Protocol Title: The effects of acute withdrawal of estradiol on mood symptoms in women with perimenopausal depression.
Protocol Number: 03-M-0175
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Total requested accrual
30 Patients
30 Volunteers

Human Research Protections Program Investigator and Staff Training:

“Just in time” human subjects protection training courses are required for investigators and staff participating on this protocol: None

Project Uses Ionizing Radiation: ☒ No ☐ Yes (attach RSC/RDSC documentation)
☐ ☐Medically-indicated only
☐ ☐ Research-related only
☐ ☐ Both

IND/IDE ☑ No ☐ Yes (attach FDA documentation)
Drug/Device/#_____________________
Sponsor_________________________

Durable Power of Attorney ☑ No ☐ Yes
Multi-institutional Project ☑ No ☐ Yes
Institution_________________ FWA #_________
Date of IRB approval__________ (attach IRB documentation)

Data and Safety Monitoring Board ☑ No ☐ Yes
Technology Transfer Agreement ☑ No ☐ Yes
Agreement type and number __________________Expiration Date_____________

Confidential Disclosure Agreement ☑ No ☐ Yes
Samples are being stored ☐ No ☑ Yes
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1. **Precis**

1.1 Perimenopause-related mood disorders cause significant distress to a large number of women (1-4). Recent studies have reported the therapeutic benefits of estradiol in women with these mood disorders (5, 6); however, a relevant pathophysiologic role of declining estradiol secretion during the perimenopause has not been demonstrated. In this protocol we wish to investigate the effects of acute withdrawal of estradiol on mood under placebo controlled conditions. Thus, mood and behavior symptoms may be precipitated by the experimental conditions of this protocol. This protocol will address the following hypothesis: women with a past history of perimenopause-related depression but not women without such a history will experience a recurrence of mood and behavioral symptoms during acute estradiol withdrawal but not during continued estradiol administration. The nature of the relationship between the declining secretion of estradiol and mood in perimenopausal depressed women will be examined as follows: Peri- and postmenopausal women reporting the onset of depression during the perimenopause and who report remission of depressive symptoms on estrogen therapy (ET) will be withdrawn from ET under blinded and placebo-controlled conditions. We will recruit as a comparison group asymptomatic women on hormone replacement and without a history of perimenopause-related depression. During a three week baseline phase, all women will be switched from their current form of hormone replacement therapy to estradiol and will complete symptom ratings to confirm the absence of mood symptoms prior to entry into the study. After the screening, all women will be randomized to receive either estradiol or placebo for an additional three weeks. Comparison of mood ratings during these contrasting treatment conditions will allow us
to examine the specific role of estrogen withdrawal in depression that is responsive to ET.

2. Purpose of Project and Scientific Justification

2.1 Objectives:

To determine whether the acute withdrawal of ET under double-blind, placebo-controlled conditions is associated with a recurrence of depressive symptoms in women who have previously experienced a perimenopause-related depression responsive to ET.

2.2 Background:

In a previous trial we demonstrated the antidepressant efficacy of ET in women with depression during the perimenopause under double-blind, placebo-controlled conditions (5). Our findings demonstrated that therapeutic response to estradiol was not associated with the level or magnitude of the increase in plasma estradiol levels nor with abnormally low levels of estradiol at baseline. Additionally, our basal hormone study in women with perimenopause-related depression showed that, with the exception of DHEA, depressed women were not distinguished from non-depressed perimenopausal women on the basis of abnormal basal plasma levels of ovarian estrogens or androgens (7). Thus, the efficacy of ET in this condition cannot be explained solely by the correction of a simple hormone deficiency state. Several mechanisms may underlie estradiol’s antidepressant effects: first, epidemiologic studies suggest that the perimenopause is more accurately characterized by estradiol hypersecretion followed by withdrawal to states of hypoestrogenism (8, 9). Thus it may be either the magnitude of the change (from high to low levels of estradiol secretion) or the rate of change in estradiol secretion that triggers the onset of depression in these women. Second, studies
of the effects of ET in osteoporosis suggest the presence of a threshold of circulating estradiol above which therapeutic effects are observed (10), and it is possible that a similar phenomenon (i.e., critical threshold) is operational in estrogen’s effects on mood. Thus, estradiol’s salutary effect on mood could be due to the maintenance of estradiol levels above a critical threshold below which mood symptoms occur. Third, the effects of estradiol withdrawal or replacement on mood in these women may reflect a differential sensitivity to estradiol withdrawal. Finally, it is possible that a direct psychotropic effect of estradiol independent of any presumed causal role of alterations in the levels of estradiol may be involved in the development of depression.

