Impact of hormone therapy on mood in a real-world clinical setting: a retrospective observational study

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Abstract

Objective: Mood disturbances—including depressed mood, irritability, anxiety, and mental exhaustion—are common during the menopause transition, affecting up to 68% of women. While menopausal hormone therapy (HT) is FDA-approved for vasomotor and genitourinary symptoms, its role in managing mood symptoms remains less well understood. This retrospective, comparative study evaluated the impact of systemic HT on mood in a cohort of HT-naive individuals.

Methods: We included 260 patients presenting to an urban, academic menopause center between 2023 and 2025 who completed the Menopause Rating Scale (MRS) before and after initiating systemic HT for FDA-approved indications. MRS psychological subdomain scores covering depressive mood, irritability, anxiety, and mental exhaustion were analyzed. Most patients (96.5%) received transdermal estradiol, had an average age of 52.1 years, and a mean follow-up of 4.5 months. Notably, 51% had a history of anxiety or depression, and 24% were on antidepressant therapy at baseline.

Results: Results showed a significant reduction in MRS psychological subdomain scores from baseline to follow-up ($P < 0.001$). The proportion of patients with severe mood symptoms (score ≥ 7) decreased from 62.3% to 24.6%. Improvement was greatest in those with severe baseline symptoms (mean change: −3.85, SE: 0.223). Treatment response did not differ by psychiatric history, age, menopausal stage, or antidepressant use.

Conclusions: These findings suggest systemic HT may improve mood symptoms in midlife, especially among those with elevated baseline severity, independent of prior mental health diagnosis, antidepressant use, or menopause stage. These findings support further investigation of HT's impact on mood in midlife women.

Key Words: Depression, Menopausal hormone therapy, Menopause, Mood, Retrospective study, Women's health.

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Menopause is a natural, universal phase of reproductive aging that marks the transition from the reproductive to the postreproductive years and is characterized by the permanent cessation of menstrual cycles due to progressive changes in ovarian function. This transition is accompanied by hormonal changes, most notably an initial increase in variability and instability of reproductive hormones, followed by a decline in estrogen and progesterone, and represents a unique life stage with diverse experiences. These hormonal changes can produce a constellation of symptoms, including vasomotor symptoms (VMS) like hot flushes and night sweats, genitourinary changes, musculoskeletal discomfort, and neuropsychiatric manifestations such as mood and sleep disturbances. The annual incidence of menopause in the United States is ~1.3 million women[1] and symptoms like VMS can last for an average of 7-10 years for higher severity, and even longer for mild symptoms or symptoms starting earlier in the transition.[2-4] While mild symptoms are often managed without clinical intervention, studies show that 60%-86% of women report symptoms severe enough to seek medical care.[5-8] Symptom burden and presentation vary across populations: Black women experience VMS that are often more severe and longer lasting than in other racial and ethnic groups (median

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This retrospective observational study was approved by the NYU Langone Health Institutional Review Board (IRB protocol i24-01943). A waiver of informed consent and HIPAA authorization was granted due to the retrospective nature of the study.

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duration 10.1 y), while Chinese and Japanese women report both lower prevalence and shorter duration of VMS (median: 5.4 and 4.8 y, respectively).[2,9] Economic strain and lower educational level are associated with increased symptom reporting across racial and ethnic groups, suggesting that socioeconomic factors compound these disparities.[2,9]

Menopausal hormone therapy (HT), consisting of systemic estrogen (oral or nonoral) with the addition of a progestogen for endometrial protection in women with a uterus, is a cornerstone of symptom management.[10] Following the publication of the Women's Health Initiative (WHI) results in the early 2000s, HT use declined sharply due to concerns about cardiovascular and breast cancer risk.[11] However, current guidelines indicate that initiating HT within 10 years of menopause onset or before age 60 is generally safe, with benefits often outweighing potential risks in appropriate candidates.[10] While HT is FDA-approved for treating VMS, genitourinary syndrome of menopause, and for the prevention of osteoporosis, it is not FDA-approved for treating mood-related symptoms, and no current consensus exists on standardized screening or treatment protocols for mood disturbances during the menopause transition.[10]

Mood symptoms during the menopause transition —including depression, irritability, anxiety, and mental exhaustion—can significantly impair quality of life. Epidemiologic studies suggest that 45%-68% of women experience mood disturbances during this period, spanning both clinical and subclinical presentations, compared with 28%-31% in premenopausal women.[12-14] The Study of Women's Health Across the Nation (SWAN) showed that women are 2-4 times more likely to experience depressive symptoms during perimenopause or early postmenopause compared with other stages of life.[15]

