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EFFICACY OF ESTRADIOL IN PERIMENOPAUSAL DEPRESSION: SO MUCH PROMISE AND SO FEW ANSWERS

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Abstract

Background: Controversy regarding the antidepressant efficacy of hormone replacement therapy (HRT) stems almost from its inception and reflects the same methodological inconsistencies that have compromised efforts to determine whether the perimenopause is accompanied by an increase in mood symptoms or depression. Methodologic differences of note (other than study design) include menopausal state (perimenopause vs. postmenopause), determination of state (earlier studies used age as a proxy measure), baseline symptomatology (asymptomatic vs. depressive symptoms vs. syndromic depression), route of hormone administration (transdermal vs. oral), and symptom or syndrome measure. Zweifel and O'Brien's 1997 meta-analysis included 26 studies of the effects of menopausal HRT on depressed mood and revealed an overall effect size of 0.68. This moderate to large effect size, showing lower ratings of depressed mood in treated patients compared with controls, implicated HRT as a potential treatment of or prophylactic for depression in menopausal women. Since this publication, multiple studies have aimed to discern the relationship between HRT and menopausal mood.

Methods: The purpose of this systematic review is to examine the findings and quality of the evidence amassed since Zweifel and O'Brien's meta-analysis.

Results: Of the 24 studies meeting criteria for review, only five RCTs examined depressed subjects, and only two of the study samples were solely perimenopausal.

Conclusions: One can generalize from the studies reviewed here only with great caution, but there is little evidence to support the use of estradiol to improve mood in nondepressed patients (not surprisingly) and some evidence to support the antidepressant efficacy of estradiol in perimenopausal but not postmenopausal women.

Keywords

hormone; depression; menopause; mood disorder; HRT

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INTRODUCTION

Despite our best therapeutic efforts, depression remains a disorder with unacceptably high rates of remission failure, complicated by an array of adverse medical sequelae. Depression during midlife is particularly worrisome, as the incidence of heart disease, the major killer of women, increases dramatically in the wake of ovarian failure (the menopause) and is adversely affected (e.g., increased mortality) by co-morbid depression.[1,2] Indeed, death due to cardiovascular disease in midlife women with depression is increased by 50%.[3] The need for more effective treatment regimens for depressed midlife women should be self-evident.

The overlapping pathophysiologic effects of depression, cardiovascular disease, and ovarian failure potentially may be addressed by reversing—with exogenously administered estradiol—the reduction in estradiol levels that occur consequent to the menopause. Three types of evidence support the antidepressant efficacy of estradiol: impact on relevant affect-mediating systems; efficacy in animal models of depression; and efficacy in human studies.

IMPACT OF ESTRADIOL ON SYSTEMS POTENTIALLY MEDIATING DEPRESSION

Substantial evidence from multiple sources (reviewed elsewhere)[4] supports the role of estradiol (E2), the physiologic form of estrogen, in affective regulation and dysregulation. This evidence includes the following: (1) E2 “beneficially” modulates systems implicated in the pathophysiology of depression (neurotransmitter deficiency, stress, neuroplasticity, cellular energetics, inflammation, and network dysregulation). E2 regulates the synthesis, metabolism, and receptor concentration/trafficking of the classical neurotransmitters implicated in depression (serotonin, dopamine, and norepinephrine);[5–9] it regulates both basal and stimulated HPA axis activity;[10–12] it acts like antidepressants (and opposite to stress) in stimulating brain derived-neurotrophic factor (BDNF),[13] a critical growth factor observed to be deficient in depression;[14–16] it is neuroprotective in a variety of models;[17–21] it improves mitochondrial respiratory efficiency and prevents the formation of the oxygen free radicals that are believed to adversely affect mitochondria energetics in depression;[22] finally, at multiple levels, it prevents or counteracts the proinflammatory processes described as contributing to depression.[23] (2) In brain imaging studies, E2 and progesterone regulate cognitive-stimulated activity in the dorsolateral prefrontal cortex (dlPFC)[24] and in BA25, the region implicated in deep brain stimulation treatment of depression (Wei et al. unpublished). Additionally, not only do reproductive steroids regulate cerebral blood flow in brain regions (e.g., amygdala, dlPFC) implicated in depression, but as well they have been shown to determine the valence of the stimulus to which brain regions such as the orbitofrontal cortex (OFC) react.[25] Finally, E2 regulates in humans the reward circuitry that is believed disturbed in depression.[26,27]