This protocol will examine two questions related to the mechanism of action of ET as well as the possible hormonal trigger of perimenopause-related depression. First, in women with a history of perimenopausal depression, will estrogen withdrawal (placebo replacement) produce symptoms of depression? Second, will women with a history of perimenopausal depression respond differentially to estrogen withdrawal compared with controls with no history of perimenopausal depression? Mood symptoms developing in women with a past history of perimenopause-related depression receiving placebo but not in those receiving estrogen would suggest that estradiol deficiency or withdrawal is a critical event for the development of mood symptoms in this group of women. Differing patterns of symptom response to estradiol withdrawal in women with and without a past history of perimenopause-related depression would suggest that only in a subgroup of women is perimenopause-related estrogen withdrawal a relevant trigger. Several recent studies have documented the development of mood and behavioral symptoms in some, but not all, women after discontinuing their use of hormone therapy (11-15); however,
predictors of those women who are at risk for these withdrawal-like symptoms are not known. Thus a past perimenopausal-related depression also might predict those women in whom dysphoric mood symptoms will develop when use of hormone therapy is discontinued. A failure to observe mood symptoms during withdrawal in the women with a past history of perimenopause-related depression may suggest the following. First, for estradiol withdrawal to trigger the onset of mood and behavioral symptoms it may be necessary for the magnitude or rate of the withdrawal to approximate that experienced during the perimenopause. The dose of estradiol employed in this study (100 micrograms/day) may not provide sufficiently high plasma levels of estradiol compared to those in the perimenopause (e.g., 80-100 pg/ml versus 300-500 pg/ml) (8, 9). If data in this study suggest the predictive value of the rate of estradiol withdrawal, we will design a subsequent study to determine the importance of this kinetic variable (15). Second, failure to observe mood and behavioral symptoms during estradiol withdrawal could suggest that the duration of time between estrogen withdrawal and the development of mood symptoms may be longer than that occurring in this study design (i.e., three weeks, determined by our prior experience with a three week latency to therapeutic response in estradiol’s efficacy in perimenopausal depression). Despite this possibility, past observations from protocol # 98-M-0079 (“The Phenomenology and Biophysicsology of Progestin Induced Dysphoria”) suggested that adverse mood symptoms are seen within several days of abrupt discontinuation of ET. Third, the failure to observe mood and behavioral symptoms during estrogen withdrawal could reflect the importance of the timing of the hormone trigger with respect to the women’s current reproductive status, and, therefore, studying women after the perimenopause may miss a
“critical developmental window” during which changes in estradiol levels impact on mood and behavior. This latter possibility is suggested by the differing efficacy of ET in perimenopausal compared to postmenopausal depressed women (5, 6, 16-18). We will examine this possible relationship between duration of amenorrhea and a differential onset of mood symptoms occurring in this study. Fourth, the subjects in this study are women with a self-defined onset of depression during the perimenopause. This reliance on a self-reported past relationship may result in the selection of subjects without the disorder of interest, thereby dramatically decreasing the power of the study. Finally, it is possible that women who experience hot flushes during estrogen withdrawal will confound our interpretation of the effects of estrogen due to an inadequate maintenance of the double-blind condition. The literature and our clinical experience suggest that in contrast to the onset of hot flushes, which take two to three weeks to improve after estrogen replacement and may emerge weeks after estrogen deprivation (19, 20), mood symptoms may be observed within a few days after estrogen withdrawal. For example, during the screening phase of protocol # 98-M-0079, “The Phenomenology and Biophysiology of Progestin Induced Dysphoria,” we observed mood symptoms develop within 1-2 days after ET was temporarily stopped in several women. Additionally, a recent clinical trial comparing the efficacies of estradiol and zolpidem with placebo in peri- and postmenopausal women demonstrated (albeit indirectly) that improvement in hot flushes does not predict antidepressant efficacy (21). However, in order to monitor this potential confound we will ask each subject whether they believe they received estrogen or placebo.
This study will not only enhance our understanding of the effects of perimenopausal hormonal changes and ET on the course of depression during the perimenopause, but it also may serve as an important source of information to women who are struggling with the decision over the necessity for hormone therapy. For example, if women associate hormone replacement with antidepressant efficacy, they may feel unable to discontinue treatment should other factors warrant it. Additionally, this study will answer the question about the need for maintenance ET in the treatment of perimenopausal depression, similar to that investigated for antidepressant therapy of depressions occurring at other times in a person’s life. Finally, the clear identification of a subgroup with E2 withdrawal-precipitated depression would furnish a clinical phenotype necessary to answer questions about differential treatment response characteristics in women with perimenopausal depression. For example, it would be of interest to see if women who experienced mood symptoms associated with estrogen withdrawal also experienced an antidepressant response to SSRIs, an observation that may have important public health implications.

