

CONSENT TO PARTICIPATE IN RESEARCH

<p>Effect of estrogen augmentation in menopausal depression on mood, quality of life and brain activity.</p>

You are asked to participate in a research study conducted by Melinda Morgan, Ph.D., Andrew Leuchter, M.D. and Ian Cook, M.D. in the Department of Adult Psychiatry in the Neuropsychiatric Institute and Hospital; Andrea Rapkin, M.D. from the Department of Obstetrics and Gynecology; and Clay Van Batenburg, MSW in the Department of Social Welfare, UCLA. This study is sponsored through a grant of the National Association of Research on Schizophrenia and Depression. You are asked to participate in this study because you suffer from depression and have had a partial response to antidepressant medication. Additionally, you are female, aged 40-60 and are experiencing perimenopause or menopause. Before enrolling in this study, you have told the physician and mental health clinician that you do not want to harm yourself or end your life, and that you have no plans to do so.

Your participation in this study is entirely voluntary. You are free to discontinue participation or withdraw at any time.

Forty perimenopausal and menopausal women will be studied. The duration of your participation will be 14 weeks. You should read the information below and ask questions about anything you do not understand before deciding whether to participate.

DISCLOSURE STATEMENT

Your health care provider may be an investigator of this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your physician.

PURPOSE OF THE STUDY

Menopause is a significant event for women as they enter their 40's and 50's. Prior to the onset of menopause (known as perimenopause) and during menopause, women often notice that many biological, psychological and social changes occur. In particular, some women experience depressive symptoms during perimenopause and menopause that are severe enough to warrant antidepressant medication. It is believed that many of these symptoms may be the result of decreased levels of a specific hormone called estrogen. Researchers have been successful in linking the negative effects of estrogen deficiency (i.e., a lack of estrogen in the body) to the skeletal and cardiovascular system. However, less information is available about how declining levels of estrogen influence brain function.

Although some women respond fully to medication, others only partially respond, and continue to experience depressive symptoms that negatively impact their quality of life.

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Expiration Date: October 31, 2003

We would like to investigate whether estrogen will help these women who only partially respond to antidepressant medications. Specifically, we will examine the effects of estrogen on mood, quality of life and brain activity.

PROCEDURES

If you volunteer to participate in this study and sign the consent form, we would ask you to do the following things:

Visit 1: (*week 0*) For perimenopausal women, on day three of your menstrual cycle, you will meet with one of the investigators and review your menstrual, physical and psychiatric history. (For menopausal women, at a convenient time, you will meet with one of the investigators to review your menstrual, physical and psychiatric history.) A blood sample will be taken at this time to evaluate your hormonal status. The blood will be taken from a vein in the forearm and consist of approximately 4 teaspoonfuls. Your blood hormone levels and pregnancy status will be evaluated in the lab. If the results of the lab test confirm that you are not pregnant, you will be notified by telephone and the second visit will be scheduled. Throughout the study you will continue taking the antidepressant medication as prescribed by your psychiatrist or primary treating physician. Your personal physician will continue to oversee your antidepressant medication management. Your personal physician must be advised of, and approve of, your participation in the study prior to the initiation of the study procedures; therefore you agree to let the investigators contact your treating physician to gain approval of your participation in the study. This visit will last approximately 2 hours.

Visit 2: (*week 1*) At this visit, you will be randomized to either estrogen or placebo. When given estrogen, the dose will be .625 mg. You will be given a two-week supply of the study medication. You will be on estrogen for 6 out of the 14 weeks of the study and on placebo for 8 weeks. Neither the investigators, staff, nor you will know which weeks you will be taking the estrogen. You will talk with one of the study investigators about your symptoms (such as your mood, energy level and your ability to perform daily activities). This visit will last approximately 2 hours.

At this time an electroencephalogram (QEEG) will be performed. Electrodes will be pasted to your scalp or suspended by a net of elastic threads wrapped over the head's surface. Once the electrodes are in place, the QEEG recording will take approximately 20 minutes.

You will also take the California Computerized Assessment Package (CALCAP). This is a test that you will take on the computer. The CALCAP lasts approximately 20 minutes during which time you will be asked to rapidly press the computer keyboard space bar when specified pictures appear on the computer screen.

You will also be given the Menopausal Quality of Life Questionnaire to complete on a daily basis. The questionnaire takes 7 minutes on average to complete (with a range of 5-15 minutes). You will return the completed questionnaire at each visit and will be given a new one for the subsequent two-week visit.

Visit 3 (*week 3*): One of the study investigators will talk with you about your mood, energy level and ability to perform daily activities. You will be given a two-week supply of study medication. This visit will last approximately 20 minutes.

Visit 4 (*week 5*): Same as week 3. This visit will last approximately 20 minutes.

