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Perimenopausal Depression Screening and Treatment Efficacy Between Antidepressants and/or Hormone Replacement Therapy

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Abstract

During the menopause transition (MT), also known as perimenopause, women are at a significantly increased risk of depression. Although the pathophysiology is not fully understood, it is likely to be complex and multifactorial. Data evaluating the involvement of HPA axis dysregulation and correlating female reproductive hormone fluctuations, specifically estradiol, are factors that may contribute to this incidence. Currently antidepressants are the treatment for depression but with biological changes occurring during perimenopause, hormone replacement therapy alone or in combination may have comparable antidepressant effects. The combination of menopause symptoms, depressive symptoms, and psychosocial challenges, make recognition and treatment depend on many variables. Perimenopausal depression is a unique subtype of depression that should be screened with specific criteria to represent the varying symptoms experienced. Since it is an underrecognized and undertreated condition, clinicians in contact with this population, commonly OBGYNs and primary care providers, should routinely screen these women with appropriate measures to adequately initiate effective treatment. The current review summarizes relevant literature regarding perimenopausal depression prevalence, predictors/etiology, screening modalities, and appropriate treatment between antidepressants and/or hormone replacement therapy. References were searched using electronic search databases PubMed and Embase using keywords and similar articles. Articles were excluded if they did not assess the specific population of perimenopause or if it did not primarily focus on depression. Results are mixed regarding the most efficacious treatment between HRT, antidepressants, or both, but all have shown promising benefits and may need specific screening to identify the main contributors to further tailor treatment.

Keywords: menopause transition, perimenopause, depression, antidepressants, hormone replacement therapy, estradiol fluctuation, depression screening, hormones, perimenopausal depression, SSRIs, climacteric

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Introduction

Women have nearly two times higher rates of depression than men starting as soon as puberty and throughout their lifespan with increased likelihood during the menopausal transition (MT) (Toffol et al., 2014). Epidemiologic research revealed that one in five women will experience a depressive disorder at some point during reproductive hormone fluctuations periods which includes premenstrual, peri/postpartum, and perimenopause. The MT is associated with a two-to-four-fold increased risk of major depressive disorder (MDD) and clinical elevations in depressive symptoms (Gordon et al., 2015). Perimenopausal women report depressive symptoms three times more commonly than premenopausal women. Women are two to five times more likely to experience a depressive disorder during perimenopause compared to late post menopause (Bromberger & Epperson, 2018). There is a high and increasing rate of suicidal ideation and attempts in perimenopausal women (ages 45-54 years) compared with pre- or postmenopausal women or men of the same age (Gordon et al., 2016). Specific mechanisms contributing to this increased vulnerability to some women are not completely understood, as it is likely complex and multifactorial. This incidence may be related to the biological changes associated with the MT. The adverse impact of perimenopausal depression also affects a woman's family as well as society.

There are definitions and guidelines characterizing the stages of MT. The World Health Organization (WHO) defines perimenopause as "the time immediately preceding the menopause, beginning with endocrine, biologic and clinical changes, and ending a year after the final menstrual period". Natural menopause is biologically defined as twelve consecutive months of amenorrhea without an obvious intervening cause (Gyllstrom et al., 2007). The median age of perimenopause is 47.5 years and the median age for menopause is 51 years. To distinguish

between early and late perimenopause, the change in cycle length and irregularity is assessed. Early perimenopause is cycle length changes by at least seven days for two consecutive cycles, or irregular bleeding in the previous three months. Late perimenopause often consists of longer duration between periods, 3-11 months, preceding three consecutive months of amenorrhea.

The MT is a biological 10–15-year time of spontaneous gonadal hormone fluctuations, leading to irregular and complete cessation of ovarian function (Toffol et al., 2014). Psychological symptoms often present first, with physical symptoms presenting later, sometimes up to five years later. This means an individual may not recognize these mood changes as related to hormones, which can inhibit the appropriate diagnoses and treatments for specific psychological symptoms. Perimenopause has a wide range of symptoms with many factors that may contribute to the exacerbation/triggering of them. Symptoms such as hot flashes, mood changes, menstrual irregularity, sleep disturbances (insomnia, night sweats), libido changes, vaginal/bladder dysfunction(s), mental fog/disruption, headaches, and more may vary by severity and frequency per individual.

Pathophysiology:

There are various neuroendocrine mechanisms that contribute to perimenopausal depression. MT is initiated when a woman's supply of ovarian follicles diminishes. In premenopausal women, antral ovarian follicles produce the protein complex inhibin B, which inhibits follicle stimulating hormone (FSH) release, which then modulates the recruitment and growth of ovarian follicles. As women go through perimenopause, there are less antral ovarian follicles, therefore less inhibin B production, leading to the concentration of FSH to increase and buildup (Gordon et al., 2015). These FSH concentrations vary during perimenopausal irregularities, making FSH values inconsistent with reproductive staging. It is not merely due to

low basal hormone concentrations rather ovarian hormone fluctuations that trigger mood disturbances in vulnerable women (Gordon et al., 2015). Schmidt et al. (2009) claims that depressive episode's cluster during MT, specifically patterned with estradiol (E2) fluctuations and withdrawals, supporting the involvement of hormones and mood.

Estrogen is a key feature regarding mood disorders in women. Alpha and Beta estrogen receptors are located on cells throughout the brain, making the central nervous system (CNS) an important target organ for estrogen (Huttner & Shepherd, 2003). Specifically, the region regulating emotion, the limbic system, is abundant in estrogen receptors. Estrogen has a multitude of actions that influence neurons in the brain via genomic and transmembrane effects. Huttner and Shepherd (2003) states that estrogen increases sensory perception, cerebral perfusion, augments CNS glucose use, and alters pain pathways. The excitatory effect that estrogen modulates, and the increased serotonin concentrations at synapses via up-regulation of serotonin postsynaptic responsivity may play a role in improving mental performance.

Estrogen plays many roles throughout the body, including increasing norepinephrine concentration at synapses, decreasing monoamine oxidase activity, raising serum serotonin levels, and activating adrenocorticoid production resulting in a more enhanced and sustained stress reaction reduction. Contrary to those effects, progesterone is conflicting as it increases monoamine oxidase concentrations at neuronal synapses, leading to more depressogenic effects (Huttner & Shepherd, 2003). Progesterone is involved in the control of opioidergic, serotonergic, and cholinergic systems with consequent anxiolytic effects. There is evidence indicating hormones during perimenopause may eventually cause brain function changes, including sleep and mood.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may play a role in the association of E2 fluctuations and mood changes. Gordon et al. (2016) provided evidence of currently depressed women with greater weekly increases in E2 were associated with higher cortisol levels, as well as more negative mood changes. Many resources provide evidence that there is a subgroup of women who are more sensitive to these hormone fluctuations making them more vulnerable to experience perimenopausal depression. The fluctuating hormones may trigger a cascade of neurobiological mechanisms that negatively influence mood. “By triggering biological changes in a women’s stress physiology, dynamic and substantial changes in E2 concentrations might increase a perimenopausal woman’s sensitivity to stress. As a result, she is more vulnerable to developing depression if exposed to psychosocial factors or if she has a genetic or personality predispositions to develop depression” (Gordon et al., 2016).