ESTRADIOL IN ANIMAL MODELS OF DEPRESSION

A variety of studies have demonstrated that acute E2 deprivation following ovariectomy precipitates increased depressive-like behavior[28–30] (often increased immobility in the

forced swim test), which can be reversed with E2 replacement.[31–33] These behavioral effects are not seen in all strains, suggesting that genetic influences may contribute to the susceptibility to E2-induced depressive-like behavior.[34] Animal studies further suggest that it is estrogen receptor beta (ER beta)—an estrogen receptor that is genetically encoded on a separate chromosome from (and structurally different than) the originally identified estrogen receptor alpha—that mediates the antidepressant-like effects of E2.[35–37]

ESTRADIOL ANTIDEPRESSANT EFFICACY IN HUMANS

To inform clinical recommendations, this last type of evidence is crucial. Yet it is precisely this category of studies that is the source of the greatest confusion regarding the antidepressant efficacy of estradiol. In a 1997 meta-analysis including 26 studies, Zweifel and O'Brien[38] reported an overall effect size of 0.68 for the effect of menopausal hormone replacement therapy (HRT) on depressed mood. (HRT refers to estrogen plus a progestin, whereas ERT refers to estrogen without a progestin.) This moderate to large effect size, showing lower ratings of depressed mood in treated patients compared with controls, identified HRT as a potential treatment of or prophylactic for depression in menopausal women. Several years following this publication, the results of the Women's Health Initiative (WHI), a study of the effects of HRT on almost 17,000 women, revealed an increase (rather than the expected decrease) in coronary heart disease, which, with the attendant increase in breast cancer, appeared to signal the end of menopausal hormone therapy.[39] Subsequent studies, however, including reanalysis of the WHI data, revealed the following important contextual factors: (1) The results seen with ERT differed from those of HRT (e.g., no increased risk of coronary heart disease with ERT); (2) the hormones used in the WHI study (conjugated estrogens + medroxyprogesterone) were more likely to produce adverse effects on the cardiovasculature and breast than other hormone preparations; (3) the adverse effects seen in older women (who were far removed from the menopause) were not observed in perimenopausal women—i.e., the effects of ERT (or HRT) on perimenopausal women could not be inferred from those on postmenopausal women.[40,41] (This last observation of the *critical window* or *gap effect* was predicted in earlier animal studies.[42,43]) Despite the emergence of a more balanced and nuanced view of the benefits as well as the risks of ERT and HRT (as a function of type, duration, and timing), little current guidance exists regarding the potential antidepressant effects of hormonal therapies.

The purpose of this review is to examine and qualitatively summarize the evidence amassed since Zweifel and O'Brien's meta-analysis regarding the therapeutic efficacy of hormonal therapy administered to women with depressive illness during the perimenopause or postmenopause.

METHODS

We searched MEDLINE, EMBASE, and PsycInfo for human studies published between 1997 and 2014. Results were restricted to the English language. Medical Subject Heading (MeSH) terms were employed when available. All results contained a word or a corresponding MeSH term from each of the following categories in their titles and/or abstracts: (1) HRT, estrogen replacement therapy (ERT), hormone therapy, estrogen,

oestrogen, estradiol, progesterone; (2) depression, depressed, depressive, mood; (3) menopause, perimenopause, postmenopausal. Of the 2,346 results returned from the initial search, titles were reviewed to eliminate (where possible) articles that did not include primary data and administration of hormones. Two hundred sixty-nine abstracts passing the first cut were reviewed to determine their appropriateness for inclusion, based on the following criteria: (1) HRT or ERT manipulation (i.e., observational studies were not included); (2) use of validated measurement of mood. Not included in this review are studies primarily investigating the following: predominantly surgically menopausal women, selective estrogen receptor modulators (SERMs), androgens, or phytoestrogens. Forty-four articles met these criteria and comprised open label, single, and double blind studies.

