THE IMPACT OF HORMONE REPLACEMENT THERAPY ON DEPRESSION IN PERIMENOPAUSAL WOMEN

by

Megan Pierobon

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Abstract

Depression during the perimenopausal transition is a significant concern for women's mental health and quality of life. Hormone Replacement Therapy (HRT), traditionally used to manage vasomotor and genitourinary symptoms of menopause, has also been investigated for its potential to alleviate depressive symptoms associated with hormonal fluctuations. This integrative literature review examined the impact of HRT on depression in perimenopausal women by analyzing articles published between 2014 and 2025, reflecting the most recent evidence following shifts in clinical practice post-Women's Health Initiative. A comprehensive search strategy using Medline (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO), and Google Scholar was employed, utilizing Medical Subject Headings (MeSH) and keywords. Six primary studies met inclusion criteria and were critically appraised and synthesized. Key themes arising out of the studies were the timing of HRT initiation, individual variability in depressive symptom response, and methodological heterogeneity across studies. Findings suggest that HRT, particularly transdermal estradiol, may be effective in reducing depressive symptoms when initiated during early perimenopause. However, inconsistencies in study design, outcome measures, and population definitions highlight the need for more standardized, high-quality research. These findings have implications for nurse practitioners and other primary care providers who play a critical role in screening, education, and patient-centered decision-making in the management of menopausal mental health.

Table of Contents

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Chapter One: Introduction

Menopause represents a significant and universal transition in women's lives, typically occurring between the ages of 45 and 55 (Santoro, 2016). This transition period, known as perimenopause, is characterized by substantial hormonal fluctuations, notably declines in estrogen and progesterone (Soares & Maki, 2010; Lokuge et al., 2011). These hormonal shifts are associated with a range of physical symptoms, including vasomotor disturbances such as hot flashes, night sweats, sleep disruptions, and significant mood changes, notably depressive symptoms (Santoro, 2016; Soares, 2014). Perimenopause has been identified as a critical "window of vulnerability," during which women are particularly susceptible to mood disorders that can significantly impact their psychological and emotional health (Bromberger et al., 2010; Soares, 2019).

Depression during perimenopause represents a significant clinical and public health concern. Studies suggest that a substantial proportion of women—up to 40%—experience notable depressive symptoms during perimenopause, reflecting the heightened vulnerability during this life stage (Shea et al., 2020). These depressive symptoms negatively influence overall quality of life, diminish social and occupational functioning, and exacerbate physical health issues such as cardiovascular disease and osteoporosis (Dennerstein et al., 2002; Kornstein et al., 2010). Furthermore, untreated depression in menopausal women contributes to increased healthcare utilization, higher medical costs, and workplace absenteeism, highlighting the economic importance of effectively managing mood disorders during this life stage (Soares, 2014).

Hormone Replacement Therapy (HRT) has been extensively utilized to alleviate physical symptoms associated with menopause, such as hot flashes and vaginal dryness. HRT typically

involves estrogen supplementation, alone or in combination with progestogen, aiming to mitigate the hormonal fluctuations experienced during menopause. Recent research suggests that HRT might also offer significant benefits for managing depressive symptoms due to estrogen's critical role in modulating neurotransmitter systems, including serotonin, which directly influences mood regulation (Herson & Kulkarni, 2022; Lokuge et al., 2011). However, existing literature on the effectiveness of HRT in managing menopausal depression remains mixed, with varying findings related to efficacy, optimal administration routes, timing, and safety considerations (Gordon et al., 2021; The North American Menopause Society, 2022).

This integrative literature review synthesizes and critically analyzes current evidence regarding the impact of HRT on depression in perimenopausal women. Clarifying the effectiveness, limitations, and optimal use of HRT for depressive symptoms can inform clinical practice, facilitate tailored patient care, and influence healthcare policies and education practices for primary care providers, including nurse practitioners (NPs). Given the growing population of menopausal women globally, enhancing our understanding of the therapeutic role of HRT in addressing menopausal depression is timely and essential for improving women's health outcomes during this critical life stage.

Chapter Two: Background

Menopause and perimenopause are universal stages experienced by women, typically between the ages of 45 and 55. Globally, it is projected that over one billion women will be menopausal or postmenopausal by 2025 (Santoro, 2016). As the global population ages, there is an increasing emphasis on addressing the specific healthcare needs of menopausal women, making this a significant public health priority (Shifren et al., 2014).

The menopausal transition represents a critical "window of vulnerability" during which women are particularly susceptible to developing depressive symptoms due to hormonal fluctuations and psychosocial stressors (Soares, 2019). Extensive research, including the Study of Women's Health Across the Nation (SWAN), has demonstrated a notable rise in depressive symptoms during perimenopause, underscoring menopause's profound psychological impact (Bromberger et al., 2007, 2010, 2011). Maintaining emotional and psychological well-being during this period is crucial, as it directly impacts women's overall health, quality of life, interpersonal relationships, and daily functioning (Dennerstein et al., 2002; Hilditch et al., 2008).

Implications of Depression in Perimenopausal Women

Depression in perimenopausal women poses substantial clinical concerns due to its far-reaching effects on physical health, social relationships, economic productivity, and overall quality of life. Women experiencing peri-menopausal depression often report heightened anxiety, cognitive impairments, sleep disturbances, and reduced energy levels, all of which can substantially impair their personal and professional lives (Kornstein et al., 2010). Economically, depression contributes to increased healthcare utilization, frequent medical visits, greater dependency on medication, and diminished workplace productivity, leading to higher absenteeism and reduced performance (Soares, 2014).

The social implications of perimenopausal depression are equally significant, often leading to social withdrawal, interpersonal conflicts, and diminished social support. This isolation can further exacerbate depressive symptoms, creating a detrimental cycle that further complicates mental health outcomes. Addressing depression proactively in perimenopausal women is essential for improving mental health, enhancing physical health outcomes, and supporting positive social interactions (Campbell et al., 2015; Soares, 2019).

Physiological Changes and Mood Disorders in Perimenopause

Perimenopause, the transitional period leading to menopause, is characterized by substantial hormonal fluctuations, particularly declining levels of estrogen and progesterone. These hormonal shifts are responsible for several physical symptoms, including hot flashes, sleep disturbances, and mood instability (Lokuge et al., 2011; Santoro, 2016; Soares & Maki, 2010). The hormonal changes notably influence neurotransmitter systems, particularly serotonin, which directly affects mood regulation. Reduced estrogen levels can disrupt serotonin pathways, significantly contributing to depressive symptoms (Lokuge et al., 2011). Additionally, estrogen affects the hypothalamic-pituitary-adrenal (HPA) axis, implicating the stress-response system in menopausal mood disturbances (Soares, 2019).

Studies consistently report a high prevalence of depression during perimenopause, with approximately 26% to 33% of perimenopausal women experiencing significant depressive symptoms (Bromberger et al., 2010). The risk is notably increased by factors such as a prior history of depression, stressful life events, and chronic health conditions (Campbell et al., 2015; Shea et al., 2020). However, diagnosis remains complex due to overlapping symptoms of depression and perimenopause itself, often leading to under-recognition and under-treatment (Soares, 2014).

Clinical Impact of Depression in Perimenopausal Women

Depression during perimenopause can significantly diminish a woman's quality of life. It can lead to social isolation, impaired interpersonal relationships, and decreased productivity both at home and at work. Untreated depression can also exacerbate physical symptoms associated with perimenopause and complicate the management of chronic conditions such as cardiovascular disease, osteoporosis, and chronic pain (Dennerstein et al., 2002; Hilditch et al., 2008).

Despite these significant impacts, barriers to effective treatment remain prevalent. The stigma surrounding mental health issues, inadequate awareness of the association between perimenopause and depression, and reluctance to seek mental health support frequently hinder timely intervention. Integrating comprehensive mental health assessments and support systems into routine menopausal care could greatly improve patient outcomes by overcoming these barriers (Shifren et al., 2014).