The HPA axis is an important region of the body’s regulation of physiological and psychological stress with the downstream byproduct of cortisol. Therefore, dysregulation of this axis via E2 fluctuations may be predictive of both onset and relapse of depression. This concept is further supported with adequate evidence for other reproductive mood disorders such as premenstrual dysphoric disorder (PMDD) and postpartum depression. Researchers Schmidt et al. (2015) tested the effects of E2 withdrawal and associated mood during perimenopause. In this study half of the participants had past perimenopausal depression (PMD) and the other half had no history of depression. The study consisted of 56 euthymic postmenopausal women who were administered with three weeks of transdermal E2 and then abruptly and blindly discontinued half of the women. For women with a history of perimenopausal depression, within 1-3 weeks after withdrawal of the transdermal E2 their depression symptoms relapsed. For the women who were in the control group (no history of depression) or those who were maintained on E2 patches, this

phenomenon was not experienced. This study investigated the effects of sudden withdrawal of estradiol on mood, specifically the severity of depressive symptoms comparing the differences between women with PMD history and women without past PMD. Data results consisted of no depressive symptoms in women withdrawn from estradiol without past PMD, as well as women who had PMD history but continued receiving estradiol. Essentially, the lack of depressive symptoms in the control group without PMD history despite identical hormone manipulation implies that estradiol withdrawal may differentially affect the CNS function in a specific group of women more susceptible to depression. The evidence suggests that a vulnerable group of women may experience depressive symptoms during perimenopause due to these estradiol changes.

Several mechanisms hypothesized regarding estradiol effects on mood. Estradiol contributes various factors involved with the pathogenesis of depression including regulation of metabolism and synthesis of neurotransmitters, stress axis activation (HPA), neuroplasticity, epigenesis, and immune system activation. Animal studies have shown evidence of estradiol transmitting through estrogen receptor (ER) beta with reversal effects of depressive and anxiety like behaviors. Estradiol modulation in human and rodent studies has also been linked to the brains reward center and responsiveness, which is disrupted with depression. Schmidt et al. (2015) states “discontinuation of long-term estradiol therapy in postmenopausal women is accompanied by decreases in medial frontal and temper-occipital metabolism. Thus, through local signaling or network-level dysfunction, particularly in frontolimbic regions, estradiol withdrawal could precipitate affective dysregulation. Identifying the differentiating factor(s) regarding the mood-destabilizing effects of estradiol withdrawal and an increased vulnerability to a specific subtype of women is unclear and complex.”

Treatments

Prescribing hormone replacement therapy can be complex as it has many different variations of dosing, administration, inclusion of progestin, etc. in which efficacy and safety must be considered. It is known that women who go through menopause without receiving a hysterectomy are given the combination of estrogen-progestin therapy (EPT). Unopposed estrogen therapy (ET) is not to be given to women who still have their uterus due to the increased risk of endometrial cancer. Adding progestin to the mix balances out the increased risk of endometrial cancer back to average risk.

EPT can be prescribed as continuous dosing or sequential/cyclical dosing. Most women prefer continuous because it decreases the likelihood of irregular menstrual-like bleeding. Cyclical EPT consists of varying dosages taken on specific days, which can mimic the more natural menstrual cycle and decrease the amount of progestin exposure, alleviating more of the negative progestin-associated side effects. However, sequential dosing can be more complicated and may increase the risk of irregular bleeding.

As stated previously, the addition of progestin can negate some of the impacts of estrogen. Per the American Cancer Society (2015), many of the women who showed an increased risk of endometrial cancer were receiving their ET via oral pill. Other administration options such as a patch or a high-dose vaginal ring may also present this risk but there is less data and research on those.

Men and women experience mental illnesses differently through various influences by biological, psychosocial, and social changes over their lifespan. Unfortunately for women, most treatment trials in general have been researched on the ‘typical’ male, making it difficult to

assess how a specific treatment might affect a female, especially with such differing hormone levels and physiologic processes.

There are obvious risks regarding perimenopausal depression medication, as stated above, endometrial hyperplasia and cancer are the main concerns. Combination of estrogen and progesterone would be required, which impacts the results of treatment, as progesterone has specific negative effects on mood and psychological status (Toffol et al., 2014). A major deterrent for clinicians looking to use HRT (hormone replacement therapy) as a treatment would be the fact that HRT is not FDA approved for the treatment of depression, including perimenopausal depression.

With everything in medicine, it is important to consider all psychosocial and physiological factors and weigh all risks vs benefits. Some of the side effects between antidepressants and HRT are similar, such as, headaches, weight loss, unstable mental health (increased anxiety, depression, mood swings, suicidal ideation), loss of libido, and nausea. Each treatment also comes with some more serious risks. Antidepressants pose the risk of serotonin syndrome and heart arrhythmias. HRT can put women at an increased risk of heart attack, stroke, and blood clots, as well as the previous mention of endometrial hyperplasia and cancer. Another consideration for treatment(s) is the process of determining the right antidepressant and dosage for an individual, just as HRT would need to consider preparation of components, route of administration, type of hormones, and dosing.

Statement of Problem:

Perimenopausal depression is an underrecognized and undertreated condition and treatment should be specific to this depression subtype. Perimenopausal women experiencing fluctuating hormone levels can exhibit various stressors which may contribute to different symptoms. Some women during the MT are more susceptible to experiencing negative mood effects due to hypersensitivity to the extreme hormone fluctuations. Early recognition and adequate screening to ensure appropriate individualized treatment is imperative.

Research Question(s):

- In perimenopausal women suffering from depression, how does antidepressant therapy and/or hormone replacement therapy compare in treatment of depression and improvement of mental health?
- How can providers improve screening modalities for prompt recognition and appropriately individualized intervention?

Methods

A literature review was performed using electronic search databases PubMed and Embase. Keywords and mesh terms were applied to define a set of literature discussing the treatment of depression in perimenopausal women. Each search consisted of the following terms: perimenopause, menopausal transition, or climacteric in combination with the MeSH terms depressed, mood, depressive, or depression as well as terms specific to the section criteria. Background information was gathered by searching additional topic terms such as epidemiology, prevalence, risk, symptoms, presentation, screening, and scales. Treatment options were searched with terms antidepressants, SSRI, SNRI, hormone replacement therapy, estrogen therapy, or estradiol. Additional research articles were discovered via Similar Articles in PubMed. When

searching “perimenopausal depression treatment” roughly 1,000 articles with websites combined were presented. Reference lists were picked and based on applicability and similar articles specific to the topic were discovered and utilized. All searches were narrowed to the year 2003 to present. Studies that were on female reproductive cycle changes but not specific to the perimenopause transition were dismissed. Multiple other studies were excluded that dealt with specific patient populations unrelated to perimenopause time frame or were not specific to depression/mood changes. Articles that did not evaluate treatment of perimenopausal depression, specifically with antidepressants or hormone replacement therapy, were excluded.

Literature Review

Specific perimenopausal depression screening modalities for earliest intervention and appropriate treatment

Recognizing the risk of depression during the menopause transition is important to appropriately treat and prevent further risks. Researchers are concerned that the regular screening of depression regarding the nine criteria items from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) may not be adequate to fully encompass all the variables that may be contributing to a women’s mood during the menopause transition. Kulkarni et al. (2018) investigated a new form of screening to rate the symptoms of perimenopausal depression. Literature reviews, clinical observations, and focus groups were utilized for the development of the Meno-D rating scale. The researchers recognized that the Stages of Reproductive Aging Workshop (STRAW) is gold standard for characterizing women’s reproductive stages into categories of early or late transition phase of perimenopause, as well as early postmenopause.

Through previous depression research, many perimenopausal symptoms overlap with MDD symptoms such as sadness, but researchers found that perimenopausal moods tend to

present with more irritability, anger, paranoia manifesting as verbal outbursts over minor stressors, in which these symptoms seem more "out of character" for the women experiencing them. Other researchers have identified a different phenomenon in perimenopausal women in what seems to be an "on-off" switch in drastic moods, lasting minutes to hours before spontaneously resolving. Many individuals with perimenopause related depression experience low energy levels and increased fatigue, which are found to be independent of sleep disturbances caused from other menopausal transition symptoms. Considering how unique perimenopause symptoms can present, a specific screening method should be produced to better differentiate perimenopausal depression from other depression subtypes (Kulkarni et al., 2018).