3. **Medication Administered in this Protocol**

3.1 Estradiol

The administration of 17ß-estradiol via a transdermal system was chosen for this study because it has several relevant advantages over oral preparations (22, 23). First, it delivers the primary ovarian estrogen, estradiol, into the circulation at a constant rate and results in sustained and easily measurable plasma levels of estradiol and in estrone/estradiol ratios less than one (as seen in the pre-climacteric period of life) (24). Second, it delivers sufficient estradiol into the circulation to raise estradiol plasma
concentrations to levels similar to those of women in the early follicular to mid-follicular phases of the menstrual cycle (22, 25-27), levels reported by some investigators as the minimum necessary for the relief of menopausal symptoms, particularly hot flushes (25), without increasing synthesis of renin substrate. An increase in renin substrate has been suggested to accentuate or initiate the development of high blood pressure in susceptible women with other predisposing factors (28) and has been implicated as a factor in the association of hypertension with the administration of oral conjugated estrogen (29). In our experience with the transdermal estradiol patch in over 100 women in several protocols, it has been well tolerated and, with the exception of an occasional skin rash, we have observed no adverse effects. With the application of the estrogen patch every three days, patient compliance has been reported to be excellent, and only occasional local irritation has been observed (25).

3.2 Provera

Provera and synthetic progestins are widely prescribed, with indications including dysfunctional uterine bleeding, endometriosis, mastodynia, galactorrhea, and precocious puberty (30). Provera is widely prescribed to induce menses and shedding of the endometrial lining in women receiving ET. In our experience and that of others (31), a daily dose of 5 mg for seven days is sufficient to successfully induce menses in women receiving 3-8 weeks of ET.

4. Criteria for Patient Selection

4.1 Selection criteria:

Subjects for this study will meet the following inclusion criteria:
Women with past perimenopausal depression -

1) Women with a past perimenopause-related depression (within 12 years) and whose depression responded to ET will be recruited to participate in this randomized, parallel-design, double-blind, placebo-controlled study. Women with histories of either perimenopausal depression that was not responsive to ET or hormone replacement therapy-induced dysphoria due to either the estrogen or the progesterone components of their hormone replacement will be excluded. The diagnosis of perimenopause-related depression will be based on a history of a past depressive episode (major or minor depression confirmed by Structured Clinical Interview for DSM-IV (SCID) or Schedule of Affective Disorders and Schizophrenia-Lifetime Version (SADS-L), respectively) at midlife in association with menstrual cycle irregularity and the history of remission (also confirmed by SCID or SADS-L) of this depression after ET. Additionally, all women will report that they were placed on HRT for the treatment of perimenopausal symptoms, including depression.

2) Age 45 to 65;

3) In good medical health.

Women without past perimenopausal depression -

To control for the effects of the hormonal manipulations in this protocol, we will also recruit a group of asymptomatic controls who are either currently on ET or were prescribed ET previously and with no previous history of perimenopause-related depression or HRT-induced dysphoria. Women who participate in this study as the asymptomatic comparison group will meet the following criteria:
1) Women who received hormone therapy (HT) with no previous history of perimenopause-related depression or HT-induced dysphoria;

2) No current mood or behavioral problems;

3) Age 45 to 65;

4) In good medical health.

4.2 Exclusion criteria:

The following conditions will constitute contraindications to participate in this protocol:

1) past history of severe major depression with suicidal ideation

2) current treatment with antidepressant medications

3) history of ischemic cardiac disease, pulmonary embolism, or thrombophlebitis

4) renal disease

5) hepatic dysfunction

6) women with a history of carcinoma of the breast

7) women with a history of uterine cancer, ill-defined pelvic lesions, particularly undiagnosed ovarian enlargement, undiagnosed vaginal bleeding

8) pregnant women

9) cerebrovascular disease (stroke)

10) recurrent migraine headaches
5. **Nature of Procedure and Design**

5.1 **Recruitment and Screening**

All subjects for this protocol will be either self-referred in response to newspaper advertisements or referred by their personal physician. The women participating in this protocol will have previously completed the screening protocol # 88-M-0131 and, therefore, will have had the presence or absence of perimenopausal or menopausal reproductive status evaluated and documented. Perimenopausal reproductive status will be defined by a history of at least six months of menstrual cycle irregularity and biological evidence of ovarian dysfunction, specifically three of four plasma FSH values > 14 IU/L on consecutive occasions drawn at two week intervals over a period of eight weeks (total of four blood samples).