The Rationale for Investigating HRT

HRT is prescribed to supplement declining levels of hormones, primarily estrogen and progesterone, during menopause and perimenopause (North American Menopause Society, 2017). HRT typically involves estrogen alone (for women who have had a hysterectomy) or a combination of estrogen and progestogen to prevent endometrial hyperplasia in women with an intact uterus (The North American Menopause Society, 2022). Treatment can be administered through various methods, including oral tablets, skin patches, topical gels, vaginal creams, and intrauterine systems (Santoro et al., 2015).

The use of HRT dramatically changed following the Women's Health Initiative (WHI) Study in the early 2000s, which initially aimed to investigate the preventive effects of HRT on

chronic conditions in menopausal women. However, findings from the WHI highlighted potential risks, including increased incidences of breast cancer, cardiovascular events, stroke, and venous thromboembolism, particularly associated with certain forms of systemic HRT (DeNeui et al., 2019; The North American Menopause Society, 2022). The significant impacts of WHI findings led to cautious clinical guidelines and a pronounced decrease in HRT prescriptions, stimulating extensive research aimed at clarifying the therapy's safety, benefits, and risks (The North American Menopause Society, 2022).

Guidelines and evidence support the prescription of HRT to alleviate vasomotor symptoms, such as hot flashes and night sweats (North American Menopause Society, 2022). However, its efficacy in addressing perimenopausal mood-related symptoms, particularly depression, remains uncertain. Current evidence suggests estrogen's regulatory role in neurotransmitter systems, as well as its neuroprotective properties, could significantly influence mood and cognitive functioning, presenting HRT as a potential therapeutic strategy for menopausal depression (Herson & Kulkarni, 2022; Rasgon et al., 2001).

Research further highlights a correlation between mood sensitivity and estrogen fluctuations, suggesting that certain women might particularly benefit from HRT during the menopausal transition (Gordon et al., 2021). Despite this promising evidence, substantial knowledge gaps remain concerning the optimal type, dosage, timing, and long-term safety and efficacy of HRT for managing depression during perimenopause (Santoro et al., 2015).

Enhanced clarity around HRT's impact on depressive symptoms can inform clinical guidelines, improve patient education about treatment options, and reduce barriers to treatment by addressing concerns about safety and effectiveness. Furthermore, comprehensive research outcomes will significantly inform NP education programs, promoting a holistic approach to

managing menopausal health that integrates both physical and psychological dimensions. On a policy level, clearer evidence could support the development of standardized care protocols, ensuring consistent, high-quality management of menopausal depression in primary care settings. This integrative review synthesizes current knowledge on the impact of HRT on depression in peri-menopausal women and identifies critical gaps in existing research.

Chapter Three: Methods

Integrative Literature Review

To address the question: *What is the impact of hormone replacement therapy on depression in perimenopausal women?*, an integrative literature review was conducted. An integrative review systematically gathers existing theoretical and empirical literature relevant to a specific topic, offering a thorough and evidence-based synthesis that can guide further theory development, clinical practice, or policy formulation (Whittemore & Knafl, 2005). This integrative literature review employed a systematic, structured approach to critically analyze existing research on the impact of HRT on depression in perimenopausal women. The integrative review methodology was selected because it allows for the inclusion and synthesis of diverse research methods—both experimental and non-experimental—thereby providing a comprehensive understanding of complex healthcare phenomena (Whittemore & Knafl, 2005). By combining findings from qualitative, quantitative, and theoretical literature, integrative reviews present a holistic view that can inform clinical practice, policy development, and future research directions (Melnyk & Fineout-Overholt, 2019; Whittemore & Knafl, 2005). Employing a structured, reproducible search method enhances the rigor of the review and ensures the process can be replicated in future research. The current integrative review employed Whittemore and Knafl's (2005) modified integrative review framework, which provides a clear and sequential approach, including defining the purpose of the review, systematically searching the literature, establishing eligibility criteria, analyzing both qualitative and quantitative data, and discussing implications and recommendations.

Formulating the Research Question

To accurately reflect the clinical issue and effectively guide the literature search, a clinical question was developed using a modified version of the PICOT framework (Melnyk & Fineout-Overholt, 2019). Specifically, a PIO (Population, Intervention, Outcome) framework was utilized to narrow and focus the question. The "comparison" element typically included in the traditional PICOT framework was intentionally omitted, as the extensive range of potential comparison treatments would require the investment of substantial resources and time that would not be feasible within this particular review (Melnyk & Fineout-Overholt, 2019). Therefore, the population (P) identified was perimenopausal women, the intervention (I) was hormone replacement therapy (HRT), and the outcome (O) was depression. The structured PIO question guiding this integrative literature review was formulated as follows: "What is the impact of HRT on depression in perimenopausal women?" This approach ensured a targeted and efficient search strategy, guiding clear inclusion and exclusion criteria and supporting focused subsequent analysis (Melnyk & Fineout-Overholt, 2019).

Search Strategy

A comprehensive and systematic search was conducted to identify literature examining the impact of HRT on depression in perimenopausal women. The literature search began with a preliminary review of Medical Education Subject Headings (MeSH) terms to identify additional words or phrases relevant to a thorough literature search. These searches were then performed separately in three primary databases: Medline (Ovid), CINAHL (EBSCO), and PsycINFO (EBSCO). These databases were selected for their extensive coverage of medical, nursing, and psychological literature relevant to women's health and mental health.

Medline is a comprehensive biomedical database managed by the National Library of Medicine, providing extensive coverage of literature from medicine, nursing, dentistry, veterinary medicine, healthcare systems, and preclinical sciences. Its robust indexing with MeSH terms supports precise and thorough retrieval of biomedical literature, making it highly appropriate for clinical research topics related to health interventions and outcomes (Melnyk & Fineout-Overholt, 2019).

CINAHL (Cumulative Index to Nursing and Allied Health Literature) Complete provides extensive coverage of literature in nursing, allied health, and related disciplines. It includes peer-reviewed articles, clinical trials, systematic reviews, and evidence-based care sheets, making it particularly valuable for nursing-specific and allied health research questions (Melnyk & Fineout-Overholt, 2019).

PsycINFO (EBSCO) is a specialized database maintained by the American Psychological Association that offers comprehensive indexing of psychological and behavioral sciences literature. It includes peer-reviewed journal articles, dissertations, and books relevant to mental health, psychology, psychiatry, and behavioral science, thereby ensuring comprehensive coverage of research addressing psychological outcomes, such as depression (Melnyk & Fineout-Overholt, 2019).

Additionally, a search was conducted using the PIO research question in Google Scholar, and the first ten pages of search results were reviewed. Google Scholar was included to capture potentially relevant literature outside the primary academic databases. Due to practical limitations of time and resources available for this review, the search was restricted to the first ten pages, ensuring relevance and manageability of retrieved articles while acknowledging potential limitations in comprehensiveness.

Searches utilized both keywords and Medical Subject Headings (MeSH) terms to ensure comprehensive identification of relevant articles. Key search terms included combinations of "hormone replacement therapy," "HRT," "menopausal hormone therapy," "perimenopause," "menopause transition," "depression," "depressive symptoms," and "mood disorders." Specific MeSH terms used in the searches were "Hormone Replacement Therapy," "Menopause," "Perimenopause," "Depression," and "Mood Disorders." This strategy was carefully developed to maximize sensitivity and specificity in identifying studies pertinent to the research question.

To enhance the thoroughness of the literature search, combinations of keywords listed in Appendix A were entered systematically into each database. Boolean operators (AND, OR) were utilized to strategically combine and link terms, broadening and narrowing the search results appropriately. Additionally, truncation symbols (*) were applied to certain keywords (e.g., "symptom*" and "depress*") to capture all potential variations of these terms, such as symptoms, symptomatic, depression, depressive, and depressed. These methods ensured the capture of a broad spectrum of relevant literature while maintaining search precision and efficiency. See Appendix A for the detailed search terms used in the integrative literature review search.

Inclusion and Exclusion Criteria

To identify literature relevant to the research question, explicit inclusion and exclusion criteria were established. A study was included if it met the following criteria: it had been published between January 2014 and March 2025, available in full text, written in English, and specifically investigated the effects of HRT on either depressive symptoms or clinical depression in perimenopausal or early postmenopausal women. The publication date range was strategically chosen to reflect current clinical practices following significant changes in guidelines due to the WHI findings. Limiting studies to those available in English was a pragmatic decision based on

resource availability, as translating non-English studies could introduce additional complexity and potential inaccuracies.