While women are not universally at risk of anxiety symptoms over the menopause transition, prospective data indicate that certain subgroups, such as those with low baseline anxiety or no prior history of anxiety or depression, may experience increased anxiety symptoms during perimenopause and postmenopause.[16-18] Identified risk factors for more severe or prolonged mood symptoms include longer perimenopause,[19] severity of VMS, stressful life events, sleep disruption, higher body mass index, and race.[13,18,20] Compounding this clinical challenge, antidepressant response can be variable, with some studies suggesting reduced selective serotonin reuptake inhibitor (SSRI) efficacy during postmenopause.[13,21]

The etiology of mood symptoms in the menopause transition is thought to be multifactorial, with evidence suggesting that fluctuations in serum estradiol contribute to mood vulnerability during this period.[22-24] Estrogen has demonstrated antidepressant properties in experimental studies: it increases serotonin and norepinephrine synthesis and availability (with effects on monoaminergic systems that overlap with those targeted by SSRIs), exerts neuroprotective effects via brain-derived neurotrophic factor stimulation, and modulates $GABA_A$ activity in mood-regulating brain regions.[24] Of the three endogenous estrogens, estradiol (E2) predominates during the reproductive years and acts on two distinct estrogen receptors found throughout reproductive, skeletal, cardiovascular, and central nervous systems. Estrogen signaling occurs via both genomic (gene transcription) and nongenomic (rapid kinase signaling) mechanisms.[25,26]

Low estrogen status has been linked to metabolic and functional changes in brain structure and activity, while estrogen repletion has been associated with improved cortical blood flow, normalized activation patterns, and partial reversal of serotonin imbalance.[26,27] These findings suggest a plausible biochemical basis for estrogen's therapeutic potential in mood disorders during the menopause transition.

Despite this biologic rationale, clinical studies of estrogen therapy for mood have yielded mixed results. Some have demonstrated benefit in perimenopausal women but not in postmenopausal populations; others have shown neutral effects in both. Two early 2000s randomized controlled trials (RCTs) demonstrated the antidepressant efficacy of transdermal 17β-estradiol in perimenopausal but not postmenopausal women.[28-30] While several trials have reported neutral effects, the Kronos Early Estrogen Prevention Study (KEEPS) found that oral estrogen improved mood scores on the Profile of Mood States (POMS) in nondepressed early postmenopausal women.[31] A 2018 RCT also demonstrated that a 12-month HT intervention prevented the onset of depressive symptoms in euthymic perimenopausal women.[22] In addition, one pilot study reported that estrogen augmentation improved SSRI response in perimenopausal women with depression,[32] and some analyses suggest that HT may eliminate the disparity in SSRI response rates between premenopausal and postmenopausal women.[13,33]

Sleep disturbances are another highly prevalent concern during menopause, affecting 40%-60% of women.[5] Sleep problems are bidirectionally linked to mood disorders such as depression and anxiety[18] and VMS can also cause sleep disturbances.[5] Poor sleep contributes to fatigue, cognitive difficulties, and the commonly reported "brain fog."[34] Given this interplay, sleep quality is an important variable when assessing mood outcomes in this population.

This study aimed to contribute to existing evidence regarding estrogen's role in mood regulation and the potential of HT to address mood and sleep changes in menopause, and to address key knowledge gaps by identifying which individuals may benefit most from HT. We analyzed longitudinal data from HT-naïve patients who rated their symptoms using the validated Menopause Rating Scale (MRS) before and after treatment. The MRS comprises 11 items across three domains (psychological, somato-vegetative, urogenital) with Likert-scaled responses, enabling multidimensional assessment of health-related quality of life.[35,36] Insomnia symptoms were evaluated as a secondary outcome. By examining the effects of systemic HT on mood response over time in this cohort of menopausal individuals initiating HT for FDA-approved indications, this study aims to contribute to the

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understanding of the potential impact of HT on mood symptoms across the menopause transition.

METHODS

This was a single-center retrospective cohort study of patients who received care at the NYU Langone Health (NYULH) Center for Midlife Health and Menopause (CMHM), a large urban clinic in New York City, between January 2023 and April 2025. All patients included were prescribed systemic HT for FDA-approved indications and were insured via commercial or CMS based insurance. Data were abstracted from the electronic medical record (Epic), including patients' history, progress notes, medications, and MRS survey responses. Variables collected included demographic data, stages of reproductive aging workshop (STRAW) menopause stage, psychiatric history, antidepressant use, HT type and dose, and MRS scores.