Whether it be neuropsychological or biosocial aspects that influence mood during perimenopause, it is known that hypothalamic-pituitary-gonadal axis have direct effects on the brain through neurotransmitters. Estrogen and progesterone impact CNS aspects including inflammation reduction, increasing neurogenesis, neuronal regeneration, and modulating dopamine/serotonin transmission. Dysregulation of the hypothalamic-pituitary-adrenal axis such as perimenopausal hormone fluctuations may increase a women's risk of developing depression and sensitivity to life stressors. During the vulnerable stage of menopausal transition, various etiologies and symptoms must be considered when assessing adequate screening techniques.

There are various depression screening models currently, but they lack the more specific menopausal symptoms and experiences (rather than impact of) somatic symptoms. These unique symptoms may contribute to the development of depression in perimenopause more than other depression subtypes. Topics such as memory problems, paranoid thinking, poor concentration, low self-esteem, and social withdrawal are not addressed in the three screenings most used in this population which include the Beck Depression Inventory II, Montgomery and Asberg

Depression Rating Scale, and the Menopause Specific Quality of Life surveys. The Meno-D was designed to capture and rate the severity of characteristic symptoms of perimenopausal depression.

The development of the questionnaire topics is based off literature reviews, clinical observation, and focus groups consisting of perimenopausal women, physicians, and mental health clinicians (Kulkarni et al., 2018). Women between the ages of 43-54 reported specific physical and mental symptoms. Twelve types of symptoms were identified and each rated on a scale of 0 to 4: energy, paranoia, irritability, self-esteem, isolation, anxiety, somatic symptoms, sleep, weight, sexual interest, memory, and concentration. The Meno-D was used as a baseline survey for two different studies recruiting women experiencing perimenopausal depression symptoms and between the ages of 45 and 65. Kulkarni et al. (2018) gathered baseline data for 39 perimenopausal women in a randomized control trial evaluating a novel treatment of perimenopause depression. The other study had 54 perimenopausal women and utilized the Meno-D to assess factors that increase the risk of anxiety during perimenopause. Totaling 93 patients, who were then also compared to the Mini International Neuropsychiatric Interview (MINI) test to confirm mood diagnosis (e.g., MDD, or not fitting any other criteria per DSM IV) and compared to the STRAW screening survey for menopausal staging. Eighty-two of the 93 patients completed the Meno-D, with an average age of 50.54 (SD = 4.446), 57% married, and 87% Caucasian.

Kulkarni et al. further divided the 12 topics into five different construct groups. The construct labeled “self” had characteristics that included paranoid thinking, self-esteem, isolation, and anxiety. Weight changes and somatic symptoms were categorized into a construct labeled “somatic”. A factor titled “sexual” consisted of the topics including sexual interest and

low energy. Memory and concentration items were assigned the “cognition” factor. “Sleep” construct had topics of irritability and sleep disturbance.

Clinically, providers should consider perimenopausal related depression as a depression subtype and can further improve individualized treatment that considers menopausal stage, psychosocial stressors, physical health, and previous depression history. Weaknesses to this study include cross-sectional design and a low sample size. A longitudinal design would benefit this study to further assess menopausal staging and possible treatment response. Overall, the Meno-D is a new tool that has the unique ability to recognize and gauge the severity of perimenopausal related depression. Women’s health, especially anything with hormones is an under-studied topic. Utilizing this screening method supported by Kulkarni et al. can improve accurate detection and early diagnosis of perimenopausal depression aiding in individual-tailored treatment to best improve the quality of a women’s life.

Research has been proving that women are at increased vulnerability and risk of depression during perimenopause, more so than pre- or postmenopause. Obstetrics and gynecology (OBGYN) specialty is a main point of medical contact for women going through the perimenopause transition, making it more important for those providers to be especially versed in recognizing and optimizing treatment of perimenopause depression.

Raglan et al. (2020) surveyed 500 practicing OBGYNs who were members of the Collaborative Ambulatory Research Network (CARN) and fellows of the American College of Obstetricians and Gynecologists (ACOG). Through advertisements and already committed volunteer participants, 209 participants responded. The survey addressed demographic information such as year of birth, number of years practicing, identification of specialty or primary care provider, and any personal experience with mental illness. The questionnaire

assessed treatment and diagnosis of depression within perimenopause via seven true/false questions of the topic. The survey also measured providers confidence in screening, diagnosing, and treatment of depression.

The questionnaire used in the study by Raglan et al. (2020) took approximately 20 to 25 minutes to complete and was completed via e-mail or mail-in. A statistical analysis was performed using Bivariate Pearson's correlations, one-way analyses of variance, chi-square tests, significance using alpha level of 0.05. Respondents average age for females was 51.2 (± 8.87) and men 61.1 (± 7.16; $p < 0.01$). Regarding screening for perimenopausal women and depression, 65.9% of respondents reported regularly screening, while 34.1% reported not typically screening. Between male and female respondents, females were more likely to screen for depression during perimenopause compared to men (72.4% female, 55.4% male, $p = 0.02$). Respondents were more likely to screen while working at a university (76.0%), group practice (73.8%), or other (75%) compared to private practice (42.9%) and multispecialty group (53.6%) ($p = 0.014$). Individuals who reported knowing a friend or family member who struggle with mental illness were more likely to screen perimenopausal women for depression (relationship: 70.8% vs no relationship: 50.0%; $p = 0.034$). Female respondents who reported a personal history of experiencing depression were more likely to screen for perimenopausal depression than males (female: 91.3%, male: 65.8%; $p = 0.02$).

Comprehensive screening training during residency resulted in significant reports in recognizing, diagnosing, treating, and screening for depression in perimenopausal women ($p = 0.01$). Respondents who had participated in Continuing Medical Education (CME) about depression were more likely to screen for perimenopausal women for depression (78.0% vs 58.9%; $p = 0.013$). Providers who scored higher on the seven-question measure of knowledge

related to perimenopausal depression were more likely to screen for depression in perimenopausal patients (5.42 ± 1.22 vs 4.98 ± 1.48; p = 0.04) (Raglan et al., 2020).

There are various barriers that may inhibit a provider to screen for perimenopausal depression, such as, time (87.5%), inadequate training (50.6%), inadequate reimbursement (30.1%), liability concerns (20.5%), patients withholding information (21.0%), lack of screening tools (18.2%), lack of diagnostic consensus (10.8%), lack of confidence in recognizing depression, and lack of safe treatments (4.5%) (Raglan et al., 2020). To diagnose depression, providers utilized various techniques, with a majority asking their own questions during an appointment (64.5%). Other diagnosis methods consisted of following up during a visit if warranted (46.3%), using a clinical intake form (38.8%), a mental health questionnaire (24.0%), or through a validated interview (5.8%).

Raglan et al. (2020) reported that only 33.1% of respondents were confident in their ability to differentiate between a depressive disorder and subclinical depression symptoms. Most were confident in their ability to treat perimenopausal depression (55.8%), with 85.7% of respondents reporting confidently recognizing perimenopause depression, 70.4% confident in diagnosing perimenopause depression, and 67.2% confident in differentiating anxiety from depression. For patients with less severe symptoms, or subclinical depression, providers are most likely to suggest lifestyle modifications (e.g., exercise, diet change, medication), and prescribing medications for clinical depression. If patients were being treated by a mental health provider, 57.6% of providers report consulting with them.