Studies that included both menopausal and postmenopausal women, included broader menopausal populations without specific differentiation, or addressed psychological conditions other than depression were excluded from consideration. Articles such as editorials, opinion pieces, and case reports were excluded. Given the critical importance of effective and safe management of depression during perimenopause, combined with uncertainties stemming from WHI findings, a deliberate decision was made to focus this integrative literature review on studies published between 2014 and 2025. This period reflects the most current evidence available following the substantial shifts in clinical and research perspectives due to the WHI findings, which dramatically reshaped guidelines on HRT use (DeNeui et al., 2019; The North American Menopause Society, 2022). By focusing on this recent evidence, this review aims to clarify the contemporary understanding of the role of HRT in treating depressive symptoms in perimenopausal women and inform clinical practice, healthcare policy, and education, particularly in primary care settings.

Article Selection Process

The initial database and Google Scholar searches yielded a total of 114 articles. The articles that were returned in these searches included systematic reviews, qualitative and quantitative primary research studies, dissertations, editorials, and some clinical guidelines. The 114 articles were uploaded into Covidence. Covidence is a web-based software platform that streamlines the process of conducting systematic and scoping reviews, offering features for screening, data extraction, and risk of bias assessment (Koscielski, 2024). Using Covidence, 66 duplicates were removed, and 48 articles remained. The titles and abstracts of these 48 articles

were screened for relevance to the research question, resulting in the exclusion of three articles due to irrelevance to the specific research question and five articles for not specifically evaluating the impact of HRT in perimenopausal or early post-menopausal women, thus not meeting the initial inclusion and exclusion criteria. The author completed a full-text review of the remaining 40 articles. Ultimately, six articles were identified for critical appraisal and data extraction as they met all inclusion and exclusion criteria and directly addressed the research question. Appendix B illustrates the full search strategy and outlines how many articles were removed and for what reason.

Of the included articles, one was a randomized controlled trial (RCT), two were systematic reviews/meta-analyses analyzing and synthesizing multiple trials, one was a clinical practice guideline informed by a systematic review, and the remaining two were cohort or longitudinal observational studies. A review of the reference list of each of these six articles was completed to identify any further articles of relevance that fit the inclusion and exclusion criteria. The articles retrieved from a review of the reference lists did not meet the inclusion and exclusion criteria and were therefore not included as primary articles for this integrative literature review. However, some of the articles from the reference list review were incorporated into the background of this review.

Critical Appraisal and Data Extraction

Critical appraisal of each of the six included studies was systematically performed using the Critical Appraisal Skills Programme (CASP) standardized quality assessment tools/checklists designed for RCTs, observational/cohort studies, and systematic reviews to evaluate methodological rigor, validity, and reliability (Critical Appraisal Skills Programme, 2023). These specific checklists were used since the articles reviewed included an RCT, three systematic

reviews/meta-analyses, and two observational/cohort studies. Data extraction was conducted using a structured form developed by the author of this integrative review to systematically and thoroughly capture pertinent details of each study, including study design, participant characteristics, interventions used, outcomes measured, and key findings. To enable a detailed and comparative summary of information gathered from the six articles included in this integrative review, Appendix C contains a comprehensive critical appraisal and data extraction matrix.

The studies underwent rigorous analysis to identify themes, subthemes, and inconsistencies between them. This process differentiated clearly between data extraction (systematically retrieving information from articles), data analysis (interpreting the extracted data), and data synthesis (integrating findings across studies to derive cohesive conclusions). The six included articles were not only relevant to the research question but were also of sufficient quality as determined by critical appraisal using the CASP quality assessment checklists. The following chapter provides the findings from the included literature.

Chapter Four: Findings

The purpose of this integrative review was to enhance the understanding of the impact of hormone replacement therapy (HRT) on depression in peri-menopausal women and the role that primary care providers, such as NPs, have in supporting peri-menopausal women in managing depression. To provide insight and relevant practice recommendations, a comprehensive search was conducted to identify relevant literature. A final cohort of six articles was selected for critical analysis.

Of the included articles, one was an RCT examining the effect of hormone therapy on mood outcomes (Gordon et al., 2018). Two were systematic reviews/meta-analyses analyzing and synthesizing multiple trials (Rubinow et al., 2015; Whedon et al., 2017).One article was a clinical practice guideline informed by a systematic review (Joffe et al., 2018)., The remaining two articles were either cohort or longitudinal observational studies investigating associations between HRT use and depression outcomes in peri-menopausal or recently peri-menopausal women (Gnanasegar et al., 2024; Wium-Andersen et al., 2022). Key characteristics of the included articles are summarized in Appendix (B). The fact that the studies included in this integrative review used diverse methodologies allowed for a more comprehensive understanding of evidence-based practice and increased their potential to generate findings to contribute to practice and policy.

Study Approaches and Designs

Gordon et al. (2018) conducted a rigorous double-blind RCT with 172 healthy perimenopausal and early postmenopausal women aged 45 to 60 in the United States, evaluating the effectiveness of transdermal estradiol combined with intermittent micronized progesterone (TE+IMP) over a 12-month period. The study highlighted significant reductions in depressive

symptoms measured by CES-D (Center for Epidemiological Studies Depression Scale) compared to placebo, particularly pronounced in early perimenopause and among women experiencing heightened stress.

Wium-Andersen et al. (2022) conducted an extensive cohort study in Denmark involving over 825,000 women. Utilizing national registry data, the authors identified a nuanced relationship between HRT initiation and depression risk. Their findings indicated an elevated risk of depression diagnosis associated with systemic HRT use before age 50, but then a reduced risk among women who begin local HRT after age 54, suggesting timing and administration routes may be critical to consider.

Gnanasegar et al. (2024) performed a prospective observational study in a specialized menopause clinic in Canada. This research included 170 women monitored over periods of 3 to 12 months. The study found significant improvements in depressive symptoms, assessed using the CES-D scale, particularly notable in those receiving systemic menopausal hormone therapy (MHT), either alone or combined with antidepressants. The study evaluated estradiol's efficacy in clinical settings as opposed to strictly controlled experimental environments. Gnanasegar et al. (2024) highlighted the importance of understanding how estradiol treatment performs under routine clinical conditions, where patient characteristics, adherence, and treatment conditions are more variable and reflective of typical clinical scenarios. This real-world perspective, from an established specialized menopause clinic, can guide clinicians in making more informed and practical decisions regarding patient care, beyond the constraints of tightly controlled experimental research environments.

Rubinow et al. (2015) undertook a systematic review of multiple studies examining estradiol's efficacy in treating perimenopausal depression. Rubinow et al. (2015) emphasized

significant methodological inconsistencies across the studies they reviewed, particularly highlighting variability in hormone formulations, dosages, and routes of administration (e.g., oral versus transdermal). They also noted considerable differences in the way that menopausal status was defined, with some studies using only age as a criterion, while others relied on hormonal markers such as follicle-stimulating hormone (FSH) levels or menstrual irregularities. Additionally, Rubinow et al. (2015) identified variability in the timing of estradiol administration relative to the onset of menopause, which further complicated the interpretation of results. Despite these limitations, their review found modest but promising support for estradiol's antidepressant effects, specifically in women who were clinically diagnosed with perimenopausal depression

Whedon et al. (2017) conducted a systematic review and meta-analysis specifically targeting bioidentical estrogen therapy and its potential role in managing depressive symptoms among menopausal and perimenopausal women. The authors employed systematic search methods to identify randomized controlled trials and observational studies that investigated bioidentical estrogen formulations, which closely mimic the molecular structure of endogenous hormones. Despite encountering methodological heterogeneity among the included studies, particularly in terms of estrogen formulations, dosing, administration routes, and measurement scales for depressive symptoms, their pooled analysis did not demonstrate substantial overall benefits (Whedon et al., 2017). Nevertheless, subgroup analyses revealed that bioidentical estrogen therapy might specifically alleviate depressive symptoms in perimenopausal women. This finding underscores the importance of targeted, population-specific treatment approaches, suggesting that bioidentical estrogen could hold therapeutic value for select groups within this broader demographic (Whedon et al., 2017).