The Grading Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to determine the overall quality of the evidence. Using this method, reviewers consider factors such as bias, imprecision, inconsistency, and indirectness, which contribute to the quality of evidence presented by studies and thereby determine the strength of derived clinical recommendations.[44] To comprehensively assess risk of bias, we reviewed all included studies using predefined criteria based on guidance in the Agency for Health-care Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews;[45] ratings can be good, fair, or poor. Two independent reviewers assigned risk of bias ratings, resolving any disagreements by consensus discussion or by consulting with a third reviewer. The following items were reviewed: randomization and blinding procedures, attrition rates (overall and between groups), statistical methods related to attrition, and potential for selective reporting. In general terms, a “good” study has the least bias, and provides results considered to be valid. “Fair” studies presumably fulfilled all quality criteria but did not report their methods to an extent that answered all of our questions. A “poor” rating indicates significant bias. Additionally, given the enormous methodological variability in the literature (which clearly complicates the ability to generalize from existing results), the following factors were used to determine the comparability of study samples and designs: menopausal status (peri vs. postmenopause); methods used to determine menopausal status (age vs. history vs. hormonal measures); baseline symptomatology (asymptomatic vs. depressive symptoms vs. syndromal depression); symptom or syndrome measures; type of hormone administered (HRT [estrogen plus progestin] vs. ERT); and route of hormone administration (transdermal vs. oral).

RESULTS

Our search yielded twenty-four randomized, placebo controlled trials (RCTs) and twenty open label or otherwise flawed trials. The twenty open label and flawed design HRT trials produced inconclusive results among an array of study designs lacking placebo controls. As such, these studies failed to impart any more than low quality evidence for HRT efficacy (or lack thereof) and were excluded from further consideration. The remaining 24 RCTs are the subject of this review and are listed in Table 1.

Among the 24 blinded, placebo-controlled studies reviewed, the majority ($n = 19$) examined the effect of HRT or ERT on mood in women either free of mood symptoms or minimally symptomatic at baseline, with the remaining five trials studying depressed patients. Upon

recognizing the disproportionately high number of trials studying nondepressed women, we decided that in spite of their low potential to contribute to our understanding of the antidepressant efficacy of HRT, these trials ought to be included in our review because they purportedly lend relevant evidence and comprise the bulk of the literature. Additionally, we noted that in many of the resultant studies, quality of life (QoL) assessments containing a mood component, rather than depression-specific measures, were used, and/or mood was not the primary outcome of the study. Again, for the sake of completeness, we reviewed such studies. In both subsets of trials (i.e., nondepressed and depressed patients), the collective results were generally conflicting. In an effort to delineate the effects of reproductive state and, by extension, menopausal symptoms, these trials are presented primarily divided into nondepressed and depressed patients, and are further categorized as older postmenopausal, younger postmenopausal, and perimenopausal populations.

ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC PATIENTS

OLDER POSTMENOPAUSAL WOMEN ($\bar{x}$ AGE = 70+)

Although studies of older postmenopausal women may benefit from the relative absence of potentially confounding menopausal symptoms in this population, these studies nonetheless produced conflicting results. In a study of cognitively normal postmenopausal women averaging 71 years of age, a normal score of 7 or less on the Brief Assessment Scale Depression Cards (BASDEC) was required for study entry.[46] Using a crossover design with each arm lasting 12 weeks, women were given low dose transdermal estradiol or placebo, with depression assessed at weeks 0, 12, and 24. A significant improvement, albeit of already normal depression scores, was observed in active treatment. In a similar sample, Almeida et al.[47] examined the effect of ERT on cognition, mood, and QoL in postmenopausal women averaging 73 years of age with average BDI scores of 6.95 at baseline. Estradiol was administered orally and on a dosing schedule that gradually increased, plateaued at 2 mg/day for 10 weeks, and decreased gradually. Following a total of 20 weeks of ERT, BDI scores were unaffected by treatment. The rationale for assessing depression after estradiol doses had been tapered down, rather than during the plateau, is unclear. A larger study with longer duration of treatment failed to find effect of oral HRT on mood in a sample of women with an average age of 71 years.[48] For 36 months, women received either HRT (ERT if hysterectomized), HRT with calcitriol, calcitriol alone, or placebo. Of these women 12% were classified as being depressed at baseline due to scores greater than 11 on the Geriatric Depression Scale (GDS). The number of depressed women per group decreased similarly across all groups by the final assessment. Pefanco et al.[49] observed slight increases in GDS scores of women receiving oral HRT or placebo for 36 months, and no between-group differences were found on any of the neurocognitive assessments performed. Average age for this sample was 75, and GDS scores were in the normal range both at baseline and posttreatment.