Eligible participants were perimenopausal or postmenopausal individuals who (a) were not taking HT at their initial consultation, (b) were prescribed HT at their first visit, (c) attended at least two visits during the study period (baseline and follow-up, typically 3 months later), and (d) completed the MRS at both visits. Patients missing follow-up data were excluded. Of 260 patients meeting inclusion criteria, 96.5% received transdermal (E2 patch or gel) 17β-estradiol of varying doses (0.025-0.1 mg/24 h) individualized to patient preference and treatment response, with 91.5% choosing the estradiol patch. In accordance with safety guidelines, patients with a uterus also received a progestogen agent (90.8%), most commonly micronized progesterone (83.1%), either in sequential (perimenopausal) or continuous (postmenopausal) manner (100-200 mg).

The MRS is a validated 11-item patient-reported questionnaire designed to rate the severity of menopausal symptoms across three sub-domains: psychological, somato-vegetative, and urogenital. Patients rate the severity of each symptom using a five-point Likert scale (0 = asymptomatic, 4 = very severe). The psychological subdomain questions (questions 4-7) include depressive mood, anxiety, irritability, and physical/mental exhaustion, yielding scores from 0 to 16 (0-3 = none/mild, 4-6 = moderate, ≥ 7 = severe). Sleep symptoms were also analyzed independently using question 3 (queries sleep problems, including difficulty falling asleep, sleeping through the night, and waking up early). Over distinct time points, the MRS allows assessment of menopause-related symptom burden and was used to characterize the complex relationship between mood symptoms with HT treatment.

The primary outcome was the change in the MRS psychological subdomain score from baseline to the first follow-up appointment. Change was assessed as a raw score difference (decrease = improvement) and as categorical shifts in severity class. We evaluated the proportion of participants whose scores improved, worsened, or remained stable. Secondary outcomes included changes stratified by STRAW stage, antidepressant use, psychiatric history, age, and race. Sleep symptom scores were analyzed to examine the relationship between sleep and mood, as were overall composite scores.

Statistical analysis was performed using R version 4.3.1 (The R Foundation, Vienna, Austria). Categorical variables were summarized as counts and percentages; continuous variables as means (SD) or medians (interquartile range), as appropriate. Changes between baseline and follow-up were compared using paired *t* tests or Wilcoxon signed-rank tests. Comparisons across > 2 groups used analysis of variance (ANOVA) or Kruskal-Wallis tests with post hoc corrections. For any subgroup without significant differences in mean changes, χ^2 tests were conducted on the counts of participants classified as improving, neutral, or worsening to assess potential clinical differences. All hypothesis testing used a two-sided $\alpha = 0.05$. ChatGPT was used to assist with coding to enhance graphics for the figures.

RESULTS

Participant characteristics

A total of 260 patients were eligible for inclusion in the study cohort. Baseline demographic and clinical characteristics are summarized in Table 1. The majority identified as White (n = 163, 62.7%) and were between 40 and 59 years (n = 249, 95.8%; mean age, 52.1 y). By menopausal STRAW stage, 23 women (8.8%) were in early perimenopause, 85 (32.7%) in late perimenopause, 110 (42.3%) were postmenopausal, and 42 (16.2%) were categorized as unknown status due to hysterectomy, endometrial ablation, use of levonorgestrel-releasing intrauterine system 52 mg (LNG-IUS, Mirena, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ), or other causes of irregular bleeding patterns. Most patients received transdermal estradiol (96.5%) and combined estrogen–progestogen therapy (90.8%), most commonly with micronized progesterone (83.1%). A history of anxiety or depression was reported by 132 women (51%); of these, 117 (45.0%) had a diagnosis of anxiety, 72 (27.7%) had a prior diagnosis of depression, and 54 (20.8%) reported a diagnosis of both conditions. At the initial visit, 63 women (24.2%) were taking an antidepressant.

Psychological outcomes

Across the cohort, psychological symptom scores improved significantly from visit 1 to visit 2 (mean difference: −2.7, 95% CI: −3.05 to −2.34; $P < 0.001$; Table 2). A Wilcoxon signed-rank test yielded a consistent result ($P < 0.001$). The proportion of patients whose psychological subdomain score placed them in the severe category decreased from 62.3% at visit 1 to 24.6% at visit 2 (McNemar test, $P < 0.001$; Fig. 1).