Joffe et al. (2018) provided guidelines informed by expert consensus and extensive literature synthesis. They recognized estrogen therapy's antidepressant properties in women experiencing vasomotor symptoms during perimenopause. However, the authors reinforced that traditional antidepressants would remain the primary recommendation for major depressive episodes, advocating estrogen therapy as a supplementary option under certain conditions.

Interventions, Comparisons, and Outcome Measures

Interventions predominantly involved systemic HRT, specifically estrogen alone or combined with progesterone, administered either transdermally or orally. Gordon et al. (2018) used transdermal estradiol with intermittent micronized progesterone, assessing depressive symptoms via the Center for Epidemiological Studies–Depression Scale (CES-D). Gnanasegar et al. (2024) similarly employed systemic menopause hormone therapy, including estrogen alone or with progestogen, and antidepressants, measuring outcomes using the CESD-10 (an abbreviated version of Center for Epidemiological Studies Depression Scale) depression scale. Whedon et al. (2017) specifically investigated bioidentical estrogens through a meta-analysis, using multiple validated depression scales. Conversely, Joffe et al. (2018) synthesized broad evidence from multiple hormone therapy modalities, antidepressants, and other treatments, applying various validated tools such as the CES-D and the Hamilton Depression Rating Scale (HDRS). Wium-Andersen et al. (2022) tracked, over a span of 11 years, hormone therapy via national prescription registries, linking exposure to clinically verified depression diagnoses.

The use of objective measures for depression was a consistent feature of all six articles; each study utilized a validated scale, such as the Center for Epidemiologic Studies-Depression Scale (CES-D), Hamilton Depression Rating Scale, or Montgomery-Åsberg Depression Rating Scale (MADRS), thereby enhancing methodological rigor and comparability across studies.

Population and Confounding Variables

A key challenge in evaluating the impact of HRT on depression in perimenopausal women lies in the variability of study populations and the extent to which confounding variables were taken into account. The reviewed studies demonstrated considerable heterogeneity in participant demographics, menopausal stage classification, and control for external influences such as socioeconomic status, baseline depression severity, and lifestyle factors.

One of the notable challenges highlighted in this integrative review was the lack of uniformity across studies in defining perimenopause and determining participants' menopausal stages. The onset of perimenopause typically occurs between ages 45 and 52; however, this range can vary considerably among individual women (Santoro, 2016). Gordon et al. (2018) and Gnanasegar et al. (2024) specifically targeted women with an average age between 47 and 52 years, aligning their selection criteria with the average age at which women typically experience hormonal fluctuations associated with perimenopause. Although selecting this age range does not guarantee hormonal fluctuations for every woman within the group, it significantly increases the probability that participants are actively undergoing the physiological transitions typical of perimenopause. In contrast, Wium-Andersen et al. (2022) included a broader age group, ranging from 40 to over 60 years old, thus encompassing both perimenopausal and postmenopausal women. This broader inclusion criterion introduced greater complexity in interpreting the findings, as outcomes appeared to differ notably depending upon whether HRT was initiated during the perimenopausal period, characterized by active hormonal changes, or later in post-menopause, when hormonal activity has significantly declined. This underscores the importance of clearly defining and reporting menopausal stages to accurately assess and compare therapeutic effectiveness.

The lack of standardization in defining perimenopausal status was a key limitation identified by Rubinow et al. (2015), who found that some studies relied solely on age criteria, while others used clinical and hormonal markers such as follicle-stimulating hormone (FSH) levels and menstrual irregularities. Since the transition from perimenopause to post-menopause typically occurs over years and is influenced by multiple physiological factors, inconsistent classification likely contributed to variations in study findings across the studies reviewed (Rubinow et al., 2015).

Adjustment for Confounding Variables

The level of control for confounding factors varied widely across the reviewed articles. For example, Gordon et al. (2018) rigorously adjusted for baseline depression severity and stressful life events, recognizing that psychosocial stress can significantly impact depressive symptoms during perimenopause. Similarly, Gnanasegar et al. (2024) accounted for pre-existing depressive symptoms and concurrent antidepressant use, ensuring that improvements that resulted after HRT was implemented were not being impacted by pre-existing mental health interventions. Both Gnanasegar et al. (2024) and Gordon et al. (2018) adjusted for age, socioeconomic status, and smoking history.

In contrast, Wium-Andersen et al. (2022) adjusted for age, socioeconomic status, and smoking history but lacked data on menopause symptoms and did not adjust for pre-existing depressive symptoms and stressful life events-, all of which are known to affect depression outcomes. This limitation makes it difficult to determine whether the observed increased depression risk in women who started systemic HRT before age 50 was due to the therapy itself or other unmeasured symptoms or lifestyle factors.

Rubinow et al. (2015) highlighted additional inconsistencies across studies regarding the extent to which researchers accounted for hormonal fluctuations. Some studies controlled for naturally-occurring hormonal variability, while others did not, making it difficult for Rubinow to draw conclusions about the specific impact of exogenous HRT on mood stabilization. Whedon et al. (2017) further noted that many studies failed to account for concurrent antidepressant use, complicating efforts to determine whether any observed improvements were due to HRT alone or a combination of treatments.

Additionally, Joffe et al. (2018) acknowledged that many studies did not adequately adjust for vasomotor symptoms such as hot flashes and night sweats, which are known to impact mood. Since HRT reduces vasomotor symptoms, failing to account for their role in mood improvement may have led some studies to overestimate the antidepressant effects of HRT.

Overall, the discrepancies in menopausal status classification, and inconsistent attempts to control for confounding variables, highlight the need for greater methodological consistency in future research to identify the true impact of HRT on perimenopausal depression.

Major Themes in the Literature

A critical review of the literature revealed five themes related to the impact of HRT on depression in perimenopausal women. These themes reflect the key factors influencing the effectiveness of HRT and provide insights into the complexity of its application in clinical practice:

1. reduction in depressive symptoms;
2. influence of menopause state and HRT administration route of HRT;
3. influence of pre-existing mental health conditions and recent experience of life stressors;

4. impact of HRT combined with antidepressants; and
5. the need for individualized treatment selection.

Theme #1: Reduction in Depressive Symptoms

Across the reviewed literature, HRT was found to be effective in reducing depressive symptoms during perimenopause and early post-menopause, particularly when using transdermal estradiol combined with micronized progesterone. Gordon et al. (2018) demonstrated in their RCT that women receiving TE+IMP had significantly lower depressive symptom scores compared to the placebo group over 12 months. Similarly, Gnanasegar et al. (2024) found that women treated with menopausal hormone therapy (MHT) in a clinical setting exhibited significant improvements in mood, particularly when HRT was initiated during perimenopause. Conversely, Wium-Andersen et al. (2022) found that, while local estrogen therapy was associated with a reduced risk of depression, systemic HRT initiated before age 50 was actually linked to an increased depression risk. This result suggests that, while HRT use can be beneficial, its effectiveness may depend on the type and timing of therapy being implemented. Rubinow et al. (2015) also found moderate support for estradiol's antidepressant effects, particularly in women experiencing hormone-sensitive mood disturbances.

Theme #2: Influence of Menopause State and HRT Administration Route of HRT

The timing of HRT initiation was a key determinant of its effectiveness, with evidence supporting the critical window hypothesis, which posits that estrogen therapy has the most pronounced effects when started early in menopause. Gordon et al. (2018) specifically defined "the right stage" for initiating HRT as early perimenopause, characterized by irregular menstrual cycles but with periods within the last three months. They found that initiating treatment during this specific phase significantly enhanced the mood benefits derived from HRT, reinforcing the

importance of precise timing (Gordon et al., 2018). Similarly, Wium-Andersen et al. (2022) demonstrated that local estrogen therapy, when started after age 54, was associated with a lower depression risk, whereas systemic estrogen therapy initiated before age 50 was linked to a higher depression risk. These findings emphasize the complexity of timing in HRT initiation and underscore the necessity of individualized clinical decisions based on menopausal stage and age.