YOUNGER POSTMENOPAUSAL WOMEN (6 MONTHS–10 YEARS POST MENOPAUSE)

In younger postmenopausal populations climacteric symptoms are a potential confound in the interpretation of the effects of HRT on mood. Consequently, we have grouped studies on the basis of whether these symptoms were identified as inclusion or exclusion criteria. In the

following set of small trials, menopausal symptoms were neither required nor exclusionary. Comparing two oral HRT regimens to placebo, Bech et al.[50] examined effects on mood in a sample of Danish women who were within 6–24 months of their last menses. Neither psychiatric history nor comorbidity of the subjects was reported. Following 12 months of treatment, “significant differences” (lower scores) were observed in Beck Depression Inventory (BDI) in both HRT groups compared with placebo. Average baseline BDI scores of all groups were well within the range of normal limits (sequential HRT = 5.3, continuous HRT = 6.1, placebo = 4.1). Of note, one of the study’s authors was directly affiliated with the manufacturer of HRT preparations used. In a study funded by the same manufacturer, Haines et al.[51] sought to elicit a dose effect of unopposed estrogen replacement therapy (ERT) in a sample of nondepressed, Chinese, postmenopausal women. Subjects took either 1 or 2 mg oral estradiol or placebo for 12 months; depression scores on the Hospital Anxiety and Depression Scale (HADS) remained unchanged across groups. Use of a washout period prior to enrollment, hormonal confirmation of menopause, and compliance monitoring throughout are methodological practices in this study that were absent in the former trial. In a mixed sample of naturally and surgically menopausal women, Pearce et al.[52] found no effect on HADS scores when nondepressed women already using ERT implants were either continued or switched to placebo. The quality of the evidence in this trial was compromised by the failure to control for the following: time since previous implant (and thereby baseline E2 levels), baseline psychiatric comorbidity, and type of menopause. To assess effects of HRT on QoL, the Women’s Health Questionnaire (WHQ) was administered to nondepressed Italian women averaging 4.6 years of menopause duration randomized to receive HRT or calcium supplements. At 6 and 12 weeks of administration, the HRT group showed significant de creases from baseline in six of nine subscales, including the six-item depression subscale.[53]

SEVERAL STUDIES BASED SAMPLE SELECTION ON THE ABSENCE OR PRESENCE OF MENOPAUSAL SYMPTOMS

Excluding those women with menopausal symptoms requiring treatment, a QoL study found no difference in depression (assessed by the depression subscale of the WHQ) between postmenopausal women averaging 4.5 years since the last menstrual period on ERT, raloxifene, or placebo.[54] Using the same scale and also excluding women with severe menopausal symptoms, no difference in the depression subscale was found between HRT-treated groups and placebo in a Danish sample of women within 5 years of menopause, despite significant changes in vasomotor, sleep, sexuality, and memory subscales in the treatment groups. Of note, the estrogen in this study was administered intranasally to produce pulsed increases in estrogen, rather than sustained elevation, and mood was not the primary outcome measure.[55] Girdler et al.[56] having excluded women with hot flushes and depressive symptoms, observed no difference between ERT, HRT, and placebo on BDI scores over 6 months of treatment. Baseline BDI scores averaged 6.4, 6.5, and 5.8, respectively. A similar study including only postmenopausal women without significant depressive or menopausal symptoms and within 2–10 years of the last menstrual period (average = 3.7 years) found no superior therapeutic effect of oral ERT on BDI scores over 6 months.[57] Though major or minor depression [as assessed by the Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS L)] were exclusion criteria for this

study, baseline BDI scores (ERT: 12 and placebo: 13) were on the higher end of the normal range,[58] and both groups responded similarly and significantly over the course of the study (BDI = 5.5, 6.4 at month 6). In the only trial exclusively evaluating women with severe menopausal symptoms, a sample of Turkish women received either one of two HRT regimens or placebo.[59] All subjects were naturally postmenopausal for at least one year, averaging age 48 years, and HRT naïve. Depression was not an inclusion criterion for this study, though baseline Hamilton Depression Rating Scale (HDRS) scores were in the range of mild depression for all groups. Similar to the findings of Bech et al.,[50] significant decreases in HDRS scores were seen in both HRT groups following 3 months of treatment. It should be noted that one of the HRT regimens required transdermal administration, and the placebo used was administered orally. The collective results of the above studies are interpreted with caution for several reasons. First, though the WHQ does assess depressed mood, measures specifically designed to characterize depression are essential for developing clinical recommendations. Additionally, and obviously, antidepressant efficacy cannot be ascertained in samples of nondepressed women. Of note, the one trial that intentionally selected women with severe menopausal symptoms observed a reduction in mood symptoms with HRT.