When stratified by baseline severity, those in the severe group had the largest mean change in the psychological symptom scores (mean change: −3.85) compared with mild (−0.47) and moderate (−0.89) groups (Table 3; Fig. 2). ANOVA indicated significant between-group differences ($P < 0.001$), and Tukey post hoc tests

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TABLE 1. Baseline demographic and clinical characteristics of the study cohort (N = 260)

Characteristic	n (%)
Mean age	260 (52.1 ± 4.3)
Age range	
30-39	2 (0.8)
40-44	11 (4.2)
45-49	49 (18.8)
50-54	127 (48.8)
55-59	62 (23.8)
60+	9 (3.5)
Race	
Asian	18 (6.9)
Black or African American	21 (8.1)
Hispanic or Latino	12 (4.6)
Middle Eastern	1 (0.4)
Unknown	45 (17.3)
White	163 (62.7)
History of depression	
No	188 (72.3)
Yes	72 (27.7)
History of anxiety	
No	143 (55.0)
Yes	117 (45.0)
STRAW staging	
Early perimenopause	23 (8.8)
Late perimenopause	85 (32.7)
Postmenopausal	110 (42.3)
Unknown	42 (16.2)
Initial antidepressant	
No	197 (75.8)
Yes	63 (24.2)
Progestogen type	
Micronized progesterone	196 (83.0)
LNG-IUS	28 (11.9)
Other	12 (5.1)
Estrogen type	
Gel	13 (5.0)
Oral	9 (3.5)
Patch	238 (91.5)

LNG-IUS, levonorgestrel-releasing intrauterine system; STRAW, stages of reproductive aging workshop.
Values are mean ± SD for age and n (%) for categorical variables.

confirmed that participants with severe baseline symptoms improved significantly more than those with mild or moderate symptoms.

Subgroup analyses showed no significant differences in psychological improvement by antidepressant use ($P = 0.95$), history of anxiety ($P = 0.43$), history of depression ($P = 0.54$), STRAW stage ($P = 0.56$; Fig. 3), race ($P = 0.40$), or age ($P = 0.83$). Analyses of improvement categories (improving, neutral, worsening) also did not reveal subgroup differences.

TABLE 2. Change in psychological, sleep, and composite scores from baseline to follow-up

Outcome	Mean change	*P*
Psychological change	−2.7 (2.91)	< 0.001
Sleep change	−1 (1.07)	< 0.001
Composite change	−7.23 (5.73)	< 0.001

Values are mean change (SD). *P* values from a one-sample *t* test versus 0.

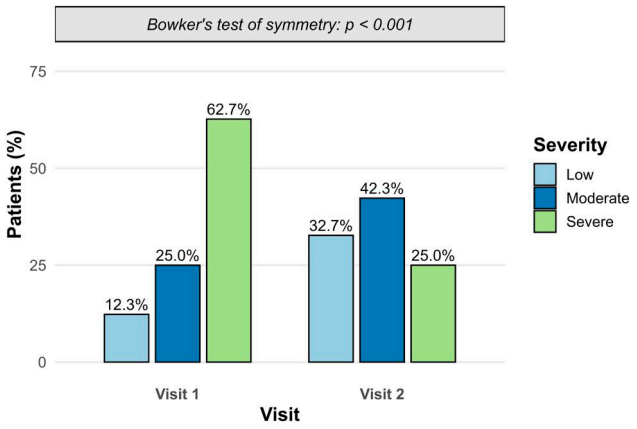

FIG. 1. Changes in symptom severity across visits. Distribution of patients reporting low, moderate, or severe symptoms at visit 1 and visit 2. Percentages are displayed above each bar. All individual severity-level comparisons were statistically significant (McNemar test, $P < 0.001$). The overall distribution differed significantly between visits as indicated by the Bowker test of symmetry ($\chi^2 = 100.77$, $df = 3$, $P < 0.001$).

Sleep outcomes

Sleep scores also significantly improved from visit 1 to visit 2 (mean difference: −1.0, 95% CI: −1.13 to −0.86; $P < 0.001$; paired *t* test; Table 2). Findings were consistent in sensitivity analyses using the Wilcoxon signed-rank test ($P < 0.001$). Subgroup comparisons showed no significant differences by antidepressant use ($P = 0.17$), history of anxiety ($P = 0.11$), history of depression ($P = 0.71$), race ($P = 0.39$), or age ($P = 0.32$) (Table 3). A significant difference was observed across STRAW stages (Kruskal-Wallis $\chi^2 = 7.96$, $df = 3$, $P = 0.047$); however, this difference disappeared when the "unknown" group (patients with irregular or absent bleeding patterns that precluded STRAW classification) was excluded from analysis. Categorization into improving, neutral, or worsening again revealed no significant subgroup differences.