These findings aligned with Rubinow et al. (2015), who noted that delayed HRT initiation reduces its efficacy in managing depressive symptoms. Additionally, Whedon et al. (2017) found that bioidentical estrogen, while controversial, might be particularly useful for perimenopausal women, suggesting that both the formulation and administration route influence outcomes.

Theme #3: Pre-existing Mental Health Conditions and Life Stressors Influence Outcomes

The reviewed articles highlighted that baseline mental health status and life stressors significantly influenced the antidepressant effects of HRT. Gordon et al. (2018) controlled for pre-existing depression and found that HRT's benefits were greatest in women experiencing heightened stress, suggesting that hormonal stabilization may interact with psychosocial factors. Similarly, Gnanasegar et al. (2024) accounted for baseline depression and antidepressant use, showing that women with pre-existing mood disorders experienced more pronounced improvements when HRT was added to their treatment regimen.

In contrast, Wium-Andersen et al. (2022) did not fully control for psychosocial stressors, which may explain why systemic HRT appeared in their study to increase depression risk in younger women. Rubinow et al. (2015) also noted inconsistencies in how baseline depressive symptoms were accounted for across studies, further complicating conclusions about HRT's stand-alone effectiveness.

Theme #4: HRT Combined with Antidepressants Shows the Most Significant Improvements

A recurring theme across the articles was that HRT alone may not be the optimal treatment for depression, but when combined with antidepressants, it produced the most significant mood improvements. Gnanasegar et al. (2024) found that the best results were observed in women who received both HRT and antidepressant therapy, suggesting a synergistic effect between hormonal and pharmacological treatments.

Similarly, Joffe et al. (2018) highlighted in their clinical guidelines that, while HRT may provide antidepressant benefits, it should not replace standard treatments for major depressive disorder. Whedon et al. (2017) also noted that studies on bioidentical hormones often failed to control for concurrent antidepressant use, making it difficult to determine whether improvements were due to HRT alone or to a particular combination of therapies.

Theme #5: Treatment Should be Individualized

Given the variability in responses to HRT, the authors emphasized the need for individualized treatment approaches. Joffe et al. (2018) recommended that treatment decisions should be guided by the menopausal stage of the individual patient, personal history of depression, symptom severity, and patient preference. Rubinow et al. (2015) and Wium-Andersen et al. (2022) similarly concluded that the effects of HRT on depression are not uniform, and clinicians must consider timing, route of administration, and patient history when deciding to prescribe HRT.

Summary

This chapter presented the key findings from six articles that examined the impact of HRT on depression in peri-menopausal and post-menopausal women. The next chapter will critically analyze and consider the findings of these articles and how they relate to the research

question posed in this integrative review. Following this analysis, recommendations for education, research, practice, and the development of future guidelines are discussed.

Chapter Five: Discussion

This integrative literature review critically assessed the impact of HRT on depression in perimenopausal women. Several key themes emerged, providing important insights into clinical practice, identifying research gaps, and outlining implications for policy and education.

Key Findings and Clinical Implications

Evidence from the reviewed studies suggested that HRT, particularly transdermal estradiol combined with micronized progesterone, can effectively reduce depressive symptoms during perimenopause (Gnanasegar et al., 2024; Gordon et al., 2018). These findings support the theory that estrogen significantly influences mood regulation, providing therapeutic potential beyond the management of vasomotor symptoms alone. Additionally, the timing of therapy initiation emerged as crucial, supporting the "critical window" hypothesis that initiating treatment early in the menopausal transition maximizes mood-related benefits and minimizes potential risks (The North American Menopause Society, 2022).

The evidence also highlighted the necessity of individualized treatment approaches. Women experiencing higher baseline depressive symptoms, significant psychosocial stressors, or a history of mood disorders were specifically identified as those who could benefit most from HRT (Shea et al., 2020; Soares, 2019). Furthermore, combining HRT with antidepressant therapy showed enhanced outcomes for patients who experienced severe or persistent depressive symptoms, reinforcing the need for integrated treatment approaches in managing menopausal depression (Soares, 2019).

Methodological Considerations and Limitations

This integrative review faced several methodological limitations. Notably, there was pronounced heterogeneity among studies regarding the definition of perimenopause, choice of

depression scales, sample populations, and HRT regimens, which hindered direct comparisons between studies and the ability to generalize findings. Rubinow et al. (2015) specifically noted these inconsistencies, emphasizing variations in menopause stage definitions and hormone assessment methods across studies.

Another significant limitation of this review is the relatively small number of primary studies that had met the inclusion and exclusion criteria, likely due to the selected publication date range (2014-2025). This restricted date range had been intentionally chosen to capture those studies and clinical guidelines published after the release of the Women's Health Initiative (WHI), which had reshaped clinical practice and research approaches toward HRT (DeNeui et al., 2019; The North American Menopause Society, 2022). However, this restriction did mean that many primary studies conducted before 2014 were excluded from the integrative review, limiting its evidence base and highlighting the critical need for additional, high-quality, standardized primary research on this topic.

Research Gaps and Future Directions

Gaps identified as part of this integrative review underscore the urgent need for rigorous future research. Specifically, there is a need for standardized RCTs with depression measurement tools that are implemented consistently across studies, clearly defined menopausal stages, and longitudinal follow-up to comprehensively evaluate the long-term efficacy and safety of HRT. Research regarding optimal HRT dosing, administration routes, and precise timing of HRT initiation also remains essential. Further investigation should also prioritize diverse populations to explore the possibility that cultural and socioeconomic factors may be influencing menopausal depression and the reported effectiveness of HRT.

Implications for Nurse Practitioner Practice, Education, and Policy

The findings from this integrative review carry significant implications for NP practice. NPs are strategically positioned in primary care settings to proactively screen and manage depression in perimenopausal women. Enhanced understanding of the potential benefits and limitations of HRT will empower NPs to provide informed, individualized counseling and treatment plans. Educational curricula for NPs should integrate comprehensive content on menopausal mental health, emphasizing the combined hormonal and psychological interventions necessary to optimize patient outcomes.

From a policy perspective, the establishment of clear, evidence-based clinical guidelines will serve to standardize care, ensuring the use of more consistent management strategies across different primary care settings. Policies should support routine mental health screening within menopausal care frameworks, promoting early identification and integrated management of depressive symptoms. Furthermore, policy advocacy should focus on securing funding and resources for continued high-quality research, bridging existing knowledge gaps, and fostering the development of comprehensive, evidence-informed recommendations that improve healthcare delivery for menopausal women.

In summary, while this review confirms the promising role of HRT in managing perimenopausal depression, methodological limitations and research gaps highlight the urgent need for additional high-quality, standardized studies. However, even before the existing evidence base is supplemented in this manner, many current clinical gaps can be addressed through targeted primary care provider education regarding perimenopause, menopause, and the experience of these life events would substantially improve outcomes for women during this pivotal life stage. The importance of NPs and primary care providers proactively educating

themselves about HRT and depression management cannot be overstated. In addition, healthcare policies and guidelines that are based on the most recent research evidence, and that emphasize the role of primary care providers in ensuring informed patient decision-making, could strongly contribute to improving women's experience of perimenopause and menopause. While awaiting further research and formalized guidelines, NPs have a crucial role in actively screening perimenopausal women for depression, sharing available evidence openly and transparently, and supporting patients in making informed decisions tailored to their individual health profiles and personal preferences.

Chapter Six: Conclusion

This integrative literature review examined the impact of HRT on depressive symptoms in perimenopausal women, providing a comprehensive synthesis of current evidence. Findings indicate that HRT, especially TE+IMP, can effectively reduce depressive symptoms when initiated during the early perimenopausal stage (Gnanasegar et al., 2024; Gordon et al., 2018). The literature consistently emphasized the critical role of estrogen in mood regulation, underscoring its potential utility beyond alleviating vasomotor symptoms (Herson & Kulkarni, 2022; Lokuge et al., 2011).

