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Research paper

Tibolone improves depression in women through the menopause transition: A double-blind randomized controlled trial of adjunctive tibolone

Jayashri Kulkarni*, Emorfia Gavrilidis, Natalie Thomas, Abdul-Rahman Hudaib, Roisin Worsley, Caroline Thew, Caitlin Bleeker, Caroline Gurvich

Monash Alfred Psychiatry Research Center (MAPrc), Central Clinical School, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia

A B S T R A C T

Background: Many women with no past psychiatric history experience severe mood symptoms for the first time in their life during the menopausal transition, with debilitating long-term consequences. Women with a history of depression can experience a relapse or worsening of symptoms during the menopause transition. Traditional antidepressants, SSRIs or SNRIs, are commonly prescribed as the first line response. However, such treatment has shown only small improvements with side effects. Hormone therapies directly targeting the perimenopausal fluctuations in reproductive hormonal systems such as tibolone, have significant potential to treat perimenopausal depression. Our study investigated the use of adjunctive tibolone, selective tissue estrogenic activity regulator, to treat de-novo or relapsing depression occurring during the menopause transition period.

Methods: Women who were going through the menopause transition with depressive symptoms were invited to participate in a double-blind, 12 week randomized control trial with two arms: tibolone (2.5 mg oral/day) or oral placebo (***NCT01470092***). Forty-four women met inclusion/exclusion criteria; 22 were randomized to tibolone and 22 were randomized to oral placebo. Symptoms were measured with the 'Montgomery- Asberg depression rating scale' (MADRS) as the primary outcome measure. Latent growth curve analysis was used to assess the MADRS scores change over time.

Results: Participants in the tibolone group demonstrated a significant improvement in depression scores, as compared to the placebo group, without any significant side effects.

Limitations: This trial only monitored tibolone's effects over 12 weeks. Future research should be conducted over an extended timeframe and explore whether the benefits of tibolone extend to other symptoms of perimenopausal depression.

Conclusions: The use of hormone therapies such as tibolone provide exciting innovations for the treatment of depression during the menopause transition.

The menopause transition is a time of significant fluctuation and change in reproductive hormones. Adverse psychological symptoms, particularly depressive symptoms, are commonly reported during this period. The term "perimenopausal depression" has been utilized to describe the specific depressive symptomatology that can occur during the menopause transition (Parry, 2008; Steinberg et al., 2008), which appears to be a subtype of depression with a unique aetiology (Kulkarni, 2017). Women experiencing perimenopausal depression may respond differently to antidepressant medications as compared to women experiencing depression outside of the menopause transition (Kornstein et al., 2000a), thus hormone treatments may be more effective for this group of women.

The perimenopausal period is defined as the time immediately prior to menopause, beginning with endocrine, biological and clinical changes, and ending the year after the final menstrual period and typically begins for women during their mid-to-late 40s (Brambilla et al., 1994a). Longitudinal epidemiological studies have shown that many women experience significant physical and mental health changes approximately 4–5 years before menopause is reached (Burger, 2008; Cohen et al., 2006). Although vasomotor symptoms such as hot flushes and night sweats occur in up to 70% of perimenopausal women (Brinton et al., 2015), the major reason that many women seek help during perimenopause is for depression and anxiety symptoms (Tam et al., 1999). For many women, these symptoms impact significantly on their quality of life, social and personal well-being (Brambilla et al., 1994b).

Accumulating data indicates that the menopause transition is associated with an increased risk of depressed mood, for women with a

* Corresponding author.
E-mail address: jayashri.kulkarni@monash.edu (J. Kulkarni).

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history of depression as well as for women with no history of depression (Freeman, 2010). For example, in the Penn Ovarian Aging Study (POAS), the risk of depressive symptoms (as measured by the Center for Epidemiological Studies Depression Scale) was nearly three times higher in women undergoing the transition to menopause as compared with premenopausal women (Freeman, 2010; Schmidt et al., 2004). Further longitudinal analysis of the POAS cohort indicated that women with no history of depression were more than four times more likely to experience depressive symptoms in the menopausal transition compared with these same women when they were premenopausal (Freeman, 2010). Mirroring this finding, the Harvard Study of Moods and Cycles reported that women with no history of depression were nearly twice as likely to experience depression in the menopausal transition compared with premenopausal women (Cohen et al., 2006).

