better than ESCIT. SSRIs such as ESCIT is known to have an adverse impact on sexual drive resulting in low libido. This reduced sexual drive and incompatibility with partner might give rise to anxiety and depression among women who are desirous to continue their sex-life even after menopause, which puts ESCIT at disadvantage compared to TIB.

At 12 weeks, both the drugs showed a significant improvement in QOL. However, scores for satisfaction with physical and psychological health were significantly higher in TIB group as compared to ESCIT group but no significant difference was present between groups in social and environmental domains. The positive impact of TIB and ESCIT on QOL has been reported in a number of previous studies. The better performance of TIB as compared to ESCIT could be attributed to its additional benefits on depression, climacteric symptoms and sexual functions as highlighted above.

No serious Alternative Dispute Resolution (ADR) was reported in any of the group that warranted discontinuation. In Group I, ADR was reported to be 23.3%; out of which 10% had vaginal bleeding, 6.7% reported breast pain, 3.3% reported pelvic pain and 3.3% had headache. In Group II, 56.7% reported ADR; out of which 13.3% patients reported nausea, 6.7% reported of restlessness, 33.3% reported sexual dysfunction, and 3.3% had dry mouth.

There were certain limitations in the study such as the present study was carried out on a small sample size and absence of a placebo group. This trial only monitored TIB's effects over 12 weeks. Longer follow-up studies may help in better understanding about the safety and efficacy of these drugs.

Future research can be taken up for replication of findings from other parts of the world. The study of change in serum estrogen levels of PMW could help in better understanding the underlying mechanisms of the drug TIB.

**CONCLUSION**

TIB was better than ESCIT in improving depression, climacteric symptoms, and physical and psychological domain of QoL with an additional benefit of restoring sexual functioning.

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Nil.

**Conflicts of interest**
There are no conflicts of interest.

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