Significant methodological limitations, including variability in menopausal stage definitions, depression assessment tools, and heterogeneous sample populations, were prevalent across studies. A notable constraint of this review was the limited number of primary studies available within the defined publication window of 2014-2024, a deliberate choice intended to reflect current research post-WHI findings (DeNeui et al., 2019; The North American Menopause Society, 2022). These limitations emphasize the necessity for additional high-quality, standardized primary research.

The review highlighted critical gaps that must be addressed through future studies, particularly regarding optimal dosing, administration routes, and timing of therapy initiation. Additionally, research needs to continue exploring how patient-specific factors, such as baseline mental health, psychosocial stressors, and lifestyle variables, can influence the efficacy of HRT in managing depressive symptoms (Shea et al., 2020; Soares, 2019).

Given the current limitations and research gaps, NPs and other primary care providers are encouraged to proactively educate themselves about the evolving evidence regarding the role of HRT in treating perimenopausal depression. Routine mental health screenings with validated

screening tools, comprehensive patient education, and shared decision-making processes are essential components of effective clinical practice. NPs who are equipped with a thorough understanding of these dynamics can better assist patients in making informed, individualized decisions about their treatment options, ultimately enhancing patient outcomes and quality of life during this vulnerable period (Shifren et al., 2014; Soares, 2014).

Ultimately, addressing these research gaps through ongoing, high-quality studies, comprehensive NP education, and informed policy development will support evidence-based practice improvements. Progress in these areas will provide perimenopausal women with optimal, holistic care during this significant life transition.

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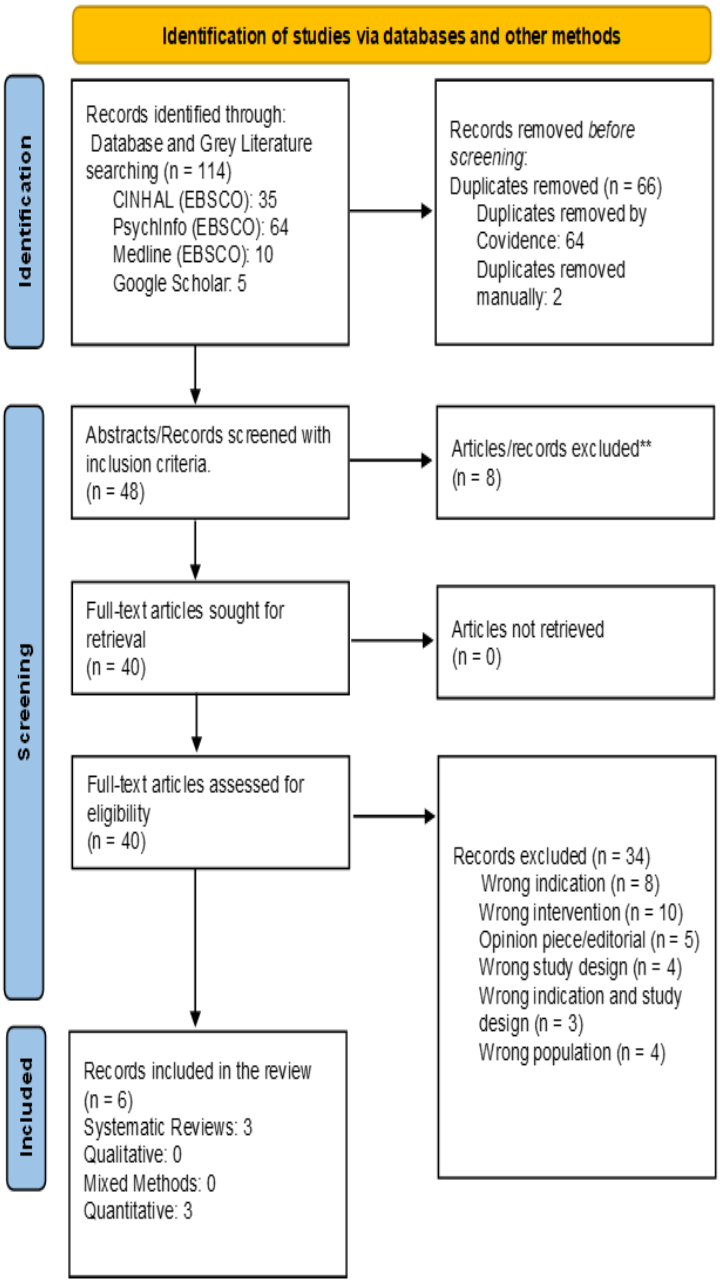
Appendix A: Search Terms for Integrative Review

Search Term	**Boolean Search Language**	Search Term	**Boolean Search Language**	Search Term
Hormone replacement therapy (MH) **OR** HRT **OR** hormone replacement therapies **OR** Menopausal hormone therapy	**AND**	Depression (MH) **OR** Depressive symptom* **OR** Emotional depression **OR** Depress* mood	**AND**	Perimenopause (MH) **OR** Perimenopausal OR Perimenopausal women **OR** Premenopause **OR** Menopause transition

MH = main heading

Appendix B: Literature PRISMA Flow Diagram



Note: Adapted from "The PRISMA 2020 statement: An Updated Guideline for Reporting Systematic Reviews," by M. J. Page, J. E. McKenzie, P. M. Bourton, T. C. Hoffmann, C. D. Mulrow, 2021, *BMJ*, 372, p. 71.

Appendix C: Literature Matrix

Quantitative Research Studies and Systematic Reviews

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
Gnanasegar, R., Wolfman, W., Hernandez Galan, L., Cullimore, A., & Shea, A. K. (2024). Does menopause hormone therapy improve symptoms of depression? Findings from a specialized menopause clinic. *Menopause: The Journal of The Menopause Society, 31*(4), 320–325. https://doi.org/10.1097/GME.0000000000002325 **Country:** Canada, Ontario	Observational cohort study assessing the effect of menopause hormone therapy (MHT) on depressive symptoms among women seeking care at a specialized menopause clinic.	Data from Jan 2020-2023 Follow-up at 3months & 12 months of treatment	170 perimenopausal or menopausal women aged 18 to 72 years attending a menopause clinic; 24% perimenopausal, 36% natural menopause, 39% iatrogenic menopause. 92.4% being White. 63.5% of participants had postsecondary education. 12.4% smoked. Data from women who attended the specialized Menopause Clinic from Jan 2020 to Jan 2023 (either virtually or in person).	**Inclusion:** Women or female-presenting individuals aged 18–72 years attending the specialized Menopause Clinic at St. Joseph's Healthcare, Hamilton. Perimenopausal or postmenopausal status is confirmed by menstrual history or hormonal levels. Completion of the Center for Epidemiological Studies Depression Scale (CES-D) questionnaire at baseline and follow-up. Those prescribed menopausal hormone therapy (MHT) as part of routine clinical care. **Exclusion:**	**Intervention** MHT using oral or transdermal estrogen alone or combined with oral or transdermal progestogen MHT with antidepressant. Antidepressants alone. **Comparison** Nothing	CESD-10 depression scale (An abbreviated version of Center for Epidemiological Studies Depression Scale).	Age, education, smoking status, and type of menopause influenced outcomes. Statistical models (e.g., ANOVA, regression) were used to account for confounding variables.	Significant reduction in CESD-10 scores with MHT. Greatest improvements seen when MHT combined with antidepressant.	**Side Effects** Mild breast tenderness Breakthrough vaginal bleeding **Adverse** None noted	**Strengths** Use of a validated scale (CES-D-10) for depressive symptoms. Adjustment for key confounders. Inclusion of a diverse range of treatments (MHT, MHT + antidepressants, non-hormonal therapies). **Limitations** Potential referral bias as participants were drawn from a specialized clinic. Limited ethnic diversity among participants. Uneven distribution of participants across treatment groups.	MHT, especially in combination with antidepressants, can be a valuable treatment for depressive symptoms in menopausal women. A personalized approach to MHT considering menopausal stage, education level, and smoking status should be implemented. Further research should examine timing of therapy initiation and optimal patient selection. Nurse Practitioner (NP) education should