During the initial screening period, a complete history, physical examination, and EKG will be performed on all subjects, and the following lab data will be obtained:

A. Blood - complete blood count; electrolytes; glucose, BUN and creatinine; liver function tests; thyroid function tests, prolactin, and lipid profile.

B. Urine - urinalysis; plasma βHCG pregnancy test.

Any subject with significant physical, EKG, or laboratory abnormalities, or who meets any of the exclusion criteria (listed below) will not participate in this protocol. Additionally, prior to participation all subjects will be examined for any contraindications to ET. Women will be examined by a gynecologist of their choice.

5.2 **Study Design, Outcome Measures, and Procedures:**

During a three week baseline phase, all women will receive estradiol (100 micrograms/day) by skin patch and will complete mood and behavioral symptom
ratings to confirm the absence of mood symptoms prior to entry into the study. After the
three week baseline period and the determination that ET does not precipitate symptoms,
women will be randomized to receive either estradiol skin patches or placebo skin
patches for three weeks. All women will receive one week of Provera (5 mg/day) at the
end of the trial to induce a progestin withdrawal bleed. After the seven week trial, those
women who were taking ET prior to the study will be re-started on their previous HT
regimen unless they request to be withdrawn from HT under medical supervision.
Outcome measures will include standardized mood and behavioral rating scales. The
main comparisons in this study will be between estradiol and placebo replacement in
women with a past history of perimenopause-related depression (i.e., the withdrawal
group) and between women with and without a past history of depression during the
estrogen withdrawal (placebo) phase. Results will be analyzed by analysis of variance
with repeated measures and post-hoc testing.

During the seven week study, the effects of estradiol or placebo on mood will be
monitored with daily symptom rating scales and weekly clinic visits every week.
Outcome measures will include the following: (1) self ratings: daily symptom ratings
consisting of an eight item visual analogue scale (VAS) and a 14 item six point likert-
type scale (32) measuring the severity of several mood and behavior symptoms including
hot flushes, the Beck Depression Inventory (BDI) (33), the Center for Epidemiologic
Studies-Depression Scale (CES-D) (34), and a visual analogue scale (VAS) measuring
the reported severity of 23 mood and behavioral symptoms; and (2) observer ratings: the
21-item Hamilton Depression Rating Scale (HDRS) (35). During these visits subjects
will also have blood pressure, pulse, and weight measured and will be assessed for any
side effects to the prescribed medications. In addition, blood samples will be drawn via venipuncture at each clinic visit; approximately 50 ml of blood will be collected at each draw (total = 350 ml). This blood will be analyzed for several measures such as the following: estradiol, testosterone, dihydrotestosterone, SHBG, CBC, renal, hepatic, thyroid and lipid functions. Blood samples for estradiol will be processed within 24 hours in the NIH Clinical Center Pathology Service and sent to a staff member not involved with patient care in order to monitor compliance with estradiol therapy.

In light of the recent Women’s Health Initiative findings, we realize that some of the women who enter our protocol, will view their participation in the protocol as an opportunity to discontinue their HRT under medical supervision. As half of the subjects in the protocol will not be withdrawn during the protocol, we will offer these subjects the opportunity to be followed with ratings by us during a voluntary, unblinded withdrawal of HRT. This will enable us to acquire experience with the consequences of HRT in the natural setting and would provide the subjects with access to information and medical supervision during their withdrawal.

5.3 End of Participation:

After the completion of this trial, all participants will be evaluated for the presence of clinically significant mood symptoms. Additionally, the results (including symptom ratings and plasma hormone levels) of the study will be reviewed with each participant. If negative mood symptoms or distressing hot flushes are present we will discuss therapeutic options prior to referral of each participant back to her community health care provider. The options include no treatment with follow-up by community health care provider, initiation of standard antidepressant therapy such as selective serotonin uptake
inhibitors with follow-up in community, or resumption of previous menopausal hormone therapy by her community health care provider.

6. **Statistical Analysis**

   Based on the results of protocol # 90-M-0088 and with a standardized difference of .7 (consistent with a recent meta-analysis of estrogen’s effects on depressed mood) (36), 15 patients and 15 controls (depending on the method of power calculation) will be required in each treatment cell to achieve a power of 80% with an $\alpha = 0.05$ to detect a significant estradiol and placebo difference with analyses of variance with repeated measures and Bonferroni t-tests in the principal outcome measures of HAM-D and CES-D scales.