There are a range of biopsychosocial factors that are likely to contribute to the aetiology of perimenopausal depression. Changes in hormones of the hypothalamic-pituitary-gonadal axis can have direct effects on neurotransmitter systems involved in the modulation of mood. This includes declines in estradiol, inhibins and allopregnanolone as well as the increase in FSH (Slopien et al., 2017; Soares and Zitek, 2008). Gonadal hormones also interact with the other major endocrine axis, the hypothalamic-pituitary-adrenal axis, with evidence indicating hypothalamic-pituitary-adrenal axis dysregulation may contribute to increased depression risk or exacerbated sensitivity to stressful situations (Gordon et al., 2016). These significant hormonal influences are likely to interact with several psychosocial factors that coincide with menopausal years such as perception of aging and childbearing status, life habits, and stressful family/life roles (such as caring for children as well as elderly parents) (Kulkarni, 2017; Li et al., 2016).

Given the evidence suggesting perimenopausal depression may be a subtype of depression linked to significant hormonal changes, it is possible that the treatment response to standard antidepressant treatment may also be different in this subgroup. Perimenopausal women have been found to be less responsive to SSRI therapy for depression than postmenopausal women (Kornstein et al., 2000b) and women of child bearing age (Thase et al., 2005). Furthermore, a common side effect of SSRIs is sexual dysfunction (Montejo et al., 2001) and this is of particular relevance to perimenopausal women who frequently report sexual dysfunction as a key determinant of quality of life (Andac and Aslan, 2017).

The efficacy of hormone therapy in improving depression associated with the menopausal transition is unclear. A meta-analysis published in 1997 included 26 studies (randomized and uncontrolled) investigating the effect of different hormone therapies on mood in groups of both perimenopausal and postmenopausal women, with depressed mood and/or other mild depressive symptoms. Results found that hormone therapies – both combined estrogen and progesterone and unopposed estrogen - were associated with a reduction in depression (with a moderate to large effect size) (Zweifel and O'Brien, 1997). A more recent review (Worsley et al., 2012) identified 16 studies that had trialled pharmacological therapy specifically for perimenopausal depression. Nine of those studies included estrogen therapy alone or as an adjunct. The authors concluded that while estrogen therapy appeared effective in improving depressive symptoms one of the difficulties of using estrogen therapy on a long term basis is the need for women with an intact uterus to be given a progestin to prevent endometrial hyerplasia. Clinically, this can be problematic as progestins can worsen depression or negate the beneficial effects of estradiol (Worsley et al., 2012).

A useful alternative to combined hormone therapy is tibolone, which is a synthetic steroid with tissue-selective estrogenic, androgenic and progestogenic properties (Kloosterboer, 2004). Unlike estrogen, tibolone has no estrogenic activity in endometrial or breast tissue. The central nervous system effects of tibolone were recently reviewed (Pinto-Almazan et al., 2017) and while there are only a few studies available, preliminary evidence suggests that tibolone has the capacity to modify brain plasticity, exert antioxidant effects and regulate neurotransmitter systems, including the serotonergic system which is particularly relevant to mood.

The clinical efficacy of tibolone in treating the physical symptoms of menopause has been demonstrated in a number of randomized clinical trials, some of which examined depressive symptoms as a secondary outcome. One 18-week randomized cross-over control trial of Tibolone 2.5 mg compared with estradiol valerate and placebo in surgically postmenopausal women ($n = 20$) who did not specifically report depression as a baseline symptom. Results reported a secondary outcome of significantly greater mood improvements in the tibolone and estradiol compared with placebo groups (Crona et al., 1988). Ross et al. (1999) conducted a RCT of tibolone or estrogen plus progesterone in 28 postmenopausal women and also found significant improvements in anxiety, irritability, memory and a number of somatic symptoms including sleep, hot flushes and night sweats within the first month.