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
				Missing data on CES-D scores from baseline or follow-up visits. Use of local estrogen therapy only, as these participants were categorized as receiving no systemic MHT. Women with incomplete treatment plans or non-adherence to prescribed MHT or antidepressant therapy.							emphasize assessing depression during menopause, the appropriate timing of treatment initiation, and individualized patient management
Gordon, J. L., Rubinow, D. R., Eisenlohr-Moul, T. A., Xia, K., Schmidt, P. J., & Girdler, S. S. (2018). Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: A randomized clinical trial. *JAMA Psychiatry, 75*(2), 149–157. https://doi.org/10.1001/jamapsychiatry.2017.3998	Double-blind, placebo-controlled randomized controlled trial evaluating whether transdermal estradiol (TE) and intermittent micronized progesterone (IMP) prevent depressive symptoms in perimenopausal and early postmenopausal women.	12 months	172 euthymic healthy perimenopausal and early postmenopausal women aged 45–60 years in North Carolina. 76% White, 19% African American. Community-recruited participants through advertisements	**Inclusion:** Women aged 45–60 years who were perimenopausal or early postmenopausal, as defined by the Stages of Reproductive Aging Workshop criteria. Medically healthy participants with no major medical or psychiatric conditions. Euthymic women (no current depressive symptoms) as confirmed by the Structured Clinical Interview for DSM-IV.	**Intervention** Transdermal estradiol (0.1 mg/day) + oral micronized progesterone (200 mg/day for 12 days every 3 months). **Comparison** Placebo	Follow-up visits for monitoring and assessments throughout and after 12 months. Scores on the Center for Epidemiological Studies-Depression Scale (CES-D).	Baseline reproductive stage; stressful life events; initial depressive symptoms at the start of the study; vasomotor symptoms; baseline estradiol levels; history of depression; and history of abuse.	12 months of TE+IMP were more effective than placebo in preventing the development of clinically significant depressive symptoms among initially euthymic perimenopausal and early postmenopausal women.	**Side Effects** Vaginal bleeding Breast tenderness Bloating **Adverse** 1 case of acute deep vein thrombosis requiring study withdrawal in treatment group. 2 cases major depressive disorder requiring withdrawal in placebo group.	**Strengths** Rigorous design (double-blind, placebo-controlled RCT). Comprehensive outcome measures (CES-D scale, stratification by reproductive stage). Addressed a clinically significant question with relevant implications for practice. Accounted for confounding variables: reproductive stage at enrollment, baseline	There is a need for individualized treatment based on patient characteristics, such as reproductive stage and stressors. Timing of diagnosis and intervention are crucial. Adeptness and awareness of validated screening tools and the difference

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
Country: USA, University of North Carolina at Chapel Hill				Availability to participate in a 12-month intervention and complete assessments **Exclusion:** History of hormone-dependent cancers, including breast cancer or endometrial cancer. Current or recent (within the last year) use of hormonal therapy. Active major depressive disorder or antidepressant use. Severe vasomotor symptoms requiring immediate treatment. Conditions contraindicating hormone therapy, such as thromboembolic disorders or uncontrolled hypertension. Significant medical comorbidities						estradiol levels, baseline vasomotor symptom bother, history of a major depressive episode, stressful life events, and history of physical or sexual abuse. Baseline characteristics (e.g., age, reproductive stage, history of depression) were balanced between groups. **Limitations** Limited generalizability to populations outside the trial's demographic (e.g., diverse ethnic groups).	between perimenopausal symptoms and clinical depression are essential in appropriate treatment. A short trial of transdermal estradiol may be appropriate for perimenopausal women with depressive symptoms seeking relief from additional menopausal symptoms. HRT appears more effective when initiated close to the cessation of ovarian activity, making the timing of HRT initiation critical.

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
				that could affect participation or outcomes.							Research should further clarify optimal timing and patient characteristics predicting treatment success. NP education should highlight timing, individualized treatment planning, and recognizing patient risk factors for depression onset during menopause transition.
Joffe, H., Bromberger, J. T., Maki, P. M., Kornstein, S. G., Freeman, E. W., Athappilly, G., Bobo, W. V., Rubin, L. H., Koleva, H. K., Cohen, L. S., & Soares, C. N. (2018). Guidelines for the evaluation	Systematic review providing clinical guidelines on the evaluation and management of perimenopausal depression, including the effects of hormone	Studies from 1980-2015	Perimenopausal and postmenopausal women, between the ages of 45 to 60 years, experiencing depressive symptoms or major depressive episodes. Primarily Caucasian,	**Inclusion:** Clinical studies assessing depression in perimenopausal and postmenopausal women using validated tools, focusing on hormone therapy, antidepressants, psychotherapy,	**Intervention** HT (estradiol and estrogen-progestin combinations), antidepressants, psychotherapy, and natural health products. **Comparison**	Beck Depression Inventory (BDI), Center for Epidemiological Studies Depression Scale (CES-D), Hospital Anxiety and	Menopausal stage, pre-existing mood disorders, psychosocial stressors, and variability in hormone levels. Differences in hormone	Recommendations for specific HRT treatments. HRT demonstrated antidepressant effects in perimenopausal	**Side Effects** Mild breast tenderness and breakthrough vaginal bleeding for hormone therapy. **Adverse**	**Strengths** Comprehensive review of clinical studies and RCTs. Use of validated measurement tools. **Limitations** High variability across studies, limited data on	While antidepressants are the frontline treatment, HT can be considered as an adjunct in select cases, particularly when

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
and treatment of perimenopausal depression: Summary and recommendations. *Menopause, 25*(10), 1069–1085. https://doi.org/10.1097/GME.0000000000001174 **Country:** USA	therapy and other interventions.		middle to upper socio-demographic. Varied in each study, most participants were recruited from clinics or research institutions.	and other therapies. **Exclusion:** None depressed women. Studies focusing solely on vasomotor symptoms without standardized assessments of depressive disorders.	Placebo or other active treatments, depending on the study.	Depression Scale (HADS-D), Structured Clinical Interview for Depression (SWAN), and the Taiwanese Depression Questionnaire (TDQ).	formulations, dosages, and routes of admin (e.g., oral vs. transdermal)	women, especially those with vasomotor symptoms. Antidepressants and psychotherapy were effective in reducing depressive symptoms.	None noted	long-term effects, lack of large RCTs, and Industry influence.	depression coexists with severe menopausal symptoms. This requires careful risk-benefit evaluation and informed discussions with patients. NPs have a key role in educating women about the relationship between menopause and mood, helping them understand their treatment options, and empowering them to actively participate in care decisions. Validated tools should be used to ensure accurate diagnosis.

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
											Early identification of women at higher risk for perimenopausal depression (e.g., history of depression, significant stressors) allows for timely intervention and prevention of severe episodes. Research is needed to refine recommendations on combined therapy and long-term effects. NP education should emphasize accurate assessment, recognition of high-risk patients, and patient-centered decision-