This study was limited in that participants were all a part of a group already involved in the survey topic, implying that this sample may be more attuned to current recommendations. This study provides evidence that improved training for providers, especially OBGYN’s, may

improve screening rates. Increasing screening is crucial in earliest detection of depression and identifying appropriate treatment for the individual. A screening protocol specific for this population could increase prompt treatment, improve quality of life, and prevent other depression associated risks such as suicidal ideation or attempts.

Efficacy of antidepressant treatment for perimenopause related depression

Ladd et al. (2005) conducted an 8-week open-label trial of extended-release venlafaxine for perimenopausal depression treatment. The primary research question was to determine if venlafaxine relieves both depressive and vasomotor symptoms in depressed perimenopausal women. Inclusion criteria for this study was: 1+ climacteric symptom with onset between 42-51 years old, current depressive disorder (per DSM axis I disorders), no psychotropic therapy or estrogen replacement therapy (ERT) for one month, and no hormonal contraception use. Exclusion criteria included suicidality, pregnancy, prior venlafaxine use, recent participation in another study, psychotherapy initiated in last three months, active substance use disorder in last six months, and any history of psychosis, mania, malignancy, hysterectomy, or oophorectomy.

This 8-week open label trial was approved by The Emory University Institutional Review Board. Of the 16 women included in the study by Ladd et al. (2005), 100% were Caucasian, 69% were married, 66% were college grads, 81% employed, and the median age was 45 years. Half of the participants denied any previous antidepressant therapy history. Baseline data was collected for all reported irregular menses, 44% hot flashes, 37% nocturnal sweating, and 6% vaginal dryness.

Ladd et al. (2005) measurements focused on 4 subtypes: psychiatric (depression + anxiety), somatic, vasomotor, and sexual dysfunction (Clinical global impression severity (CGI/S), Greene Climacteric Scale (GCS)). The CGI/S consists of 3 observer-rated items to

assess symptom severity, global improvement, and therapeutic response. The GCS is a 21-item questionnaire measuring common bothersome psychological (anxiety, depression), physical (muscle and joint pains, headaches), and vasomotor (hot flashes, night sweats) menopausal symptoms. Standardized measurements utilized Hamilton Depression (Ham-D) rating scale, Hamilton Anxiety (Ham-A) rating scale, as well as FSH and estrogen concentrations.

Participants started the study on days 10, 11, or 12 of their menstrual cycle for data collection with standardized timing. Subjects were administered 37.5mg of extended-release venlafaxine daily for the first week and 75mg daily during the second week. Visits were conducted at the end of weeks 2, 4, and 8. If clinically warranted during follow-up visits, venlafaxine doses were increased in increments of 75mg at week 2 and/or week 4. At each visit, participants reported side effects, completed rating scales, and provided a venous blood sample to assess serum FSH and estradiol levels (Ladd et al., 2005).

Researchers assessed the baseline entry data and treatment response data throughout the trial. Results consisted of psychotropic effects evident by week 2 and sustained through week 8, 81.3% displayed antidepressant response (>50% Ham-D reduction) ($p < 0.001$), 75% achieved remission (Ham-D ≤ 7) ($p < 0.001$), GCS Total and psychiatric scores were identified early and sustained. Additionally, at week 8 the GCS Total scores were 60% lower ($p < 0.001$), depression subscores 71% lower ($p < 0.001$), anxiety subscores 61% lower, along with GCS somatic subscores were 65% lower. The overall conclusion from this trial is that venlafaxine treatment can improve mood (Ham-D reduction >50% representing antidepressant response) and overall well-being in depressed perimenopausal women (decreased CGI/S and GCS scores, $p < 0.005$). There are some strengths and weakness to this study by Ladd et al. Standardized timing with participant menstrual cycles contributes to its strength, yet a small sample size and a lack of

placebo control weaken the study. Additionally, there may be variation in study visits as the details of how tests were applied were not provided. Overall, this is a good start at looking at the different effects and efficacy of antidepressants (specifically an SNRI, venlafaxine) and perimenopausal depression treatment.

Soares et al. (2006) compared the efficacy and tolerability of escitalopram (ESCIT) and estrogen/progesterone therapy (EPT) for treatment of depressive symptoms and other bothersome menopause symptoms such as vasomotor symptoms, sleep changes, and quality of life in peri- and postmenopausal women. Between June 2001 and September 2003, 43 study participants were recruited in Boston, MA. Women ranging from 40 to 60 years old presenting with a depressive disorder and menopause-related symptoms were considered for the study. There were certain exclusions, such as any clinical contraindication to estrogen therapy or other serious medical conditions. Participants demographics including race, age, weight, marital status, education, employment, previous use of oral contraceptives (OC), and depressive disorders (major depressive disorder, minor depressive disorder, dysthymic disorder) were all recorded. Additionally, the Montgomery-Asberg Depression Rating Scale (MADRS), GCS, and CGI scores were recorded. Using Pearson's and/or Fischer's test, and Mann-Whitney tests, evidence of nonsignificant differences between treatment groups were found ($p > 0.05$ for all comparisons).

Soares et al. (2006) methods of measurement for depression consisted of The Mini International Neuropsychiatric Interview (confirmation of depression diagnosis), and the Montgomery-Asberg Depression Rating Scale (MADRS) for severity. Menopausal staging was assessed and defined with specifically defined criteria. Climacteric symptoms were evaluated via the GCS, addressing psychological, physical, and vasomotor symptoms. To assess menopausal

symptoms effect on functioning, the Hot Flush Related Daily Interference Scale (HFRDIS) and the Menopause Quality of Life Questionnaire (MENQOL) were administered. Sleep characteristics and changes were monitored via the Pittsburgh Sleep Quality Index (PSQI). Patient and investigator versions of the Clinical Global Impressions-Improvement were administered at each visit evaluation (P-CGI and I-CGI) to measure overall improvement, symptom severity, and treatment response.

Participants were randomly selected to receive an 8-week open-label trial of either ESCIT or EPT (Soares et al., 2006). All participants had an initial MADRS score of 13 or above. Three subjects did not participate; thus 20 participants were assigned ESCIT treatment and 20 assigned to EPT. The two groups did not significantly differ regarding demographic data. The ESCIT group started treatment dosing of escitalopram 10mg/day for 4 weeks, and further dosing adjustments made for the remainder of the study with max dose up to 20mg/day. Adjustment of ESCIT dosing was based off I-CGI recommendations. Participants in the EPT treatment group received fixed dosing of ethinyl estradiol 5 µg/day plus norethindrone acetate 1mg/day. Assessments of MADRS, GCS, HFDIRS, and CGI were evaluated at weeks 2, 4, and 8. PSQI and MENQOL were evaluated at baseline, and treatment weeks 4 and 8. Depression remission was defined as MADRS scores less than 10 at week 8. Menopausal related symptoms remission was considered with a 50% decrease in GCS scores from initial intake to week 8, and vasomotor subscores less than 2. Overall remission was achieved if participants had remission in both depression and menopausal symptoms. At the end of the 8-week study, a few participants had dropped out, final analysis included 32 participants, 16 in each group.