Composite symptom outcomes

The composite MRS score improved significantly from visit 1 to visit 2 (mean difference: −7.23, 95% CI: −7.93 to −6.53; $P < 0.001$; paired *t* test; Table 2). Findings were consistent in sensitivity analyses using the Wilcoxon signed-rank test ($P < 0.001$). Subgroup analyses revealed no significant differences by antidepressant use ($P = 0.67$), history of anxiety ($P = 0.33$), history of depression ($P = 0.92$), STRAW stage ($P = 0.22$), race ($P = 0.51$), or age ($P = 0.18$) (Table 3). Categorical improvement analyses again showed no differences among subgroups.

Multivariable models

Linear regression did not identify any demographic or clinical factors that predicted change in psychological scores (adjusted $R^2 = -0.01$, $P = 0.74$). Logistic regression models also did not identify significant predictors of improvement (all $P > 0.05$).

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TABLE 3. Change in psychological, sleep, and composite scores from baseline to follow-up, stratified by baseline severity group

Outcome	Low	Moderate	Severe	*P*
Psychological change	−0.47 (1.72)	−0.89 (2.18)	−3.85 (2.72)	< 0.001
Sleep change	−1.00 (1.11)	−0.86 (1.01)	−1.05 (1.09)	0.494
Composite change	−4.59 (4.29)	−5.15 (5.00)	−8.57 (5.84)	< 0.001

Values are mean change (SD). *P* values from one-way ANOVA across severity groups.

DISCUSSION

In this cohort of menopausal individuals initiating HT for FDA-approved indications, psychological, sleep, and composite MRS scores improved significantly over a mean of 144 days. The greatest benefit was observed in participants with severe baseline psychological symptoms, and improvements were consistent across demographic and clinical subgroups. Taken together, these findings suggest that HT (consisting of transdermal estradiol and micronized progesterone in the majority of patients) may offer clinically meaningful benefits for mood-related symptoms during the menopause transition.

Psychological symptoms are highly prevalent in midlife, with depressive symptoms affecting nearly two-thirds of perimenopausal women compared with less than one-third of premenopausal women.[12-14] Despite a strong biologic rationale for estrogen's effects on mood regulation, prior clinical trials evaluating HT have yielded mixed results. Benefits have been demonstrated in some perimenopausal populations, while other studies have shown neutral effects, particularly in postmenopausal cohorts.[13,28,31,34,37] This heterogeneity has contributed to ongoing uncertainty regarding the role of HT in mood management. In this context, our findings add to the growing body of evidence suggesting that systemic HT may improve mood-related symptoms across the menopause transition, including early postmenopause.

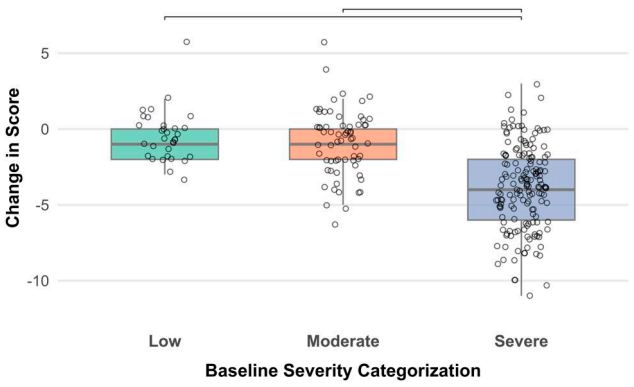

FIG. 2. Change in Menopause Rating Scale (MRS) psychological score by baseline severity. Boxplots show the change in the MRS psychological subdomain score between visit 1 and visit 2, stratified by baseline severity at visit 1. Boxplots display median and interquartile range with individual data points. Statistical comparisons (ANOVA with Tukey post hoc and Kruskal-Wallis with Bonferroni correction) demonstrated significant differences between severe versus low and severe versus moderate groups ($P < 0.001$). Sample sizes: low (n = 32), moderate (n = 65), severe (n = 163), total N = 260. Median values: low = –1, moderate = –1, severe = –4.