In addition to the trials noted above, several large RCTs with extended treatment periods have been conducted in samples containing both older and younger postmenopausal women. These trials also failed to identify effects of HRT on mood in asymptomatic women. The Heart and Estrogen/Progestin Replacement Study (HERS) followed women on a combined continuous oral HRT regimen or placebo for 36 months. No effect was found on mood, although women experiencing hot flushes at the time of enrollment did have improved depressive symptoms when assigned to HRT.[60] Data collected as part of the WHI and reported by Hays et al.[61] showed no significant change of mood in women receiving HRT compared to those receiving placebo. A third RCT, the Women's International Study of long Duration Oestrogen after the Menopause (WISDOM), yielded similar results.[62] The value in this set of trials is in their large sample sizes, similar duration, comparable dosing, regimen and route of hormones, and use of similar depression indices (WISDOM used the 20-item Center for Epidemiologic Studies depression scale (CES-D); HERS and WHI used the 8-item scale developed by Burnam et al.,[63] which includes six items from the CES-D). In an offshoot of the WHI, the Women's Health Initiative Study of Cognitive Aging (WHISCA) sought to examine the effects of HRT on cognition and, to a lesser extent, affect. Using the Positive and Negative Affect Schedule (PANAS) and GDS, no effect of unopposed ERT[64] or HRT[65] was seen on affect. An inherent limitation of these studies is that women participating were affectively asymptomatic at baseline and, in the case of WHI, discouraged from participating if menopausal symptoms were present. In general, these large RCTs do not reveal the risk of bias displayed by the studies listed above (see table). Nonetheless, taken together, HERS, WHI and WISDOM data provide moderate-strong evidence for a statement of limited clinical value: HRT does not prevent or remediate symptoms of depression in an affectively asymptomatic, postmenopausal population.

PERIMENOPAUSAL WOMEN

In the only RCT studying mood in nondepressed perimenopausal women, a crossover design was used with each arm lasting 6 months.[66] An oral HRT regimen of 2 weeks conjugated equine estrogens (CEE) followed by 2 weeks CEE and medroxyprogesterone acetate (MPA) comprised the active arm, and depressive symptoms were assessed monthly via the Zung Self Rating Depression Scale (ZSRD). Subjects were enrolled on the bases of age and menstrual irregularity and/or climacteric symptoms. Without regard to order of treatment, the effects of HRT and placebo on mood did not differ, though when the active arm came second, there was a significant, consistent improvement in measures of depression, feelings of inadequacy, and composite score, comprised of items from the ZSRD, the State-Trait Anxiety Inventory (STAI), and the Self Rating Score of Distress (SRSD). The authors postulated that this effect may have been due to the placebo-first group having time to "deteriorate or even calibrate" themselves prior to HRT, thereby making any difference more noticeable than it would have been for the treatment-first group. As admitted by the authors, it appears that this study would have benefitted from a run-in period and perhaps shorter treatment arms. Additionally, without obtaining serum estradiol levels throughout the study, it is impossible to rule out a significant confound, namely spontaneous occurrences of ovarian function (i.e., production of endogenous E2) common in perimenopausal women.

WOMEN PRESENTING WITH AND MEETING CRITERIA FOR DEPRESSION

PERIMENOPAUSAL WOMEN

Antidepressant efficacy of transdermal ERT was found in two RCTs in perimenopausal women.[67,68] In each of these studies, subjects met criteria for major or minor depression or dysthymia and were confirmed to be perimenopausal via elevated follicle stimulating hormone (FSH) levels and history of menstrual cycle irregularity. Depression was initially confirmed using structured diagnostic interviews and was further assessed by both the CES-D and the HDRS,[67] and by the Montgomery–Åsberg Depression Rating Scale (MÅDRS).[68] Both studies measured serum estradiol throughout subjects' participation to ensure compliance and to monitor spontaneous production of E2. Though sample sizes were small, (31 and 45, respectively) the use of similar designs, valid depression metrics, and clinical diagnostics to establish homogeneous patient samples all contribute to the quality of these two trials.

YOUNGER POSTMENOPAUSAL WOMEN

With respect to depressed postmenopausal women, there have been two RCTs with discordant results. The first study failed to show efficacy of transdermal estradiol compared to placebo in women with mild to moderate depression, with an average baseline HDRS score of 14.5.[69] In this study, following a single blind run-in period and 8 weeks of treatment, both active treatment and placebo subjects experienced comparable decreases in HDRS scores, with significantly greater response to placebo seen in women with a history of major depression. The other study found significant improvements in HRSD scores after 24 weeks of treatment.[70] Subjects had a mean HRSD score of 18.8 at baseline, and while complete psychiatric history was not assessed at baseline, histories of premenstrual syndrome and postpartum depression were obtained (but did not predict outcome). Despite a

reasonable design, the latter study was funded by the manufacturer of the hormonal preparation tested and had exceptionally high dropout rates (32.3% of HRT group, and 57.8% of placebo group). Also of note, the difference in mean subject age between these two samples was approximately 6 years (62, 56.1, respectively). Women in the first study were an average of 17.1 years post menopause, while 73.6% of subjects in the second study were three or more years post menopause.