7. **Risks and Discomforts**

   7.1 **Estradiol Replacement**

   Nausea is the most common side effect of estrogen administration. At conventional replacement doses, higher than those employed in this protocol, this complaint seldom interferes with eating, and no weight loss has been reported. Breast engorgement, endometrial hyperplasia and bleeding are also common side effects of estrogen administration. Pre-existing fibroid tumors of the uterus may enlarge under the effects of estrogen; however, at the dosage and for the duration of estrogen administration in this protocol this risk is small.

   The relationship between estrogen, both endogenous and exogenous, and the development of endometrial carcinoma has been suggested by several different lines of investigation (37). Numerous retrospective case control studies published since 1975 have indicated that post menopausal exposure to unopposed estrogens for more than one
year results in a two to 12 fold increased relative risk for endometrial cancer. A relationship between the dose and duration of estrogen use and the risk for endometrial cancer has also been shown, the risk being increased after one to four years of estrogen use and rising also with the dosage employed. However, the addition of progesterone to estrogen therapy appears to decrease the risk of endometrial hyperplasia and endometrial cancer to equal or below that of women receiving no hormonal treatment. Recent studies suggest that the optimal regimen to prevent hyperplasia and thus, inferentially, the risk of carcinoma, consists of 12 to 13 days of progestin treatment each month when estrogens are administered (38). There is an increase in thromboembolism and stroke in women receiving estrogen therapy (39-45); however, this complication is unlikely at the dose and duration of estrogen therapy employed in this protocol and in the younger age of the women participating in this trial (46). One study (25) reported no effect of the estrogen patch on the four clotting indices previously shown to be altered by oral contraceptive use (38, 47, 48). Additionally, a recent case-control studies (49, 50) observed that an increased risk of venous thromboembolism was associated with oral but not transdermal estrogen compared with nonusers (odds ratios = .42 [95% CI, 1.5 to 11.6] and 0.9 [95% CI, 0.4 to 2.1] respectively). Blood pressure, on average, appears to be unaffected by estrogen replacement therapy, although both increases and decreases have been reported. Post menopausal estrogen therapy has been observed to increase the relative risk of cardiovascular disease in some (43, 51, 52) but not all studies (53-55). Indeed recent analyses of the Women’s Health Initiative demonstrate that the adverse effects of estrogen therapy on cardiovascular outcomes were largely confined to older women compared with younger perimenopausal women (56-64). High doses of oral estrogens
have been reported to elevate hepatocellular enzyme levels and, less commonly, cause cholestatic jaundice. The risk for gall stones and hepatocellular adenomas has been reported to be increased in association with oral contraceptive use, and although uncommon these complications may also occur with the use of replacement doses of estrogen (65-67). Further, most studies have suggested an increased relative risk of breast cancer after four or five years’ use (56, 68-80), similar to the risk expected if the onset of menopause was delayed for a comparable length of time.

Estrogens may precipitate migraine headaches, and depression has also been reported to occur with the use of estrogens. In general, considering the dose and duration of treatment that we propose to use in this protocol, the risk of developing such side effects is negligible.

Due to the publicity surrounding the cancellation of the treatment arm of the Women’s Health Initiative study (81, 82) that involved the administration of combined conjugated estrogens and medroxyprogesterone acetate (Prempro), we have included the following statement in the consent documents:

**Adverse Events Related to Combined Hormone Replacement and the Results of the Women’s Health Initiative (WHI):**

The WHI study demonstrated that continuous administration of one form of estrogen (conjugated estrogens) in combination with one form of progesterone (medroxyprogesterone acetate) is associated with an increased risk of dementia, heart attacks, stroke, blood clots, and breast cancer. Estradiol, the form of estrogen that we use in this study, is administered for a short time (three to six weeks) and as a sole agent (followed by one week’s administration of medroxyprogesterone acetate) and,
consequently, should not pose the increased risks observed with the chronic combination of the conjugated estrogens and medroxyprogesterone administered in the WHI study.

Estrogens may precipitate migraine headaches, and depression has also been reported to occur with the use of estrogens. In general, considering the dose and duration of treatment that we propose to use in this protocol, the risk of developing such side effects is very small. Also, we have excluded any subjects with a history of mood worsening in association with ET.

Menstrual bleeding, hot flushes, vaginal dryness, and changes in mood may occur after estradiol withdrawal; otherwise there are no known medical risks associated with estradiol withdrawal.