Article Reference/ Study ID	Study Design & Aim	Study Duration	Population Description & Recruitment Method	Inclusion & Exclusion Criteria	Intervention & Comparison	Outcome Measures	Confounding Variables	Reported Outcomes	Side Effects & Adverse Effects	Methodological Strengths & Limitations	Implications
											making regarding HRT use.
Rubinow, D. R., Johnson, S. L., Schmidt, P. J., Girdler, S., & Gaynes, B. (2015). Efficacy of estradiol in perimenopausal depression: So much promise and so few answers. *Depression and Anxiety, 32*(8), 539–549. https://doi.org/10.1002/da.22391 **Country:** USA	Systematic review summarizing the evidence regarding the therapeutic efficacy of HT in women with depression during perimenopause or post-menopause.	Studies from 1997-2014	Women in perimenopause or post-menopause stages with and without depressive symptoms. Recruitment varied across studies & was not detailed.	**Inclusion:** Women confirmed as perimenopausal or postmenopausal via clinical and hormonal criteria, such as follicle-stimulating hormone (FSH) levels and menstrual irregularities. Participants meeting diagnostic criteria for depressive disorders, including major or minor depression or dysthymia. Studies employing validated mood assessment tools such as the CES-D or HDRS. **Exclusion:** Non-interventional or observational studies. Studies involving predominantly	**Intervention** Transdermal estradiol and oral estradiol or a combination of estradiol (patch or oral) with oral micronized progestogen. **Comparison** Placebo	Validated depression scales (e.g. CES-D, HDRS, MADRS) and serum estradiol levels in some studies.	Variability in the timing of estradiol administration relative to menopause onset. Differences in hormone formulations, dosages, and routes of administration (e.g., oral vs. transdermal) Baseline psychiatric history, such as prior depressive episodes or postpartum depression.	HT demonstrated evidence of significant reductions in depressive symptoms in perimenopausal women but limited or no benefit in postmenopausal women.	**Side Effects** Breakthrough vaginal bleeding **Adverse** Increased risk of thromboembolic with oral estrogen.	**Strengths** Systematic review of RCTs. **Limitations** Inconsistent measures of menopausal state throughout studies. Heterogeneity among studies.	A short trial of transdermal estradiol may be appropriate for perimenopausal women with depressive symptoms seeking relief from additional menopausal symptoms. HRT appears more effective when initiated close to the cessation of ovarian activity, making the timing of HRT initiation critical. Future research should focus on standardizing menopausal stage

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				surgically menopausal women or those on selective estrogen receptor modulators (SERMs), androgens, or phytoestrogens. Trials lacking validated measures for mood or depressive symptoms. Research that did not clearly define menopausal status or mix peri- and postmenopausal populations without distinction.							definitions and clarifying the most responsive patient subgroups. NP education must emphasize careful patient selection, counseling about potential benefits and risks, and shared decision-making.
Whedon, J. M., KizhakkeVeettil, A., Rugo, N. A., & Kieffer, K. A. (2017). Bioidentical estrogen for menopausal depressive symptoms: A systematic review and meta-analysis. *Journal of Women's Health, 26*(1), 18–27. https://doi.org/10.1089/jwh.2015.5628	Systematic review assessing the efficacy and safety of bioidentical estrogens for depressive symptoms in peri- and postmenopausal women.	Studies from 2008-2015	Peri- and postmenopausal women including women without hysterectomy who had no menses for at least 12 months before enrollment, women with bilateral oophorectomy with or without hysterectomy, women over 40 with any of the following: irregular menses, self-reported	**Inclusion:** Randomized controlled trials (RCTs) comparing bioidentical estrogens (e.g., 17-beta estradiol, estriol, estrone) with placebo. Participants: Perimenopausal and postmenopausal women aged 40 years or older. Use of validated depression scales (e.g.,	**Intervention** Oral, transdermal and vaginal bioidentical estrogen (estradiol, estrone). Addition of progestins for those with an intact uterus. **Comparison** Placebo	Validated depression scales. Hamilton Rating Scale for Depression most used.	Heterogeneity in the dose and route of bioidentical estrogen delivery (e.g., oral vs. transdermal) Variability in participant menopausal status (e.g., peri- vs. postmenopausal) influencing outcomes. Concurrent use of	Bioidentical estrogen demonstrated minimal effect on depressive symptoms but significant improvement in vasomotor symptoms.	**Side Effects** Vaginal bleeding **Adverse** None noted	**Strengths** Comprehensive search, use of validated tools, and subgroup analyses. **Limitations** High heterogeneity among studies, exclusion of non-English studies, and inconsistent quality in primary research. Of the 12 included studies, 6 demonstrated	Bioidentical estradiol is effective for vasomotor symptoms, which may indirectly benefit mood in some patients. While the overall evidence does not strongly support bioidentical estrogen for depressive symptoms, individual

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Country: USA			vasomotor symptoms, or serum follicle stimulating hormone level >25 lIU/mL, and all women over age 60. Recruitment varied across studies but was generally clinic recruitment.	Hamilton Rating Scale, CES-D) to assess outcomes. Minimum study duration of 4 weeks, ensuring adequate time for pharmacologic impact on depressive symptoms. Studies with bioidentical estrogen administered orally, transdermally, or vaginally, with or without adjunctive progestogen. **Exclusion:** Concurrent psychiatric disorders Studies that did not include a validated depression scale. Trials shorter than four weeks in duration. Studies involving populations with mixed menopause and unrelated depressive conditions.			adjunctive therapies such as progestogens, some of which were not bioidentical. Differences in baseline severity of depressive symptoms across studies.			methodological quality concerns according to the Cochrane Risk of Bias Tool (missing key information about outcomes assessments).	patient preferences and symptom profiles may guide shared decision-making. NP education should stress evidence-based counseling on bioidentical hormones, individual patient preferences, and shared decision-making processes based on patient symptom profiles and personal goals.

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				Use of non-bioidentical estrogen as the primary intervention. Concurrent use of antidepressants or other psychoactive medications in over half the included participants, unless adequately documented.							
Wium-Andersen, M. K., Jørgensen, T. S. H., Halvorsen, A. H., Hartsteen, B. H., Jørgensen, M. B., & Osler, M. (2022). Association of hormone therapy with depression during menopause in a cohort of Danish women. *JAMA Network Open, 5*(11), e2239491. https://doi.org/10.1001/jamanetworkopen.2022.39491 **Country:** Denmark	Register-based longitudinal cohort study examining whether the use of hormone therapy (HT) during menopause is associated with a subsequent diagnosis of depression.	11 years	825,238 primarily Caucasian Danish women aged 45 years were followed to the age of 56 years. **Recruitment:** Danish Civil Registration System HT prescriptions were tracked using the Danish National Prescription Registry Danish Psychiatric Central Research Register and Danish National Patient Register, using ICD-10 and ICD-8 codes to identify depression diagnoses	**Inclusion:** Women aged 45 years and older, living in Denmark, between Jan 1, 1995, and Dec 31, 2017. No prior history of oophorectomy, breast cancer, or cancer in reproductive organs before the age of 45. Women without prior depression diagnoses or antidepressant use in the year before turning 45. Those initiating systemic or local HT for the first time during the study period.	Systemic (oral or transdermal) HT with estrogen only or estrogen-progestin combinations. **Comparison** Local HT or nothing.	Registry follow-up Depression diagnosis using ICD-10 and ICD-8 codes for hospital-based diagnoses.	Age, menopause status, marital status, education level, parity, prior depression, initial depressive symptoms at start of study, and comorbidities.	Systemically administered HT initiated before age 50 was associated with an increased risk of depression, particularly within the first year of use. Locally administered HT was associated with a reduced risk of depression after age 54.	**Side Effects** None reported **Adverse** Higher risk of depression	**Strengths** Nationwide data with a large cohort and long follow-up. Use of self-controlled case series analysis. **Limitations** Lack of data on menopausal status and symptoms. Possible residual confounding due to unmeasured variables.	Clinicians should exercise caution when prescribing systemic HT to women under 50, while locally administered HT may be safer for older women. Research needs to explore causal mechanisms and differential impacts by delivery method. NP education should focus on nuanced patient

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				Exclusion: Women with a history of breast or reproductive cancer, or oophorectomy. Women registered with HT use before the age of 45. Participants with a diagnosis of depression or antidepressant use within the year before HT initiation or study entry. Women with incomplete data due to emigration or loss of follow-up during the study period.							counseling about risks, personalized treatment selection, and careful monitoring for mood changes.

HRT = hormone replacement therapy; HT = hormone therapy; MHT = menopausal hormone therapy; TE = transdermal estradiol; IMP = intermittent micronized progesterone; CES-D = Center for Epidemiological Studies Depression Scale; CESD-10 = an abbreviated version of the Center for Epidemiological Studies Depression Scale; BDI = Beck Depression Inventory; HADS-D = Hospital Anxiety and Depression Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; SWAN = Structured Clinical Interview for Depression; TDQ = Taiwanese Depression Questionnaire; NP = nurse practitioner; RCT = randomized control trial; FSH = follicle stimulating hormone; SERMs = selective estrogen receptor modulators; ICD-8 = International Classification of Diseases 8th edition; ICD-10 = International Classification of Diseases 10th edition