The median MADRS scores were significantly decreased in both groups at the end of the 8-week study by Soares et al. (2006). However, depressive symptoms were significantly

improved to a greater extent for participants in the ESCIT group (median decline = 19.2 with range score 10-34) compared to the EPT group (median decline = 9.4 with range score -6 to 30) ($p = 0.03$). Dose adjustments in the ESCIT group consisted of six women increasing to 20mg/day at week 4. More women in the ESCIT group had depression remission (MADRS score <10) compared to the EPT group (ESCIT: 12 out of 16 (75%), EPT: 4 out of 16 (25%), $p = 0.01$). Depression remission in both treatment groups was not associated with demographic characteristics, menstrual or reproductive history, menopausal staging, or depression subtype ($p>0.05$ for all comparisons). Improvement of hot flashes in both groups proved to be statistically significant without a difference between the two groups ($p = 0.64$). GCS scores, assessing menopause-related symptom severity, were overall significantly greater in the ESCIT group than the EPT group ($p = 0.01$). More women in the ESCIT group also achieved a significantly greater decrease of menopause-related symptoms (GCS score decreased >50% and vasomotor scores ≤2) compared to the EPT group (ESCIT: 9 out 16 (56.2%), EPT: 5 out of 16 (31.2%), $p = 0.03$) (Soares et al., 2006). Sleep characteristics showed significant improvement in both treatment groups (ESCIT: $p = 0.01$; EPT: $p = 0.03$), without any significant differences between the two. EPT and ESCIT groups did have different improvements in specific subscores of sleep characteristics. Both groups had nonsignificant weight changes.

The study done by Soares et al. (2006) is significant in that it shows evidence of superior efficacy for treatment of perimenopausal related depression with an SSRI compared to HRT. EPT did have an effect on depression, but not as many participants achieved full depression remission. Low participant numbers are a limitation to this study as well as using an open-label design. Recruitment details of participants were vague and therefore difficult to assess the ability to represent the general population. Additionally, participants were not specifically divided

between perimenopausal and postmenopausal, which may influence data. These preliminary results regarding the utilization and safety of hormone interventions suggest the idea of nonhormone interventions in managing menopause related symptoms.

Efficacy of hormone replacement therapy (HRT) treatment for perimenopause related depression

Gordon et al. (2018) conducted a clinical trial evaluating the efficacy of hormone replacement therapy via EPT utilizing transdermal estradiol (0.1mg/d) plus intermittent micronized progesterone (TE+IMP) in the prevention of depressive symptoms in the menopause transition. Between October 2010 to February 2016, the University of North Carolina hosted a double-blind, placebo-controlled randomized trial of 172 participants. The participants must have been euthymic perimenopausal and early postmenopausal women from the community between the ages of 45 to 60 years. Participants were self-referred from community advertisements posted on social media and received up to $1425 in compensation for full participation. The mean age for participants was 51 years old. Race/ethnicity percentages between the placebo group and the treatment group respectively consisted of 70% vs 81% white participants, 23% vs 15% African American participants, and 7% vs 4% reported as other. The researchers also accounted for education, income, reproductive stage (early perimenopausal, late perimenopausal, and early postmenopausal), plasma estradiol, body mass index (BMI), current smoker, history of major depressive disorder (MDD), any physical/sexual abuse, stressful life events, as well as prestudy Center for Epidemiologic Studies- Depression Scale (CES-D) scores and GCS (psychological, somatic, and vasomotor). They were randomly assigned to either group in a blind study without any statistical significance in baseline scores or demographics.

Depressive symptoms were measured using the CES-D scale at each visit, with significant depression reported as a score of 16 or more (Gordon et al., 2018). Other measures included serum baseline estradiol levels, vasomotor symptoms via Vasomotor Subscale of the GCS, reproductive staging for women with an intact uterus via menstrual cycle patterns, and MDD history using the Structured Clinical Interview for the DSM-IV. Researchers also addressed stressful life events for the six months preceding baseline evaluation via Life Events Survey interview (only moderate to severe events included), and experiences of sexual/physical abuse using a validated interview.

The researchers found that those in the placebo group were more likely to report significant depression (CES-D score ≥16) than the women receiving TE+IMP ($p = 0.03$), as well as more visits with significant depression ($p = 0.002$). The placebo group also reported higher overall CES-D scores over the 12-month intervention vs the treatment group with the CES-D mean (SD) unadjusted scores between the placebo group and treatment group, respectively, being 5.6(5.7) and 4.2 (5.3) at visit six, 5.7(7.6) and 4.0(5.0) at visit 12 ($p = 0.03$). Regarding reproductive staging relevance, only women in early perimenopause (not late perimenopausal or early postmenopausal) in the treatment group experienced better mood via reduction in CES-D scores ($p < 0.001$), less visits having a CES-D score ≥16 ($p = 0.03$) and two less occurrences where participants experienced significant depressive symptoms. Women in the late perimenopausal and early postmenopausal stages did not see treatment significance. While looking at stressful life events, Gordon et al. (2018) found that the more stressful life events showed increased treatment benefit. The researchers gave a progesterone regimen to women in the treatment group to produce vaginal bleeding, which in turn resulted in increased adverse effects reported from the TE+IMP women.

The researchers could have methodically measured serum estradiol levels at different intervals to better assess the idea that the degree of estradiol fluctuations may predict TE+IMP mood effects. Although there were only 172 participants, this study was able to record measurements of symptoms bimonthly over 12 months. The study was able to measure a range of psychosocial variables enabling the researchers to look at various factors assessing treatment response. Many other studies are researching a similar idea, but this study in particular is interesting as it looks at hormone replacement therapy for the *prevention* of the depression risk within the menopause transition. (Gordon et al., 2018).

Schmidt et al. (2021) assessed the efficacy of short-term estrogen-like compounds for women with PMD using placebo-controlled conditions. Plant-derived estrogen-like compounds such as selective estrogen receptor modulators (SERMs) and phytoestrogens may have tissue-specific properties of estrogen agonist and antagonist actions as well as different estrogen receptor affinities to ERalpha and ERbeta. Female rodent studies suggest that ERbeta has a stronger mechanism of antidepressant effects. Raloxifene hydrochloride is a specific SERM that has many MT but lacks estrogen-like effects on breast and uterine tissue, inferring that raloxifene is an estrogen antagonist to these tissues. Rimostil contains many multiple types of phytoestrogens, including genistein, a potent ERbeta agonist, but is now discontinued from the market, for unknown reasons. These compounds have shown benefit in postmenopausal women, which leads researchers investigating the effect during perimenopause.

Participants for this study consisted of perimenopausal women aged 40-60 with onset of depression during perimenopause and were participants at the National Institute of Mental Health (NIMH) midlife clinic between 2002 and 2014 (Schmidt et al., 2021). The study was conducted at an outpatient clinic within the NIH Clinical Center. The onset of depressive symptoms

reported by women may have been associated with personal distress or occupational impairment regarding menstrual irregularity for at least six months but no more than one year of amenorrhea. The participants were self-referred via local advertisements or physician referred.

Research participant criteria for the study by Schmidt et al. (2021) consisted of 1) a current episode of minor or major depression confirmed with DSM-IV, 2) elevated FSH levels (> 14 IU/L) on three of four screening phase visits to assess reproductive staging, 3) scores ≥ 10 for a minimum of three of four clinic visits during the two month screening phase via various screening tools such as Center for Epidemiologic Studies- Depression Scale (CESD), Beck Depression Inventory (BDI), or the 17-item Hamilton Rating Scale for Depression (HRSD/HAMD). Exclusions included women who reported suicidal thoughts, met severe depression criteria, had a medical illness, contraindications to TE, and women receiving psychotropic medications or other possible pharmacotherapy interactions with study compounds.

Before starting the study by Schmidt et al. (2021), participants were assessed during a 6–8-week screening phase which included four to five clinic visits at 2-week intervals. During these visits, mood ratings were completed as wells as blood samples taken. All women also participated in a history and physical, EKG, UA, and other blood lab assessments. The CESD, BDI, and HAMD were administered during this time and the average score throughout the weeks was used as a baseline value.