The clinical evidence is therefore supportive of the efficacy of tibolone in improving mood in postmenopausal women. There is, however, less evidence of efficacy for tibolone in women who present specifically with depressive symptoms. In one four-week randomized trial of tibolone compared with estrogen plus progesterone in 61 perimenopausal women with no psychiatric disorder, tibolone was found to be just as effective as sequential estrogen-progesterone therapy in significantly improving depressive symptomatology (as measured by the Beck Depression Inventory) (Inan et al., 2005).

The aim of the current study was to determine the clinical efficacy of adjunctive tibolone for depression experienced during the menopause transition. Specifically, we conducted a twelve-week double-blind, placebo controlled randomized controlled trial in women that were perimenopausal or early postmenopausal with depression (with a first-onset, relapse or persistent depressive symptoms that commenced during the peri menopause) to determine whether women taking tibolone (2.5 mg oral/day) in adjunct to standard antidepressant treatment showed a greater improvement in depression symptoms as compared to women receiving adjunctive placebo.

1. Method

1.1. Participants

174 women were screened for eligibility (see Fig. 1). Forty-four women met inclusion/exclusion criteria and were included in the 12-week, double –blind, placebo controlled adjunctive trial. Twenty-two women were randomized to adjunctive tibolone (2.5 mg oral/day), and 22 were randomized to oral placebo.

Inclusion criteria required women to be between 45 and 65 years of age, have no physical illnesses, and to hold a current diagnosis of major depressive disorder (or symptoms that would likely meet criteria for depression if formally assessed). Exclusion criteria were venous thromoemblic events, any unstable chronic medical illnesses, current use of ECT or menopausal hormone therapy, psychotic disorders, tobacco smoking (20 cigarettes per day), or pregnancy/lactation. Diagnosis of major depressive disorder was made by treating psychiatrists and confirmed by research staff using the mini international neuropsychiatric interview (MINI) (Sheehan et al., 1998). To ensure patient safety mammograms, breast ultrasound, and Pap smear examination details were obtained prior to beginning the study, as well as performing an ECG and routine blood tests checking renal, liver, thyroid function, plus electrolytes and full blood examination.

This study was approved by The Alfred Hospital Ethics Committee, Melbourne Australia. All participants provided written informed consent (according to the guidelines of the Australian National Health and Medical Research Council). The trial was registered at *ClinicalTrials.gov identifier (NCT number): NCT01470092*.