MIXED SAMPLE

Only one RCT examined ERT in a mixed sample of peri- and postmenopausal women.[71] Requisite for participation were both unipolar depressive disorder and insomnia syndrome, as confirmed by the Structured Clinical Interview for Axis I Disorders (SCID). Following a 1-week run-in period, subjects were randomized to receive transdermal estradiol, oral zolpidem, or placebo for 8 weeks. While MÅDRS scores improved comparably for all groups, post hoc analyses found increasing serum estradiol levels (due to ERT or spontaneously occurring) to be predictive of depression improvement in perimenopausal women, a trend not observed in the postmenopausal group. Further, for both peri- and postmenopausal women, improved sleep quality was predictive of depression improvement, though when sleep remained unchanged in perimenopausal women whose estrogen increased, depression was still improved.

In sum, the clinical implication of this small set of studies is that perimenopausal women are more likely than postmenopausal women to experience alleviation of depressive disorders as a result of ERT. The GRADE assessment of the quality of the evidence for the antidepressant efficacy of estradiol in this context was determined to be C (i.e., low quality, requiring additional higher quality evidence to inform clinical recommendations).

DISCUSSION

Reports of increased mood symptoms and depressive disorders accompanying the menopause appeared well before the 20th century and gave rise to the belief that symptomatic benefit could be achieved with ovarian hormone replacement.[72,73] Considerable controversy has surrounded the putative antidepressant efficacy of HRT almost from its inception,[73] in part as a consequence of methodological inconsistencies and shortcomings similar to those that have compromised efforts to determine whether affective disturbance is a concomitant of the perimenopause. Unfortunately, the paucity of well-controlled RCTs since the meta-analysis performed by Zweifel and O'Brien does little to advance our understanding of the antidepressant efficacy of estradiol or to inform clinical practice. In our evaluation of the literature, we first used a Risk of Bias method as suggested by the AHRQ guidelines and the GRADE method to determine the quality of the individual studies and the overall quality of the evidence, respectively. Only six studies showed a low risk of bias.[60–62,64,65,68] The assessments were additionally targeted to answer a question that is critical to the relevance, reliability, and generalizability of the findings: were the right measures employed in the right population to answer the question, "does hormone therapy successfully treat depression during or after the menopausal transition?" Only five studies met this minimal requirement.[67–71] Of these five studies, two were rated as poor (e.g.,

having high risk of bias): one due to both differential attrition and overall attrition[70] and the other due to a pertinent difference between groups at baseline (e.g., likelihood of having history of depression).[69] Consequently, we used the GRADE system to assess the overall quality of the evidence regarding the role of ERT or HRT in the treatment of depression. Consistent with the Endocrine Society Scientific Statement on Postmenopausal Hormone Therapy, we concluded that the overall level of evidence in support of the antidepressant efficacy of estradiol in perimenopausal women or the lack of beneficial effects on mood of ERT or HRT in postmenopausal women is, at best, C (i.e., low quality evidence, wherein conclusions could change with the accumulation of higher quality evidence).[74]