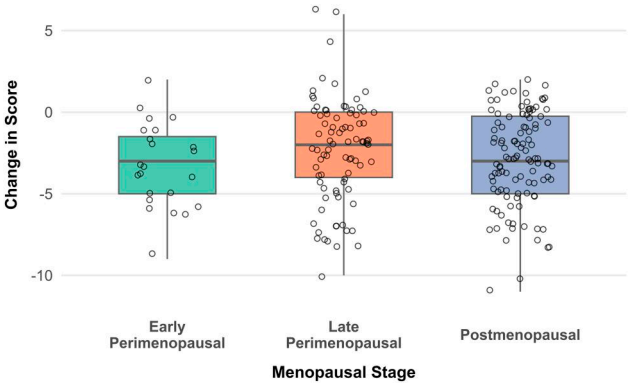

FIG. 3. Change in the Menopause Rating Scale (MRS) psychological score by menopausal stage. Boxplots show the change in MRS psychological subdomain score between visit 1 and visit 2, stratified by menopausal stage according to STRAW+10 criteria. No significant differences were observed between stages (ANOVA $P = 0.421$; Kruskal-Wallis $P = 0.413$). Early and late perimenopause were additionally compared with postmenopause, also demonstrating no significant difference (Welch *t* test, $P = 0.525$; Wilcoxon, $P = 0.638$). Sample sizes: early perimenopause (n = 23), late perimenopause (n = 85), postmenopause (n = 110), total N = 218. Median values: early perimenopause = –3, late perimenopause = –2, postmenopause = –3.

SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRI) remain first-line therapy for treating depression and in the menopausal population are effective in improving mood as well as vasomotor, sleep, and pain symptoms.[22,38-40] However, pooled analyses suggest that antidepressant response may diminish after menopause, a gap that may be attenuated by concurrent HT use.[13,32,33] Our results show evidence of comparable improvements in psychological symptoms among individuals already using antidepressants, suggesting that HT may potentially provide additive benefits for mood symptoms in this population.

Our data also contribute to existing evidence that shows the benefits of systemic HT on mood, as improvements in psychological symptoms were consistent across menopausal stage, psychiatric history, antidepressant use, and other demographics. Notably, postmenopausal women (95% of whom were within 10 years of their final menstrual period) benefited as much as perimenopausal women, suggesting that mood-related benefits of HT extend into postmenopause. In addition, participants with severe baseline psychological symptoms experienced the greatest improvement, highlighting baseline symptom severity as a potential predictor of response. Finally, we

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found no difference in treatment response by psychiatric history or antidepressant use.

Sleep disturbances and VMS are linked to depressive symptoms and are highly prevalent in midlife women during the menopause transition.[5,18] For this reason, we also analyzed the MRS sleep item and composite score. In this cohort, sleep scores improved modestly, supporting a benefit of HT on midlife insomnia that was independent of psychiatric history or medication use. Improvements in composite MRS scores, which encompass vasomotor, psychological, and urogenital domains, were similarly robust and align with the established efficacy of systemic HT for overall menopausal symptom burden. Together, these findings reinforce the broad clinical utility of HT in improving symptom burden during and after the menopause transition.

Beyond the direct health burden, untreated menopausal symptoms have real-world consequences for patients and health systems, including substantial health care utilization and widespread use of non–evidence-based and nonregulated treatments. In parallel, the global market for over-the-counter products targeting menopausal symptoms is projected to reach $22.7 billion by 2028. These patterns reflect the broad impact of untreated symptoms on sleep, mental health, metabolism, personal relationships, and workplace productivity.[41-44] In this context, the improvements in psychological and sleep symptoms observed with systemic HT suggest that effective, evidence-based treatment may have implications beyond symptom relief, potentially reducing downstream burden for patients and strain on health systems.

Strengths of this study include a well-characterized and demographically diverse cohort, real-world individualized dosing, and the use of a validated questionnaire that captures both subclinical and clinical symptoms. Limitations include the observational design without a placebo control (where regression to the mean may contribute to observed changes in symptom scores), reliance on self-reported outcomes, and potentially limited generalizability due to the predominantly commercially insured population. In addition, only one type of estradiol was utilized, and most patients received micronized progesterone as the progestational agent, which may limit generalizability to women using other regimens. As with all observational studies, residual confounding from unmeasured variables may be present. However, these reflect real-world choices of patients and practitioners in a diverse, urban, menopause-focused practice. The absence of subgroup differences, despite the established effects of SSRIs and SNRIs on mood and VMS, may reflect limited statistical power. In addition, the relatively short follow-up period limits assessment of the durability of observed mood improvement.