Schmidt et al. (2021) used a four-arm, parallel-design, double-blind, placebo-controlled trial of raloxifene, Rimostil, and TE in the treatment of PMD. Once approved from screening, participants were randomly assigned to one of four treatment groups for an 8-week study. Arm #1 included the administration of TE at a daily dose of 100 µg per day and placebo capsules. Women in Arm #2 received daily oral dosage of 60mg of raloxifene and a placebo skin patch.

Participants in Arm #3 were given daily administration of Rimostil 1,000 mg BID and a placebo skin patch. The fourth Arm was identical to Arms 1-3 but substituted placebo capsules and skin patches for active agents. At the end of the trial, all women administrated one week of oral Provera (5 mg/d) to induce a progestin withdrawal menses, not including participants in Arm #4. All participants, principal investigator(s), care providers, and rating clinicians were blind to treatment group assignments. Analyses were done with SAS version 9.4 software using PROC MIXED models.

The study by Schmidt et al. (2021) started out with 69 eligible women, three dropped before randomization. Sixty-six women were randomized into the study, four women discontinued the trial, leaving 62 women included for the final data analysis. In the group of women who did not complete the trial, one was randomized in the TE group and dropped out three days after randomization to placebo, and three women who received Rimostil dropped out. The final data results include 17 women in the TE group, 16 women in the raloxifene arm, 11 women in the Rimostil arm, and 18 women in the placebo group.

In the study by Schmidt et al. (2021) there was a significant difference between treatment groups and HRSD score ($p = 0.0037$), and HRSD scores differed across weeks ($p = 0.0068$), reflecting the declining HRSD score (symptom improvement) over the 8 weeks of study in all treatment groups. Across the entirety of the study, participants in Rimostil arm reported the highest HRSD scores (most symptomatic) while women in the TE arm had the lowest HRSD scores during weeks 4, 6, and 8. Combined weekly HRSD scores were pairwise compared and resulted in score improvements for women in the TE group compared to the Rimostil group ($p = 0.0005$). Within each treatment group across time, HRSD scores demonstrated improvement for women in the TE group, but similar findings were not supported in any other group. Women in

the TE arm reported decreased HRSD scores at weeks 6 and 8 ($p = 0.0001$) compared to week 2 ($p = 0.0065$), TE women also reported lower scores during weeks 6 and 8 compared with the Rimostil group ($p = 0.0008$ and 0.0011, respectively). HRSD scores did not differ significantly at any time between TE and raloxifene. Comparatively, at weeks 2 and 8, women in the raloxifene group showed lower HRSD scores than women on Rimostil ($p = 0.0063$ and 0.0034, respectively).

Neither CESD nor BDI scores displayed effects of treatment group. All four treatment groups were found to have similar patterns overtime with CESD and BDI scores and none of the pairwise comparisons between the different arms showed any significant treatment group differences in any of the four weeks. Blood lab work results, on average, women on TE had higher estradiol and lower FSH and LH levels than the other three treatment groups (Schmidt et al., 2021).

There were five nonserious adverse events worth mentioning that occurred during this study. One woman in the Raloxifene group experienced two events, one of which included right shoulder/arm pain which was relieved with an NSAID, and secondly chest pain reported three weeks later. The patient received cardiac work-up which resulted in negative cardiac enzymes. Another nonserious event happened to a woman in the Rimostil group who experienced extreme dizziness and lightheadedness resulting in study discontinuation. Patient had history of similar episodes prior to trial participation. She was consulted by a neurologist which was determined to be unrelated to the phytoestrogen administration. A woman in the placebo group experienced transient worsening of episodic seasonal asthma which resulted in Singular treatment for breathing. Another woman developed a temporary rash on her trunk, identified as pityriasis rosea, which lasted 10 days and did not require any intervention.

Schmidt et al. (2021) study overall found no significant improvement of outcome measures in any of the active treatment groups when compared to placebo. Nevertheless, comparing between groups there was a difference in HRSD scores (P = 0.0037), reflecting TE's beneficial effect on HRSD compared to Rimostil (P = 0.0005), but not quite with the placebo group. Benefits of this study include the fact that many of these compounds are viewed as safer alternatives to estradiol due to a more favorable pattern of side effects, lower risk of stimulating breast and endometrial cancers, and the positive perception of being a type of "dietary supplement." This study was limited with low participant numbers and sample sizes. Additionally, the manufacturers' decision to discontinue Rimostil limited the number of women randomized into the group. Considering the binding affinity of certain compounds to ERalpha and ERbeta, it is important to consider dosing impact, as phytoestrogens bind to ER with an affinity of only 35%, compared to estradiol. Overall, this study did not provide adequate evidence of the estrogen-like compounds (Rimostil or Raloxifene) benefitting mood during perimenopause. The data does support the use of TE over Rimostil or Raloxifene if seeking hormone-like treatments for PMD.

Efficacy of combination therapy (HRT + antidepressants) for treatment of perimenopause related depression

Huang et al. (2013) conducted a 2-month clinical study assessing the treatment of women with perimenopause related depression with combo therapy of remifemin (herbal black cohosh for symptomatic relief) and antidepressant paroxetine (SSRI). A total of 120 patients with perimenopausal depression were randomly divided via digital randomizer. Sixty patients participated in the treatment group receiving the combo therapy (oral remifemin TID + paroxetine 20mg QD), and the other 60 patients were placed in the control group consisting of a

daily dose of paroxetine 20mg. The study measured depression symptoms via The Hamilton Depression Scale (HAM-D) and menopausal symptoms via the Kupperman scale. Additional screenings to evaluate side effects consisted of urinalysis (UA), electrocardiography (ECG), liver function (LFT), and kidney function (CMP), blood (CBC), and blood pressure.

The total effective rates of depression improvement in perimenopausal women via HAM-D found that the treatment group effectiveness was 88.3% and the control group was 78.3%. After the 8-week trial, Kupperman menopausal indices were 9.89 ± 3.76 for the treatment group and 15.75 ± 5.84 for the control group ($p < 0.01$). Regarding other diagnostic studies involved, there were no significant side effects altering lab values. The therapeutic efficacy of the treatment group (combo therapy) was significantly higher than the control group ($p < 0.05$). This clinical trial supports the treatment of perimenopausal depression with combo therapy of antidepressant (paroxetine) and alternative HRT. Participant details (demographics, screening/selection) were vague and limited this study. Methods of scale explanations and assessment timing were not reported (Huang et al., 2013).

Fluctuating estrogen levels during the perimenopausal transition increase the risk of mood disorders. Estrogen replacement therapy (ERT) may stabilize the fluctuations and subsequently minimizing mood changes in the perimenopause. Rasgon et al. (2002) assessed the effects of ERT for treatment of clinical depression in perimenopausal women with monotherapy ERT treatment and ERT as adjunct treatment for women who were nonresponders or partial responders to SSRIs. Advertisements seeking females with depressive symptoms received 31 patients to evaluate. Once inclusion/exclusion criteria were assessed, 16 women met criteria to participate. Participants mean ± SD age was 46.7 ± 3.3 (ranging from 40-55). Years of education was averaged 15 ± 3.1 (ranging from 12-20) and mean socioeconomic level of middle class. The

participant demographics consisted of 87.5% Caucasian, 6.25% African American, and 6.25% Asian American. Regarding relationship status, 25% were married, 25% single, 37.5% divorced, and 6.25% widowed.

Rasgon et al. (2002) utilized various methods of depression measurement consisting of the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Education (SCID-I/P) and the 28-item Hamilton Rating Scale for Depression (HAM-D). A baseline score of 18 on the HAM-D scale was required to participate and diagnosis of unipolar MDD via SCID-I/P. Patients who were already receiving fluoxetine 8 weeks prior to baseline intake needed a score of 14 on the HAM-D to be considered with nonremission depression with antidepressants.