7.2 Progesterone and Synthetic Progestins

Side effects reported in women taking progestins are uncommon but may include breakthrough bleeding, edema, change in weight (increase or decrease), cholestatic jaundice, rash (with or without pruritus), depression of mood, easy fatigue, lack of initiative, and chloasma. Since progestins are often used in women with antecedent menstrual irregularity, it is not clear whether the breakthrough bleeding represents an effect of the medication or refractoriness to treatment. In the large majority of patients, menstruation occurs predictably following withdrawal of progestins. Finally, one investigation observed no differences in reports of physical or emotional symptoms between medroxyprogesterone acetate and placebo when they were added to ET under double blind crossover conditions (83). Similarly, in protocol # 90-M-0088 we did not observe significant mood changes during the addition of Provera to ET (5).
Side effects observed in patients receiving combined oral contraceptives include nausea, breast soreness, vaginal discharge, fluid retention, hypertension, and clotting abnormalities, which have been associated with the estrogen component of the oral contraceptive. Thromboembolic disorders including thrombophlebitis, pulmonary embolism, and cerebral and coronary thrombosis appear to occur with greater frequency in women taking oral contraceptives. While the increased incidence of these disorders has been associated with the estrogen component of the oral contraceptives, it is now believed that the progestin component may, to a lesser extent, contribute to the increased risk. There are relatively few reports associating oral contraceptives with the development of carcinomas (vaginal, uterine, hepatic, and mammary) despite the vast use of these agents, although this may reflect the latent period needed for cellular transformation. Finally, several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies.

7.3 Symptom Provocation

Some women may experience a recurrence of their previous depressive symptoms during the estradiol withdrawal phase. These symptoms are likely to be similar in severity to those experienced prior to study entry. However, if symptoms are intolerable we will discontinue their participation in the study.

7.4 Blood Drawing

Total research blood withdrawal during this six week study is 450 cc and falls within NIH guidelines (450 ml. per six week period). Fifty cc’s of research blood will be drawn at each of seven clinic visits in this protocol (total = 350 cc). One potential discomfort of this study may result from the venipuncture and multiple blood sampling.
8. **Subject Safety Monitoring**

Subjects are evaluated by one of the Associate Investigators. After completing the study, subjects will either be discharged from this protocol with a referral to the community, or will be referred to other NIMH studies.

Patients will be warned not to become pregnant during the study and will be advised to employ barrier contraceptive methods.

9. **Consent Documentation and Process**

Each patient will receive a verbal and written explanation of the purpose, procedure, and potential hazards of this project. A record of the communication of this information and of the consent to participate in this study will be placed in the medical record. The right of the subjects to withdraw from the study or to refuse any procedure will be made clear. Any patient whose symptoms become excessive during this study will be offered another medication without completing the six week trial. Confidentiality of patients will be assured according to the laws of the State of Maryland. In case of published data resulting from the study, care will be taken to protect the anonymity of patients.

10. **Human Subjects Protection**

Subject selection:

Subjects are evaluated by one of the associate investigators. Medical history and physical assessments occur at each clinic visit including interviews, symptom assessments, vital signs, and laboratory testing when clinically indicated. After completing the study, subjects will either be discharged from this protocol with a referral to the community, or will be referred to other NIMH studies.
All subjects must meet the inclusion and exclusion criteria listed in Section 4. We will select physically healthy adult female individuals. The proportion of ethnic minorities (vs. Caucasians) in the total sample, will be approximately consistent with the overall U.S. population proportions.

Justification for inclusion/exclusion of children:

We will exclude children or minors because the study population is women with past perimenopausal depression.

Qualifications of investigators:

Peter J. Schmidt, M.D., is an investigator with the Section on Behavioral Endocrinology, NIMH. He has over 20 years experience performing studies that examine the effects of reproductive hormones on mood and behavior in women with reproductive endocrine-related mood disorders. He will be allowed to obtain consent.

David R. Rubinow, M.D., is a special volunteer and collaborator within the Section on Behavioral Endocrinology, NIMH. He has over 30 years experience in reproductive endocrinology and psychiatry. He will not be involved in obtaining consent.

Lynnette K. Nieman, M.D., is a senior investigator in the Reproductive Biology and Medicine Branch, NICHD and has extensive experience with clinical research studies in endocrinology and reproductive biology. She will not be involved in obtaining consent.