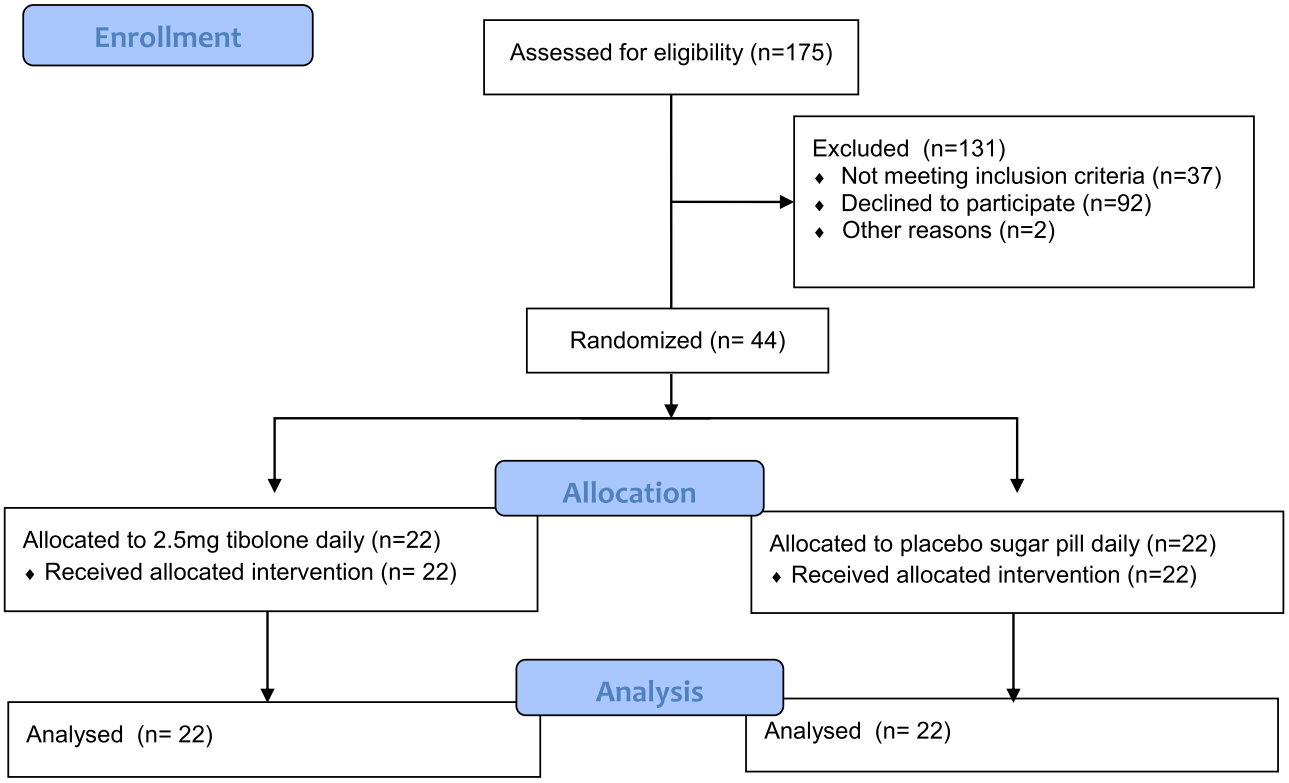

Fig. 1. CONSORT flow diagram.

1.2. Interventions

Participants were individually randomized by The Alfred Clinical Trials Pharmacy to receive either: 2.5 mg daily tibolone; or placebo according to a computer generated randomization list. Medication was given as an adjunct to participant's standard medication. All study personnel and participants remained blind to treatment assignment for the duration of the study.

1.3. Outcome measures

The **Montgomery Asberg depression rating scale (MADRS)** (Montgomery and Asberg, 1979) was the primary outcome measure. The MADRS was administered at baseline, week 2, 4, 8, and 12. The MADRS is a semi-structured interview with ten questions, targeting the core symptoms of depression. Each item is scored between 0, representing no symptomology, to 6 representing severe symptomology. Hence, higher scores were associated with more severe depression symptoms.

The **adverse symptom checklist (ASC)** (ASC Program Steering Group, 2001) was a secondary outcome measure and is used to assess common psychotropic medication side-effects. The ASC was administered at baseline, week 2, 4, 8, and 12. Scoring of each side effect was marked as present or absent.

1.4. Statistical analysis

Latent growth curve (LGC) analysis (Bollen and Curran, 2006) was used to assess the MADRS scores change over time. Scores were collected over 5 time points; baseline, week two, week four, week eight and week twelve. Descriptive statistics for the sample details are reported in Table 1. The LGC method utilises the advantages and strengths of both structural equation and the hierarchical linear mixed modeling (Raudenbush and Bryk, 2002). Typically, LGC models estimate fixed and random coefficients across participants repeated scores and allow for the inclusion of time invariant covariates used in interventional trials. Furthermore, LGC is flexible with spacing of time values (λ) which are coded to reflect growth time intervals.

Table 1
Participants details & total score means (SD) for each time point.

Variable	Tibolone (n = 22)	Placebo (n = 22)
Age - years	52.8 (5.75)	51.0 (4.69)
SNRI	3 (13.64%)	5 (22.73%)
SSRI	10 (45.45%)	6 (27.27%)
MADRS _ Total score baseline	26.86 (11.57)	25.21 (9.49)
MADRS _ Total score week 2	21.74 (12.64)	22.45 (9.79)
MADRS _ Total score week 4	19.61 (12.96)	20.00(9.57)
MADRS _ Total score week 8	15.54 (11.03)	22.53 (9.10)
MADRS _ Total score week 12	13.77 (11.39)	19.21 (8.26)

SD (standard deviation); SNRI: serotonin and norepinephrine reuptake inhibitors;
SSRI: *Selective serotonin reuptake inhibitors.*

An important advantage of LGC model is that it enables for the assessment of the overall fit of the final solution. In addition, other empirical non-linear growth features can be explored.