Conclusions that can be drawn from our review are as follows: (1) Evidence for the improvement of mood in nondepressed samples is poor, particularly in the absence of menopausal symptoms. On one hand, this parallels the observation of Yaffe et al.[75] that the cognitive benefits of ERT were seen only in women who experienced other menopausal symptoms. On the other hand, it is obvious that examination of mood—often apparently as an opportunistic afterthought—in a nondepressed population should (and does) tell us nothing about the possible efficacy of estradiol as an antidepressant. That said, placebo controlled trials collectively have shown little evidence for the efficacy of HRT in mood improvement in nondepressed, postmenopausal women. (2) Based primarily on data from three RCTs, estradiol may have antidepressant efficacy in perimenopausal but not post-menopausal depressed women. This finding is consistent with the “critical window hypothesis,” which suggests that the beneficial effects of estradiol are observed only if it is administered proximate to the cessation of ovarian activity.[76–78] Indeed, acute replacement of estradiol results in cardioprotective and neuroprotective effects, which are not demonstrated if estradiol is given after a considerable latency.[79–81] Zhang et al.[82] provide a possible explanation for the critical window: they observed that 10 weeks following oophorectomy, the ER in brain was increasingly ubiquitinated (degraded) and hence unavailable for estrogen signaling. By extension, providing estradiol to a woman who has not “seen” estradiol for 10 years is both unlikely to be effective (due to a different signaling context) and more likely to result in adverse effects. Diaz Brinton[22] has illustrated the latter point by showing that the beneficial effects of estradiol on cell function in healthy cells (e.g., improved mitrochondrial respiratory efficiency) are replaced by detrimental effects in unhealthy cells (e.g., increased cell death), just as estradiol’s benefits on the cardiovasculature are replaced by adverse effects (plaque destabilization) in the presence of age-related atherosclerosis.[79] Speculative neurobiology notwithstanding, existing data permit the use of a short term (2–3 weeks) trial of transdermal estradiol for treatment of a depressive syndrome in perimenopausal women who are seeking relief of other perimenopausal symptoms, who do not wish to take conventional antidepressants, or who have demonstrated lack of response to conventional antidepressants. Available data provide no guidance on how long estradiol should be administered if a successful antidepressant response to estradiol is achieved. Similarly, the extent to which the populations showing antidepressant responses to estradiol and conventional antidepressants are superimposable, overlapping, or exclusive components of a Venn diagram is unknown, as are predictors of response to estradiol or the indicators for monotherapeutic versus adjunctive use.

Apart from the variety of study designs employed, why, more than 15 years after Zweifel and O'Brien's meta-analysis, are the findings in the literature so relatively uninformative? The answer, in part, lies in the myriad methodologic variables that must be attended to in the design of studies intended to evaluate the antidepressant efficacy of estradiol. First, as noted above, the menopausal state needs to be selected and defined. Perimenopausal and postmenopausal women should not be mixed as if they were in the same physiologic state. Additionally, menopausal state ideally should be defined using a combination of clinical and hormonal measures, as specified in the Stages of Reproductive Aging Workshop (STRAW) criteria.[83] Second, post hoc inferences about antidepressant effects should not be drawn from a nondepressed study sample. Third, depression is a syndromal diagnosis that should be established according to clinical criteria rather than a threshold score on a rating scale. Scales to measure symptom variation over the course of the study should also be standard measures rather than less well-validated symptom subscales. Fourth, the type of hormone regimen may well affect the outcome observed. Biologic effects of conjugated estrogens differ from those of estradiol,[41] and the presence of a progestin in combined HRT creates a different effects profile from that of estradiol when given as ERT.[84] Additionally, the use of progestins either in tandem or in sequence with estrogen may cause mood destabilizing effects.[56,85] Fifth, the route of administration may influence outcome, as transdermal estradiol, with the absence of hepatic first pass effects, is not associated with some of the adverse consequences of oral estrogens (e.g., induction of prothrombotic proteins).[86] Sixth, previous depressive episodes and current vasomotor symptoms have been shown to increase a woman's risk of developing depressive symptoms during the menopause transition.[87,88] These important covariates are often not examined or reported.

In conclusion, of the 24 studies meeting criteria for review, only five RCTs examined depressed subjects, and only two of the study samples were solely perimenopausal. One can generalize from the studies reviewed here only with great caution, but there is little evidence to support the use of estradiol to improve mood in non-depressed patients and some evidence to support the antidepressant efficacy of estradiol in perimenopausal but not postmenopausal women.

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TABLE 1.

Randomized, placebo-controlled trials of HRT or ERT on mood in women (1997–2014)