Pedro E. Martinez, M.D., is a staff clinician within the Section on Behavioral Endocrinology, NIMH and has performed endocrine studies examining the effects of aging and reproductive hormones on mood and behavior in both adults and children. He will be allowed to obtain consent.
Rivi Ben Dor, M.D., is a clinical staff fellow within the Section on Behavioral Endocrinology, NIMH. She is trained in both family medicine and pediatrics. She will be allowed to obtain consent.

The Principal Investigator has verified that all individuals working on this protocol required to take HRPP training under OHSRP SOP 25 (Training requirements for the NIH Human Research Protections Program) have completed all required training.”

Qualifications of telephone interviewers:

Screenings are performed by Merry Danaceau, a registered nurse, who retired from the Clinical Center, after over a decade of employment in our group. She performs approximately 85% of the screening calls in person. The remaining 15% are performed by Annie Shellswick, who is a licensed social worker in our group, and who is in charge of our recruitment and outreach activities. Personally identifiable information is not obtained in callers who are determined to be ineligible, and the screening forms are not retained in the research records.

11. **Anticipated Benefits**

   There are no direct benefits of participating in this study. Nevertheless, the information obtained may help study subjects make decisions about the need for hormone therapy.

12. **Alternatives to Participation**

   Subjects either do not receive any treatment in this study or forego treatment in order to participate in this study. The alternative, therefore, is not to participate.

13. **Data and Safety Monitoring**

   The PI will serve as the data and safety monitoring official. As we are
administering doses of estradiol designed to produce physiologic levels, we expect - and have seen - no unexpected adverse events. However, there may be adverse events that are not anticipated with the dose of estradiol that we propose to use. Nonetheless, we see subjects every two weeks during their clinic visit and advise them in the consent form that if they experience side effects, they should notify the investigator immediately. Any adverse events will be reported as per NIH policy.

14. **Quality Assurance:**

   A. Quality assurance monitor

   In addition to the routine monitoring by the PI and research team this protocol will be included in the NIMH Intramural QA/QI monitoring program, coordinated by the Office of the Clinical Director, NIMH.

   B. Quality assurance plan

   The NIMH Office of the Clinical Director has established a system for oversight and monitoring of the conduct of clinical trials and other intramural clinical research consistent with the NIH Intramural Research Program Standards of Clinical Research. The QA/QI program was created to ensure the safety of participants and protect the integrity and validity of data for NIMH intramural research. The objective of the program is to monitor and improve human research protection effectiveness, quality and compliance with organizational policies and applicable federal, state and local laws, and to ensure the reliability of study data. Auditing activities include investigator self-assessment, IND start-up audits, GCP monitoring, and routine and for-cause audits in addition to the protections provided by the Human Subjects Protection Unit.

15. **Reporting of Unanticipated problems, adverse events and protocol deviations**
The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the CD.

Serious unanticipated problems and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing not more than 7 days after the PI first learns of the event. Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing not more than 14 days after the PI first learns of the event.

Deaths will be reported to the Clinical Director within 7 days after the PI first learns of the event.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

16. **Overall Risk Assessment for Study**

   The overall risks for this study are more than minimal.

   There are low risks to individual subjects in the use of medication and procedures under the conditions stated in this protocol. Patients stand to gain effective and scientifically validated pharmacologic treatment of a condition that is frequently associated with pronounced debilitation.

17. **Conflict of Interest**
NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts-of-interest to report. Non-NIH investigators will abide by the conflict-of-interest policies of their own Institutions.

18. **Storage of Data and Human Tissue Samples**

Samples and data will be stored using codes that we assign. Data will be kept in password-protected computers. Samples will be kept in locked storage. Only study investigators will have access to the samples and data.

19. **Reimbursement and Travel Compensation**

Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

Each volunteer will be compensated according to the following schedule:

<table>
<thead>
<tr>
<th>Description</th>
<th>Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial evaluation, physical exam (2 hours)</td>
<td>30.00</td>
</tr>
<tr>
<td>Screening phase</td>
<td>30.00</td>
</tr>
<tr>
<td>Clinic visits (weekly) X 8</td>
<td>160.00</td>
</tr>
<tr>
<td>Venipuncture X 8</td>
<td>160.00</td>
</tr>
<tr>
<td>Psychological testing X 8</td>
<td>80.00</td>
</tr>
<tr>
<td>Investigational drugs:</td>
<td></td>
</tr>
<tr>
<td>Estradiol Patch X 2</td>
<td>60.00</td>
</tr>
<tr>
<td>Provera</td>
<td><strong>30.00</strong></td>
</tr>
<tr>
<td></td>
<td><strong>550.00</strong></td>
</tr>
</tbody>
</table>

Compensation will be prorated for parts completed if subjects do not complete the study.