Of the 16 participants, six were already taking fluoxetine and ten were not on any antidepressant therapy. During this 8-week open-label treatment phase, both groups received ERT treatment (17β-estradiol dosed 0.3mg/day). ERT dosage was not changed unless negative side effects occurred (Rasgon et al., 2002). Certain researchers apart of the study met with participants once a week to evaluate mood changes and administer medication. HAM-D scores were recorded at each weekly visit and researchers compared baseline scores to each successive week. Partial response was defined as a final HAM-D score $\leq 50\%$ of the intake score and full remission as a score of ≤ 7. Statistical analysis was performed confirming significant decrease in depression levels in both groups ($p < 0.001$).

Significant mean reduction in HAM-D scores after 1 week of treatment were present in both groups; ERT ($p < 0.05$); ERT+SSRI ($p < 0.05$) and responses maintained throughout the study. The mean baseline HAM-D score for ERT-alone group was 18.30 ± 3.71 with a final score of 7.11 ± 7.70. Of the ten women in the monotherapy ERT group, six achieved full remission, three achieved a partial response, and one had no response. For the six women in the

ERT+SSRI group, the mean HAM-D score at initial intake was 23.20 ± 5.72 with a final score of 10.60 ± 2.94. Only one patient had full remission while the other five achieved partial response. This study was limited with a small sample size and a lack of a placebo control group (Rasgon et al., 2002).

Discussion

Although large longitudinal studies are difficult to attain in this specific population, a compilation of studies researching similar topics and details can be analyzed to develop appropriate hypothesis of effective screening and treatment options. Several researchers have evaluated the pathophysiology of depression during the perimenopausal transition and the variations of appropriate treatment between antidepressants, hormone replacement therapy, and/or a combination of the two.

Based upon the results of the studies examined in this literature review, there still seems to be conflicting data on this topic when comparing different treatment options. When evaluating antidepressants, hormone replacement therapy, or a combination of the two, multiple studies found each of those options efficacious. Antidepressant therapy is the mainstay treatment for depression in general and was found to be effective for treatment of perimenopausal depression. Ladd et al. (2005) assessed antidepressant effects with the SNRI, venlafaxine, which showed beneficial results through psychotropic effects via the HAM-D, GCS Total, and Psychiatric scores with 81.3% of participants displaying antidepressant response, and 75% achieving depression remission. However, the low participant numbers as well as lack of placebo control limit the study. The data supports the use of antidepressant therapy, specifically with venlafaxine, for overall improvement of both mood and quality of life for depressed perimenopausal women.

When comparing between the two, antidepressants vs HRT, Soares et al. (2006) data supported the idea that antidepressant therapy with escitalopram was found to be slightly more effective than HRT. Both treatments showed depression improvement, but ESCIT responded in a stronger degree with lower MADRS score and with more overall remission. However, division between perimenopausal and postmenopausal participants were not differentiated. Nevertheless, this study remains significant as there was still depression improvement between both treatments, which may suggest that both pathways can contribute to mood and should be applied depending on patients' severity, other climacteric symptoms, and menopausal staging. This may support the idea that hormones do have a role in improving mood, but for a specific population and more so as adjunct therapy. Hormone replacement effectiveness may vary based on dosing, preparation utilized, mode of administration, and type of estrogen/progestin combination.

Hormone replacement therapy comes with risks that may warrant further conversations about family history and health maintenance to determine risks vs benefits. It is not a new treatment for women going through the menopause transition and is showing promising data to help improve depressive symptoms specifically during perimenopause. Gordon et al. (2018) conducted a clinical trial of low dose and short duration of transdermal HRT which showed significantly lower CES-D scores compared to placebo.

Furthermore, menopausal stages were differentiated separately to assess the effective timing of HRT, which revealed that early perimenopause showed the most benefit. Although, with HRT during the progestin administration there were more negative side effects associated with climacteric and menstrual symptoms. The data recorded contributes to the current study with evidence that hormone replacement therapy alone did have a significant benefit of mood improvement for perimenopausal depression, compared to a placebo with no hormones or

antidepressants administered. Gordon et al. (2018) found that when assessing bleeding patterns and the presence of stressful life events may help early recognition of patients who may benefit most with TE+IMP during the menopause transition.

The results from Gordon et al. (2018) support the theory that TE+IMP treatment can prevent women in this population from experiencing clinically significant depression symptoms. Regarding the theory that hormone replacement therapy may be perceived as better if other menopausal symptoms are alleviated as well, Gordon et al. found that the results were still significant after adjusting for other vasomotor symptom problems. This signifies that TE+IMP treatment may independently have a prophylactic benefit on mood rather than just decreasing bothersome menopausal symptoms. This study helps support the idea that hormone therapy, specifically TE-IMP at the lowest doses and least amount of time, is safe for perimenopausal and early postmenopausal women for treatment of menopausal symptoms. Treatment may be specifically effective for women in the early menopause transition if they report more baseline stressful life events. Contrary to other studies, Gordon et al. found that a previous history of MDD and vasomotor symptoms were not significant at moderating TE+IMP effects. Suggesting that women are more susceptible to perimenopausal depression with having a history of previous depression, through mechanisms that may be unaffected by TE+IMP.

When assessing TE and estrogen-like compounds, Schmidt et al. (2021) did not find significant mood improvement with the substances when compared to placebo. When comparing between the three treatment groups, it was found that TE had a beneficial impact on HRSD scores. Yet, this study is significant as a steppingstone in researching alternative estrogen-like compounds and supporting the impact that hormones and estrogen may play a role in mood during perimenopause.

When researchers assessed the effects of estrogen-like compounds for the treatment of perimenopausal depression, Schmidt et al. (2021) discovered that TE was more beneficial in improving mood than phytoestrogens and SERMs. Although the data did not support the use of estrogen alternatives, the research on estrogen receptor signaling and modulation between ERalpha and ERbeta may play a more important role in hormone replacement therapy than previously hypothesized.

Paroxetine as antidepressant therapy and remifemin combination therapy was found to be efficacious in decreasing depression severity in perimenopausal women (Huang et al., 2013). However, certain study details such as participant gathering, and evaluation methods were not reported making it difficult to ascertain those parameters. Yet, the information attained during this study still contributes to the indication that combination therapy is an effective option in treating women with depression during the perimenopause transition. Like Huang et al. (2013), Rasgon et al. (2002) evaluated HAM-D scores while treating perimenopausal women with combination antidepressant and hormone replacement therapy. Rasgon et al. identified that both treatment groups (mono antidepressant and combination antidepressant + HRT) had significant therapeutic improvement but women in the combination group, especially with more severe MDD, showed significantly stronger results. Therefore, combination therapy of HRT and antidepressants has evidence of accelerating antidepressant response as well as being more beneficial for women who are not complete responders to individual (mono) antidepressant treatment.

The varying degrees of screening tools throughout this research does make this topic more difficult to assess and compare. Most of the studies had comparable definitions and criteria for perimenopausal staging. When Kulkarni et al. (2018) assessed different depression

screenings comparatively to the depression subtype during perimenopause, they concluded that various other factors contribute to perimenopause depression that are not represented in other depression screenings. With appropriate research, they generated a more inclusive questionnaire specifically for perimenopausal women experiencing bothersome symptoms that proved to be more accurate by including both neuropsychological and biosocial aspects of mood contributors. Most practices utilize a more basic depression screening tool such as PHQ-9, HAM-D, MINI, MADRS, CES-D, Kupperman scale, and SCID-I/P, but the MENO-D proves to be a better tool for the specific age group of women during perimenopause.