Author	Population	Intervention	Comparator	Outcome measure	Findings	Design
Asymptomatic/minimal symptomatic						
Almeida et al.[47]	86 cognitively normal postmenopausal women age 70+	Oral ERT	Placebo	BDI	No difference between active treatment and placebo groups	Parallel
Bech et al.[50]	105 Danish postmenopausal women within 6 and 24 months of last menses	Oral combined continuous or sequential HRT	Placebo	BDI	BDI scores significantly improved (lowered) in active treatment groups; no change in placebo group scores	Parallel
Demetrio et al.[57]	66 women within 2–10 years of last menses; all without severe hot flushing	Oral ERT	Placebo	BDI, POMS	No difference between active treatment and placebo groups	Parallel
Gambacciani et al.[53]	50 Italian postmenopausal women averaging 4.6 years since menopause	Oral HRT	Calcium supplement	WHQ subscale	Significant improvement in 6 of 9 WHQ subscales in active treatment group; no change in placebo group scores	Parallel
Girdler et al.[56]	54 asymptomatic postmenopausal women without significant psychiatric history	Oral ERT or combined continuous HRT	Placebo	BDI, POMS	No difference between active treatment and placebo groups on either measure	Parallel
Haines et al., 2003[51]	152 hysterectomized postmenopausal Chinese women	Oral ERT	Placebo	HADS, WHO-QOL	No difference between active treatment and placebo groups	Parallel
Hays et al.[61]	16608 postmenopausal women averaging age 63	Oral HRT	Placebo	Burnam scale	No difference between active treatment and placebo groups.	Parallel
Hlatky et al.[60]	2246 postmenopausal women with documented coronary artery disease averaging age 67	Oral HRT	Placebo	Burnam scale	No difference between active treatment and placebo groups	Parallel
Karşidağ et al.[59]	181 Turkish postmenopausal women with severe menopausal symptoms	Oral or trans-dermal HRT	Placebo	HRSD	Significant improvement in HRSD scores in active treatment groups	Parallel
Khoo et al.[66]	83 women presumed to be **perimenopausal** on bases of age and symptoms	Oral HRT	Placebo	ZSRD	No effect of treatment when order of allocation is ignored	Crossover
Nielsen et al.[55]	335 Danish postmenopausal women	HRT or unopposed intranasal ERT (if hysterectomized)	Placebo	WHQ subscale	No difference between active treatment and placebo groups	Parallel
Pearce et al.[52]	40 women naturally postmenopausal or bilaterally oophorectomized	ERT implant	Placebo	HADS	No difference between active treatment and placebo groups	Parallel
Pefanco et al.[49]	57 postmenopausal women averaging age 75.5	Oral HRT or ERT (if hysterectomized)	Placebo	GDS	No difference between active treatment and placebo groups	Parallel
Resnick et al.[65]	1416 WHI participants without probahle dementia averaging age 73.8 at initial assessment	Oral HRT	Placebo	PANAS, GDS	No difference between active treatment and placebo groups.	Parallel

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Author	Population	Intervention	Comparator	Outcome measure	Findings	Design
Resnick et al.[64]	886 hysterectomized WHI participants without probable dementia averaging age 73.8 at initial assessment	Oral ERT	Placebo	PANAS, GDS	No difference between active treatment and placebo groups	Parallel
Schiff et al.[46]	19 cognitively normal postmenopausal women averaging age 71	Transdermal ERT	Placebo	BASDEC	Improvement of scores in active treatment arm	Crossover
Strickler et al.[54]	373 postmenopausal women averaging age 54.7	Oral ERT	Placebo, raloxifene	WHQ subscale	No change in depression subscale observed in any group	Parallel
Welton et al.[62]	2130 postmenopausal women averaging age 62.8	Oral HRT	Placebo	CES-D	No difference between active treatment and placebo groups	Parallel
Yamanchili and Gallagher[48]	412 postmenopausal women averaging age 71	Oral HRT or ERT (if hysterectomized)	Placebo	GDS	No difference between active treatment and placebo groups	Parallel
Depression Joffe et al.[71]	72 peri- and postmenopausal women with depressive disorders, hot flushing, and sleep disorders	Transdermal ERT	Placebo, zolpidem	MÅDRS, BDI	No difference between active treatment and placebo groups	Parallel
Morrison et al.[69]	57 postmenopausal women diagnosed with depressive disorders (major, minor, dysthymia)	Transdermal ERT + 2 weeks MPA	Placebo	CES-D, HRSD	No difference between active treatment and placebo groups	Parallel
Rudolph et al.[70]	71 postmenopausal women with mild to moderate depressive episodes	Oral HRT	Placebo	HRSD	Significant improvement in HRSD scores in active treatment group	Parallel
Schmidt et al.[67]	31 women meeting diagnostic criteria for perimenopause related depression	Transdermal ERT + 1 week MPA	Placebo	CES-D, HRSD	Significant improvement in CES-D and HRSD scores in active treatment group	First phase parallel; Second phase placebo group crossover
Soares et al.[68]	45 perimenopausal women diagnosed with depressive disorders (major, minor, dysthymia)	Transdermal ERT	Placebo	MÅDRS	Significant improvement in MÅDRS scores in active treatment groups	Parallel