No escort fee will be provided.
Flow Sheet

Protocol Schematic

+PMD

ASC

Baseline W0 W3 W6 W7

+PMD = Women with a past history of perimenopause-related depression responsive to Estrogen

ASC = Asymptomatic controls

- Estradiol 100 μg/day (skin patch)
- Placebo (skin patch)
- Provera 5 mg daily (PO)
20. **References**


22. Appendix A

Adverse Experiences/Concurrent Illnesses

Any event of an adverse nature that is reported or observed to occur during the study after initiation of treatment, whether or not believed to be related to the use of the test article will be documented in the patient record and on the Adverse Event Case Report Form.

Definition of Terms

An adverse event includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic function as indicated by physical signs, symptoms, and/or clinically significant changes in laboratory parameters occurring after administration of the test article. This includes any exacerbation of pre-existing conditions, intercurrent illnesses, drug interactions, or significant worsening of the disease or condition under study that is not documented elsewhere in the protocol or medical literature.

Exacerbation of pre-existing conditions means any condition or disease state that was present prior to first treatment with test article that changes adversely in nature, severity, or frequency during the study.

A serious adverse event is one that suggests a significant hazard, contraindication, or side effect. Such events include those that are fatal or immediately life threatening, permanently disabling, require or prolong hospitalization, are associated with congenital anomaly, cancer, overdose, or which require intervention to prevent serious consequences or disability to the patient.
Life threatening means the subject is at immediate risk of death as a result of the event as it occurred. It does not mean that a reaction, had it occurred in a more serious form, might have caused death.

Eliciting Reports of Adverse Events

In addition to documenting observed changes in a subject’s medical or physical condition, information regarding the occurrence of adverse events during the study will be solicited through non-directed questioning of the subject by the investigator at each clinic visit. Subjects will also be asked if they have been hospitalized for any reason, had any accidents, used any new medications, or changed dose or regimen of any concomitant medication (prescription or over-the-counter), and the reasons for such.

Reporting Adverse Events

All adverse events reported or observed during the study will be documented in patient records and on the Adverse Event Case Report Form. Severity, date of onset, and date of resolution will be recorded as well as any required treatment or drug therapy on the medical record. Discontinuation or adjustment of dosage of the medicines required for the management of the adverse event will also be documented. A determination will be made by the investigator as to the causal relationship of the event to treatment with the test article.

Assessment of Causality

The relationship or association of the test article in causing or contributing to the adverse event will be characterized using the following classification and criteria:
**Unrelated:** there is no causal association between the treatment with test article and the reported event. The event can be explained by causes other than by treatment with the test article.

**Possible:** there is a rational basis for belief that treatment with the test article caused or contributed to the adverse event, i.e., the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the test article, but could also have been produced by other factors.

**Probable:** this relationship suggest that, based on the temporal sequence of the event relative to administration of test article, known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or in clinical experience, a causal association of the vent with the test article seems likely, but other causes cannot be ruled out.

**Related:** a definite causal relationship exists between treatment with the test article and the adverse event based on the temporal sequence of the event relative to administration of test article, known pharmacological action of the drug, known or previously reported adverse reactions to the product, or judgment based on clinical experience that cannot be reasonably explained by other causes. One or more of the following may be confirmatory:

- occurs immediately following administration of the test article
- improves on stopping treatment with the test article
- reappears on repeat exposure
- there is a positive reaction at the application site
Assessment of Severity

The severity or intensity of the adverse event will be rated as mild, moderate, or severe using the following guidelines:

Mild: an event that is noticeable by the subject or the observer, but causes minimal discomfort or concern, may require minimal or no treatment, and does not usually interfere with the subject’s daily activities.

Moderate: the event may result in a low level of discomfort, inconvenience, or concern for the subject, may interfere somewhat with normal functioning or daily activities, and may be ameliorated by simple therapeutic measures.

Severe: the event may cause significant discomfort or incapacitation, and may require prescription drug therapy, or other treatment or intervention.

Reporting Serious Adverse Events

A Serious Adverse Event Report Form will be completed for each serious adverse event as defined above, in addition to being reported on the medical record.

Any serious, unexpected adverse event associated with the use of the test article will be reported to the FDA according to the Code of Federal Regulations (CRF ‘312.32).

All adverse events will be followed clinically, or with appropriate laboratory studies until the event has resolved, stabilized, or returned to baseline status.