CONCLUSION

In summary, systemic HT, when initiated for FDA-approved indications, was associated with improvements in psychological and sleep symptoms across diverse patient groups, including individuals with psychiatric histories and those using antidepressant medications. These findings support the potential role of HT as part of a comprehensive approach to symptom management during the menopause transition and demonstrate that HT improves psychological, sleep, and overall menopausal symptom burden, with the greatest benefit observed in women experiencing severe baseline symptoms. Importantly, postmenopausal women within 10 years of menopause showed equal benefit to perimenopausal women, suggesting that the therapeutic window of HT for mood benefit may extend into postmenopause. The consistency of response across subgroups indicates that mood improvements are applicable across diverse populations and specifically independent of psychiatric history or medication use. Together, these results highlight the potential of HT to address the psychological symptom burden in perimenopausal and postmenopausal women, beyond traditional vasomotor and genitourinary complaints. Future RCTs powered for psychological endpoints, using standardized treatment protocols and longer follow-up, are needed to confirm these findings and to further define the role of HT in managing mood and sleep disturbances during this critical life stage.

REFERENCES

1. Peacock K, Carlson K, Ketvertis KM *Menopause StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2023.
2. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175:531-539. doi:10.1001/jamainternmed.2014.8063
3. Freeman EW, Sammel MD, Lin H, Liu Z, Gracia CR. Duration of menopausal hot flushes and associated risk factors. *Obstet Gynecol* 2011;117:1095-1104. doi:10.1097/AOG.0b013e318214f0de
4. Maki PM, Thurston RC. Menopause and brain health: hormonal changes are only part of the story. *Front Neurol* 2020;11:562275. doi:10.3389/fneur.2020.562275
5. Duralde ER, Sobel TH, Manson JE. Management of perimenopausal and menopausal symptoms. *Brit Med J* 2023;382: e072612. doi:10.1136/bmj-2022-072612
6. Guthrie JR, Dennerstein L, Taffe JR, Donnelly V. Health care-seeking for menopausal problems. *Climacteric* 2003;6:112-117. doi:10.1080/713605371
7. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Fehnel SE, Clark RV. Healthcare seeking and treatment for menopausal symptoms in the United States. *Maturitas* 2007;58:348-358. doi:10.1016/j.maturitas.2007.09.006
8. Constantine GD, Graham S, Clerinx C, et al. Behaviours and attitudes influencing treatment decisions for menopausal symptoms in five European countries. *Post Reprod Health* 2016;22:112-122. doi:10.1177/2053369116632439
9. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol* 2000;152:463-473. doi:10.1093/aje/152.5.463
10. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022;29:767-794. doi:10.1097/gme.0000000000002028
11. Santen RJ, Stuenkel CA, Burger HG, Manson JE. Competency in menopause management: whither goest the internist? *J Womens Health* 2014;23:281-285. doi:10.1089/jwh.2014.4746
12. Brown JP, Gallicchio L, Flaws JA, Tracy JK. Relations among menopausal symptoms, sleep disturbance and depressive symptoms in midlife. *Maturitas* 2009;62:184-189. doi:10.1016/j.maturitas.2008.11.019
13. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary

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and recommendations. *Menopause* 2018;25:1069-1085. doi:10.1097/gme.0000000000001174
14. Timur S, Sahin NH. The prevalence of depression symptoms and influencing factors among perimenopausal and postmenopausal women. *Menopause* 2010;17:545-551. doi:10.1097/gme.0b013e3181cf8997
15. Bromberger JT, Kravitz HM, Chang YF, Cyranowski JM, Brown C, Matthews KA. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol Med* 2011;41:1879-1888. doi:10.1017/s003329171100016x
16. Bromberger JT, Kravitz HM, Chang Y, et al. Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. *Menopause* 2013;20:488-495. doi:10.1097/GME.0b013e3182730599
17. Mulhall S, Andel R, Anstey KJ. Variation in symptoms of depression and anxiety in midlife women by menopausal status. *Maturitas* 2018;108:7-12. doi:10.1016/j.maturitas.2017.11.005
18. Brown L, Hunter MS, Chen R, et al. Promoting good mental health over the menopause transition. *Lancet* 2024;403:969-983. doi:10.1016/s0140-6736(23)02801-5
19. Hickey M, Schoenaker DA, Joffe H, Mishra GD. Depressive symptoms across the menopause transition: findings from a large population-based cohort study. *Menopause* 2016;23:1287-1293. doi:10.1097/gme.0000000000000712
20. Davis SR, Pinkerton J, Santoro N, Simoncini T. Menopause—biology, consequences, supportive care, and therapeutic options. *Cell* 2023;186:4038-4058. doi:10.1016/j.cell.2023.08.016
21. Pae CU, Mandelli L, Kim TS, et al. Effectiveness of antidepressant treatments in pre-menopausal versus post-menopausal women: a pilot study on differential effects of sex hormones on antidepressant effects. *Biomed Pharmacother* 2009;63:228-235. doi:10.1016/j.biopha.2008.03.010
22. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Xia K, Schmidt PJ, Girdler SS. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry* 2018;75:149-157. doi:10.1001/jamapsychiatry.2017.3998
23. Joffe H, de Wit A, Coborn J, et al. Impact of estradiol variability and progesterone on mood in perimenopausal women with depressive symptoms. *J Clin Endocrinol Metab* 2020;105:e642-e650. doi:10.1210/clinem/dgz181
24. Soares CN. Anxiety and depression in midlife transition and beyond: the role of estrogens. *Curr Opin Endocr Metab Res* 2023;31:100457. doi:10.1016/j.coemr.2023.100457
25. Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. *Adv Protein Chem Struct Biol* 2019;116:135-170. doi:10.1016/bs.apcsb.2019.01.001
26. Yang JL, Hodara E, Sriprasert I, Shoupe D, Stanczyk FZ. Estrogen deficiency in the menopause and the role of hormone therapy: integrating the findings of basic science research with clinical trials. *Menopause* 2024;31:926-939. doi:10.1097/gme.0000000000002407
27. Schmidt PJ, Rubinow DR. Sex hormones and mood in the perimenopause. *Ann N Y Acad Sci* 2009;1179:70-85. doi:10.1111/j.1749-6632.2009.04982.x
28. Soares CN. Menopause and mood: the role of estrogen in midlife depression and beyond. *Psychiatr Clin North Am* 2023;46:463-473. doi:10.1016/j.psc.2023.04.004
29. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 2000;183:414-420. doi:10.1067/mob.2000.106004
30. De Novaes Soares C, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry* 2001;58:529. doi:10.1001/archpsyc.58.6.529
31. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-cognitive and affective study. *PLoS Med* 2015;12:e1001833. doi:10.1371/journal.pmed.1001833
32. Morgan ML, Cook IA, Rapkin AJ, Leuchter AF. Estrogen augmentation of antidepressants in perimenopausal depression: a pilot study. *J Clin Psychiatry* 2005;66:774-780. doi:10.4088/jcp.v66n0617
33. Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: sex-age interactions. *J Womens Health* 2005;14:609-616. doi:10.1089/jwh.2005.14.609
34. Gava G, Orsili I, Alvisi S, Mancini I, Seracchioli R, Meriggiola MC. Cognition, mood and sleep in menopausal transition: the role of menopause hormone therapy. *Medicina (Kaunas)* 2019;55:668. doi:10.3390/medicina55100668
35. Hauser GA, Huber IC, Keller PJ, Lauritzen C, Schneider HP. Evaluation of climacteric symptoms (Menopause Rating Scale). *Zentralbl Gynakol* 1994;116:16-23.
36. Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Outcomes* 2004;2:45. doi:10.1186/1477-7525-2-45
37. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353. doi:10.1001/jama.2013.278040
38. Freeman MP, Hill R, Brumbach BH. Escitalopram for perimenopausal depression: an open-label pilot study. *J Womens Health* 2006;15:857-861. doi:10.1089/jwh.2006.15.857
39. Soares CN, Arsenio H, Joffe H, et al. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women. *Menopause* 2006;13:780-786. doi:10.1097/01.gme.0000240633.46300.fa
40. Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL, Cohen LS. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. *J Clin Psychiatry* 2003;64:473-479. doi:10.4088/jcp.v64n0419
41. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause* 2020;27:976-992. doi:10.1097/gme.0000000000001609
42. Research GV. Menopause market size, share & trends analysis report by product, by distribution channel, by region, and segment forecasts, 2022–2028. 2022. Accessed August 14, 2025. https://www.grandviewresearch.com/industry-analysis/menopause-market.
43. Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health* 2013;103:1583-1588. doi:10.2105/ajph.2013.301295
44. Faubion SS, Enders F, Hedges MS, et al. Impact of menopause symptoms on women in the workplace. *Mayo Clin Proc* 2023;98:833-845. doi:10.1016/j.mayocp.2023.02.025

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