Unconditional linear LGC model (without the effect of tibolone as covariate) was first estimated to determine the shape of the scores migration over time and assess the variance in the intercept (baseline). In this model, the metric of time was coded $\lambda = 0$, $\lambda = 1$, $\lambda = 2$, $\lambda = 4$, $\lambda = 6$ and the path loadings for the intercept were fixed at 1.

Conditional LGC model examined the intervention effect of tibolone (time invariant covariate) on the linear scores progression over time. The model fitness was examined via χ^2 test, comparative fit index (CFI), Tucker-Lewis index (TLI) and root mean square error of approximation (RMSEA). CFI and TLI values greater than 0.90 and an RMSEA less than 0.1 indicate adequate fit. Analyses were conducted by IBM SPSS and Amos software (ver 22).

2. Results

Participant's details and baseline scores are presented in Table 1. Forty four women with depression who were around the menopause or postmenopause were included in these analyses (22 received tibolone and 22 placebo). Participants from each group did not differ by age ($p = 0.27$) or baseline total MADRS score ($p = 0.19$). Twenty-four (54.55%) participants were stable on antidepressant medication (36.36% on SSRI; 18.18% SNRI) and antidepressant use did not differ significantly between groups ($p = 0.39$).

2.1. Unconditional model

The unconditional linear model with five repeated MADRS scores showed an overall fit indices of ($\chi^2 = 17.8$, $p = 0.09$ CFI = 0.96, TLI = 0.94, RMSEA = 0.09). The adequate fit for the data supports the use of linear model in subsequent analysis. The variance of the intercept factor in the model was 97.1 ($SE = 23.8$; $p < 0.001$), indicating significant individual differences in scores at baseline. The variance of the slope factor was 0.96 ($SE = 0.35$; $p = 0.006$) which indicates a significant individual differences in MADRS scores across time points. The estimated mean of the slope was −1.04 which shows the mean level of scores in the sample dropped about one point every two weeks.

2.2. Conditional model

The conditional LGC model fit indices were ($\chi^2 = 24.0$, $p = 0.05$ CFI = 0.94, TLI = 0.91, RMSEA = 0.10). The fixed loadings from the latent slope factor to each of the five observed time points (MADRS scores) were 0, 1, 2, 4, and 6, representing the time interval measured by week (see Fig. 2). The slope negative regression coefficient showed that treatment with tibolone significantly predicted the linear slope ($b = -1.14$, $SE = 0.36$, $p = 0.001$). For participants in the tibolone group, the MADRS scores significantly dropped by 1.65 compared to the placebo group. The intercept positive coefficient ($b = 1.36$, $SE = 3.19$, $p = 0.66$) indicated baseline MADRS scores for both groups were not significantly different (albeit slightly higher for the tibolone group). The model revealed that even with the treatment effect estimated, the residual variances were still significant for the intercept factor and the slope factor which denote an additional individual variation in scores at baseline and over time.

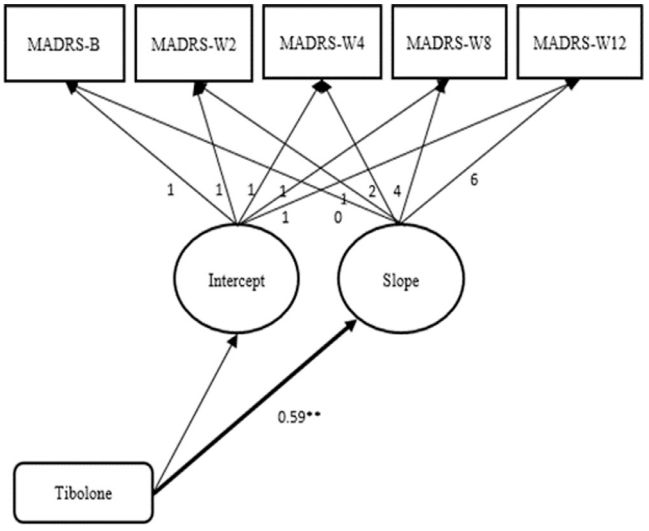

Fig. 2. Conditional latent growth curve model showing standardized path coefficient from Tibolone to the intercept and slope of MADRS scores from baseline (B) to week 12 (W12). $^{**}p < 0.01$.