Having a measurement tool that can access the contributing factors to this specific population's depression symptoms can improve initial interpretations and further breakdown which aspects of symptoms are most severe and bothersome. The data from this study supports the idea that specific screening methods and measurements should be utilized for this specific population, especially for OBGYNs and primary care providers who are more likely to encounter these individuals on a regular basis. Raglon et al. (2020) has supporting evidence that the providers who are better educated and individuals who have more life experiences (personal, social, family, CME, etc.) are more likely to appropriately screen, accurately diagnose, and optimize treatment of women with perimenopausal depression.

Rasgon et al. results (2002) provide evidence that ERT should be considered in the treatment of clinical depression in perimenopausal women. Both groups (ERT alone and ERT+SSRI) found statistically significant treatment response within the first week and sustained throughout the 8-week trial. Specifically, this study also has evidence to suggest that ERT may be more effective in individuals with a more rigorous diagnosis of MDD while focusing on the perimenopausal population. The researchers also reported that ERT efficacy for perimenopausal

depression was independent of vasomotor symptom, so that improved mood was not solely from decreased vasomotor disturbances. It is important to consider with individualized perimenopausal depression treatment that ERT may be beneficial as an alternative antidepressant treatment or as adjunct to antidepressants. Combination therapy (ERT+SSRI) may even accelerate antidepressant response to treatment, especially in partial and non-responders to basic antidepressant treatment.

Currently the first-line pharmacotherapy treatment of depression is antidepressants. Regarding this special subtype of depression during perimenopause, there are many complex variables to consider when selecting appropriate screening and treatment. There are various antidepressants ranging from selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), atypical, tricyclic, monoamine oxidase inhibitors (MAOIs), and deciding which one is best for an individual takes trial and error and time. So far from these studies, paroxetine, venlafaxine, and escitalopram have all shown therapeutic responses for perimenopausal depression (Huang et al., 2013) (Ladd et al., 2005) (Soares et al., 2006).

Conclusion

Perimenopause is a unique time in a women's reproductive cycle and life stage in which some women may be at an increased vulnerability for depressive symptoms. Depression and perimenopause have been linked in multiple prospective longitudinal studies with varying populations. Interpretation and standardization of these studies are complex with varying designs, definitions, and analyses making it difficult to comparatively summarize. Regardless, evidence supports the idea that perimenopause and depression symptoms may be more intertwined via complex pathways and multifactorial circumstances than previously recognized.

Perimenopausal depression is not a one-size-fits-all treatment disorder and individualized evaluation is imperative in making the right decisions. Therefore, a screening tool that represents this specific subtype of depression, with symptoms that may not be recognized with general depression screenings should be utilized. Additionally, screening should be routine in healthcare visits, especially for primary care and OBGYN specialties, to ensure earliest recognition and therefore best outcome for appropriate and timely treatment. These symptoms should be promptly recognized and longitudinally followed rather than dismissed as physiological complaints of middle-aged women.

Evident research supports the data that perimenopausal depression is a complex condition with varying factors of influence. There is a subset of women who are more sensitive to the hormone fluctuations associated with MT in which are more vulnerable to mood disorders and depression. The limbic system in the brain, which is responsible for processing and regulating emotions has an abundant amount of estrogen receptors indicating hormone/estrogen involvement of mood during this transition. With a unique etiology, perimenopausal depression should have various considerations regarding appropriate treatment per the individual.

Potential treatments to consider include antidepressants for moderate to severe symptoms, psychotherapy to target psychological and interpersonal factors, and hormone therapy for women with first onset MDD or elevated depressive symptoms and at low risk for adverse effects (Bromberger & Epperson, 2018). Per the American Cancer Society (2015), EPT studies do not show an increased risk of endometrial cancer.

The research is inconsistent regarding which treatment is more efficacious compared to the other but is consistent in data proving that both modalities (antidepressants and/or HRT) have a beneficial impact for improving mood in women with perimenopausal depression. Long term

research, data, risks, and benefits have yet to be investigated to determine the overall safety of HRT and the role it has during perimenopause. Long term comparison studies longitudinally should be further researched to determine the overall treatment recommendation.

The International Menopause Society (IMS), recently updated in 2016, has research-based recommendations for practice guidelines for individualized hormone therapy treatment (Baber et al., 2016). Hormone replacement therapy has many different variations of formulary and needs to be appropriate for each individual, EPT vs ET needs to be investigated and considered.

Overall, the research does indicate providers to utilize a more specific screening tool for these women, and the Meno-D showed promising results. Once perimenopausal depression is identified, a more individualized treatment plan needs to be designed based on patient's symptom(s) severity, effect of quality of life, and other bothersome climacteric symptoms.

Future research should include a larger trial of participants to sufficiently analyze variables of interest that can influence a patient's response(s) to appropriate treatment. Additionally, researchers should evaluate the relationship between genetic polymorphisms and reproductive hormone fluctuations impacting the likelihood of PMD. Continuing to research women going through active perimenopause/menopause transition stages is imperative in discovering optimal treatment and recognition of PMD.

Women who present with more stressful life events and more intense depression should start initial therapy with antidepressants. Women should also seek behavioral health involvement, especially if they are experiencing any moderate to severe symptoms and/or suicidal ideation. Hormone replacement therapy can be added to antidepressant treatment to further accelerate therapeutic responses, as well as assist treatment for women who do not fully

respond to mono-antidepressant therapy. Perimenopausal women who struggle with more vasomotor and climacteric symptoms along with depression may benefit more with HRT. When utilizing HRT, early intervention along with low dose and low duration transdermal treatment is most optimal in alleviating and/or preventing depression during perimenopause. Although estrogen is not FDA approved to treat mood disturbances, the involvement of fluctuating hormones during this life stage must be considered and further researched as it may play a stronger role in women's mood than previously given credit for. Estrogen-based therapies may augment the clinical response to antidepressants and can help with bothersome vasomotor symptoms as well.

Application to Clinical Practice

These data representations provide necessary information for providers encountering women within MT experiencing depression. Clinicians such as OBGYNs, psychiatry, endocrinology, and primary care providers should recognize the vulnerability of this population and screen perimenopausal patients for depressive symptoms. Early recognition of this disorder as well as appropriate specific treatment is essential in minimizing the progression of the symptoms and in turn preventing patient harm to their health and/or themselves. Providers should utilize as many beneficial resources regarding this condition, which should include a specific and sensitive screening tool that is effective and efficient, such as the Meno-D. Additionally, the IMS has research-based recommendations for practice guidelines for individualized hormone therapy treatment for appropriate references and resources.

This review highlights the importance of appropriate screening for women within this age group. Many social factors influence a women's depression onset and severity. Providers should frequently assess a patient's current stressors, as well as their ability to cope with their

stressors. Depressive symptoms during the MT are common and should not be negatively perceived. A primary care provider can and should evaluate women for depression as well as follow appropriate treatment guidelines, while considering antidepressants and HRT (alone or in combination), and CBT (cognitive behavioral therapy) as needed. Considering the unique presentation and varying symptom involvement of perimenopausal depression, providers should be cognizant of this specific system involvement such as cognitive changes, fatigue, sexual function/libido, urinary incontinence, sleep disturbances, etc.

Treatment guidelines strongly recommend early screening and initiating a dialogue regarding perimenopause and mood symptoms. Short-term hormone replacement therapy may be more effective in women experiencing other symptoms of perimenopause. Unless otherwise indicated, antidepressant therapy and psychotherapy should be the first line treatment for women with perimenopausal depression. Providers should also make an effort in decreasing the negative stigma of depression, especially for women at such a vulnerable stage in their life with varying stressors. Perimenopausal is a treatable condition and should be treated and taken seriously like any other medical condition.

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