Table 2
Proportion of participants who experienced adverse effects by treatment group ($n = 22$ in each group).

	Tibolone	Placebo	*P value*[a]
Somnolence	12(54.5%)	9(41%)	0.55
Tiredness	15(68%)	14(64%)	0.99
Insomnia	10(45%)	13(59%)	0.55
Headache	10(45%)	12(55%)	0.76
Dry mouth	8(36%)	9(41%)	0.99
Nausea/vomiting	11(50%)	5(23%)	0.12
Constipation	8(36%)	8(36%)	0.99
Sexual dysfunction	4(18%)	3(14%)	0.99
Dizziness	7(32%)	6(27%)	0.99
Menstrual irregularity	6(27%)	5(23%)	0.99
Blurred vision	6(27%)	4(18%)	0.72
Urinary hesitancy	4(18%)	1(5%)	0.34
Breast engorgement	2(9%)	4(18%)	0.66
Concentration difficulty	9(41%)	13(59%)	0.37

[a]Two-tailed Fisher exact tests.

2.2.1. Side effects

Side effects did not significantly differ between groups (Table 2). The most common side effect experienced in both groups was tiredness, which is a symptom commonly described during menopause.

3. Discussion

This 12 week randomized controlled trial compared the adjunctive tibolone to adjunctive placebo in improving depression severity in perimenopausal women experiencing a first-onset, relapse or persistent depressive symptoms. Results support the hypothesis that adjunctive tibolone significantly improved depression scores, without any significant side effects.

This study is the first study to specifically investigate the antidepressant efficacy of tibolone for depressive disorders in women who are around the menopause or postmenopause. This study adds to the literature that support the use of third generation hormone treatment in alleviating psychological symptoms experienced by women during times of great hormonal fluctuation (Dennis et al., 2008), and more specifically, during the menopause transition (Soares et al., 2001; Schmidt et al., 2000).

There are a number of potential mechanisms by which tibolone may exert its antidepressant effect. Tibolone is classed as a selective tissue estrogenic activity regulator (STEAR). The 3α-hydroxy and 3-hydroxy metabolites of tibolone are responsible for estrogenic effects of tibolone in the brain by activating estrogen receptors (ERα, and to a lesser extent, ER β) (Genazzani et al., 2006; Kenemans, 2004). The beneficial effects of estrogen on mood are considered to be related to estrogen's capacity to modulate dopaminergic and serotonergic activity (McEwen and Alves, 1999). Animal studies have provided initial evidence supporting the capacity for tibolone to modulate the serotonergic system (Espinosa-Raya et al., 2012). There is also preliminary evidence that tibolone can restore β-endorphin levels (Notelovitz, 2007), which drop during menopause, and this tibolone induced increase in endorphins may contribute to the antidepressant effects. One further mechanisms by which tibolone administration can improve mood is via tibolone's capacity to increases CNS allopregnanolone levels, a neurosteroid with sedative and anxiolytic properties (Genazzani et al., 2006).

One limitation of the current study is that this trial only monitored tibolone's effects over 12 weeks. Perimenopausal depression symptoms can be experienced for several years, with symptoms in some cases reported up to five years before the cessation of a woman's menstruation. Therefore, longitudinal studies spanning the menopause transition including biomarker and bleeding criteria to stage the menopause transition, as well as exploring the benefits and long term safety of tibolone are necessary. While the current study focused specifically on

depressive symptoms, future research should be conducted to investigate other symptoms associated with the menopause transition. For example, there is only preliminary evidence suggesting tibolone may improve cognition during the menopause transition (Pinto-Almazan et al., 2017).

In conclusion, this randomized controlled trial found that 12 weeks of tibolone significantly improved depression severity in women around the menopause who presented with depression, without any significant side effects. Future research should be conducted to explore the benefits of longer term tibolone use and whether tibolone can improve other symptoms commonly reported during perimenopause. Furthermore, investigating the efficacy of tibolone for depression at early and late stages of the menopause transition is important given previous research indicating hormone therapies can show differential benefits for peri- and post- menopausal women (Cohen et al., 2003). The use of hormone therapies such as tibolone is an ongoing area of work, which provides exciting innovations for the treatment of perimenopausal depression in this substantial group of women.

Declarations of interest

None.

Authors' contributions

Author Kulkarni participated in the conception and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. Author Gavrilidis provided assistance in the setup of the study including ethics and budget as well as acquisition of data. Authors Thomas and Bleeker were involved in the acquisition of data and drafting of this manuscript. Author Hudaib undertook the analyses and writing of the study results. Author Worlsey participated in the conception and design as well as revision of the manuscript. Author Thew provided critical revision of the manuscript. Author Gurvich participated in the analysis and interpretation of data; and played a significant role drafting this manuscript. All authors contributed to and have approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.04.103.

References

Andac, T., Aslan, E., 2017. Sexual life of women in the climacterium: a community-based study. Health Care Women Int. 1–12.
ASC Program Steering Group, 2001. Using the ASC program: a training guide. J. Psychiatr. Pract. 7, 64–68.
Bollen, K.A., Curran, P.J., 2006. Latent Curve models: A structural Equation Perspective. Wiley, New York.
Brambilla, D.J., McKinlay, S.M., Johannes, C.B., 1994. Defining the perimenopause for application in epidemiologic investigations. Am. J. Epidemiol. 140, 1091–1095.
Brinton, R.D., Yao, J., Yin, F., Mack, W.J., Cadenas, E., 2015. Perimenopause as a neurological transition state. Nat. Rev. Endocrinol. 11, 393–405.
Burger, H., 2008. The menopausal transition–endocrinology. J. Sexual Med. 5, 2266–2273.
Cohen, L.S., Soares, C.N., Poitras, J.R., Prouty, J., Alexander, A.B., Shifren, J.L., 2003. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. Am. J. Psychiatry 160, 1519–1522.
Cohen, L.S., Soares, C.N., Vitonis, A.F., Otto, M.W., Harlow, B.L., 2006. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch. Gen. Psychiatry 63, 385–390.
Crona, N., Samsioe, G., Lindberg, U.B., Silfverstolpe, G., 1988. Treatment of climacteric complaints with org OD 14: a comparative study with oestradiol valerate and placebo. Maturitas 9, 303–308.
Dennis, C.L., Ross, L.E., Herxheimer, A., 2008. Oestrogens and progestins for preventing and treating postpartum depression. Cochrane Database Syst. Rev CD001690.
Espinosa-Raya, J., Neri-Gomez, T., Orozco-Suarez, S., Campos, M.G., Guerra-Araiza, C., 2012. Chronic administration of tibolone modulates anxiety-like behavior and enhances cognitive performance in ovariectomized rats. Horm. Behav. 61, 76–83.
Freeman, E.W., 2010. Associations of depression with the transition to menopause. Menopause 17, 823–827.
Genazzani, A.R., Pluchino, N., Bernardi, F., Centofanti, M., Luisi, M., 2006. Beneficial effect of tibolone on mood, cognition, well-being, and sexuality in menopausal women. Neuropsychiatr. Dis. Treat. 2, 299–307.
Gordon, J.L., Rubinow, D.R., Eisenlohr-Moul, T.A., Leserman, J., Girdler, S.S., 2016. Estradiol variability, stressful life events, and the emergence of depressive symptomatology during the menopausal transition. Menopause 23, 257–266.
Inan, I., Kelekci, S., Yilmaz, B., 2005. Psychological effects of tibolone and sequential estrogenprogestogen therapy in perimenopausal women. Gynecol. Endocrinol. 20, 64–67.
Kenemans, P., 2004. Tibolone: how does its mechanism of action translate into clinical effects. Maturitas 48 (Suppl 1), S1–S3.
Kloosterboer, H.J., 2004. Tissue-selectivity: the mechanism of action of tibolone. Maturitas 48 (Suppl 1), S30–S40.
Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Davis, S.M., Harrison, W.M., Keller, M.B., 2000a. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am. J. Psychiatry 157, 1445–1452.
Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Davis, S.M., Harrison, W.M., Keller, M.B., 2000b. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am. J. Psychiatry 157, 1445–1452.
Kulkarni, J., 2017. How to treat- perimenopausal depression. Aust. Doctor 17–24.
Li, R.X., Ma, M., Xiao, X.R., Xu, Y., Chen, X.Y., Li, B., 2016. Perimenopausal syndrome and mood disorders in perimenopause: prevalence, severity, relationships, and risk factors. Medicine 95, e4466.
McEwen, B.S., Alves, S.E., 1999. Estrogen actions in the central nervous system. Endocr. Rev. 20, 279–307.
Montejo, A.L., Llorca, G., Izquierdo, J.A., Rico-Villademoros, F., 2001. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish working group for the study of psychotropic-related sexual dysfunction. J. Clin. Psychiatry 62 (Suppl 3), 10–21.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Notelovitz, M., 2007. Postmenopausal tibolone therapy: biologic principles and applied clinical practice. MedGenMed 9, 2.
Parry, B.L., 2008. Perimenopausal Depression. Am. J. Psychiatry 165, 23–27.
Pinto-Almazan, R., Segura-Uribe, J.J., Farfan-Garcia, E.D., Guerra-Araiza, C., 2017. Effects of tibolone on the central nervous system: clinical and experimental approaches. BioMed Res. Int. 2017, 8630764.
Raudenbush, W.R., Bryk, A.S., 2002. Hierarchical Linear models: Applications and Data Analysis Methods, 2nd ed. Sage, Thousand Oaks, CA.
Ross, L.A., Alder, E.M., Cawood, R.H.H., Brown, J., Gebbie, A.E., 1999. Psychological effects of hormone replacement therapy: a comparison of tibolone and a sequential estrogen therapy. J. Psychosomatic Obstet. Gynecol. 20, 88–96.
Schmidt, P.J., Haq, N., Rubinow, D.R., 2004. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. Am. J. Psychiatry 161, 2238–2244.
Schmidt, P.J., Nieman, L., Danaceau, M.A., Tobin, M.B., Roca, C.A., Murphy, J.H., Rubinow, D.R., 2000. Estrogen replacement in perimenopause-related depression: a preliminary report. Am. J. Obstet. Gynecol. 183, 414–420.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33 quiz 34–57.
Slopien, R., Pluchino, N., Warenik-Szymankiewicz, A., Sajdak, S., Luisi, M., Drakopoulos, P., Genazzani, A.R., 2017. Correlation between allopregnanolone levels and depressive symptoms during late menopausal transition and early postmenopause. Gynecol. Endocrinol. 1–4.
Soares, C.N., Almeida, O.P., Joffe, H., Cohen, L.S., 2001. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: A double-blind, randomized, placebo-controlled trial. Arch. Gen. Psychiatry 58, 529–534.
Soares, C.N., Zitek, B., 2008. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? J. Psychiatry Neurosci. 33, 331–343.
Steinberg, E.M., Rubinow, D.R., Bartko, J.J., Fortinsky, P.M., Haq, N., Thompson, K., Schmidt, P.J., 2008. A cross-sectional evaluation of perimenopausal depression. J. Clin. Psychiatry 69, 973–980.
Tam, L.W., Stucky, V., Hanson, R.E., Parry, B.L., 1999. Prevalence of depression in menopause: a pilot study. Arch. Women's Mental Health 2, 175–181.
Thase, M.E., Entsuah, R., Cantillon, M., Kornstein, S.G., 2005. Relative antidepressant efficacy of venlafaxine and SSRIs: sex-age interactions. J. Women's Health 14, 609–616.
Worsley, R., Davis, S.R., Gavrilidis, E., Gibbs, Z., Lee, S., Burger, H., Kulkarni, J., 2012. Hormonal therapies for new onset and relapsed depression during perimenopause. Maturitas 73, 127–133.
Zweifel, J.E., O'Brien, W.H., 1997. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology 22, 189–212.