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Visit 5 (week 7): A second QEEG, CALCAP and blood draw of approximately 2 teaspoonfuls will be conducted at this time. Blood hormone levels and pregnancy status will be evaluated in the lab. You will also speak with a study investigator regarding mood, energy level and ability to perform daily activities. You will be given a two-week supply of medication. This visit will last approximately 2 hours.

Visit 6 (week 9): One of the study investigators will talk with you about your mood, energy level and ability to perform daily activities. This visit will last approximately 20 minutes.

Visit 7 (week 11): Same as week 6. This visit will last approximately 20 minutes.

Visit 8 (week 13): Same as week 6. This visit will last approximately 20 minutes.

Visit 9 (end of week 14). A final interview, QEEG, CALCAP, and blood draw of approximately 2 teaspoonfuls (to evaluate blood hormone levels and pregnancy status) will be conducted at this time. This visit will last approximately 2 hours.

POTENTIAL RISKS AND DISCOMFORTS

Your depression may improve, get worse or remain unchanged during the 14 weeks of the study. You may leave the study at any point. If you choose to leave the blinded portion of the study, you will be offered the opportunity of an open label trial for the remainder of the six-week portion of the study. You will be monitored closely by the research staff and if your condition worsens significantly, you will be removed from the study and referred for immediate care.

Typical risks of QEEG are fatigue and boredom. The QEEG may cause minor scalp irritation and possibly light bleeding at the places where the electrodes are attached.

You may experience discomfort when having blood drawn; this may be a source of mild pain, and some mild swelling may occur at the site of the blood draw. Although it is uncommon, this may also cause you to feel faint, to bleed slightly, or rarely to develop an infection at the site of the blood draw.

It is possible that you may feel stressed or frustrated as a result of taking the California Computerized Assessment Package. You do not have to answer any question that you may not wish to answer.

The risk of estrogen for 6 weeks is negligible. Side effects of this menopausal dose of estrogen may include breast tenderness, bloating, irregular bleeding, nausea and headaches. The side effects are reversible at the termination of estrogen therapy and any individuals reporting bothersome symptoms will be withdrawn from the study. Long-term continuous administration of estrogen therapy for over one year without the addition of progesterone has been shown to be associated with thickening of the uterine lining (endometrial hyperplasia), however this is not an issue in this study because estrogen will only be taken for 6 weeks. Serious side effects of high dose estrogen such as blood clots, heart attack and elevated blood pressure are highly unlikely due to the low dose and short duration you will be receiving estrogen. In addition, this research may involve risks that are currently unforeseeable.

Due to the risk of pregnancy, you agree to use a medically effective barrier method of birth control, such as a condom, diaphragm, or cervical cap, while participating in the study.

ANTICIPATED BENEFITS TO SUBJECTS

Your depression may improve while you are participating in this study. Of course, because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

ANTICIPATED BENEFITS TO SOCIETY

The potential benefits of this research to society are a better understanding of mood and brain function as it pertains to estrogen augmentation in perimenopausal and menopausal depression. Estrogen augmentation refers to taking estrogen in pill form to supplement the natural decline in estrogen during perimenopause and menopause. Estrogen may improve mood in depressed women who do not fully respond to antidepressant treatment. Estrogen may also have effects in the slowing of age related cognitive decline in healthy postmenopausal and menopausal women. This study promotes the understanding of estrogen, brain function and the menopause in an effort to improve the health of women in midlife and beyond.

ALTERNATIVES TO PARTICIPATION

Estrogen replacement therapy is clinically available to perimenopausal and menopausal women without participation in the study.

PAYMENT FOR PARTICIPATION

You will be paid \$50.00 for each of the three visits that includes an EEG, for a total of \$150.00. If you present to the QEEG lab for a scheduled appointment and there is an equipment failure or some other unforeseen reason that the testing cannot be conducted, you will be reimbursed \$25.00 for your time. You may consult with Drs. Rapkin or Morgan without charge regarding future estrogen replacement therapy or for feedback on the cognitive testing.

Payments are processed through UCLA administrative offices and the exact timing of payment is not under the direct control of the investigators. You will probably receive your check within a few weeks, but a delay of six to eight weeks might occur.

FINANCIAL OBLIGATION

Neither you nor your insurance company will be billed for your participation in this research study. This includes the cost of estrogen medication, visits with study personnel and all laboratory and QEEG testing. However, you are responsible for all costs related to treating your depression. This may include the cost of antidepressant medication you are currently taking and the cost of your visits to your personal physician or psychiatrist.

EMERGENCY CARE AND COMPENSATION FOR INJURY

If you are injured as a direct result of research procedures not done primarily for your own benefit, you will receive treatment at no cost. The University of California does not provide any other form of compensation for injury.

PRIVACY AND CONFIDENTIALITY

The only people who will know that you are a research subject are members of the research team and EEG technicians. However, the study sponsor, The National Association for Research on Schizophrenia and Depression, may choose to review subject records. No information about you or provided by you during the research will be disclosed to others without your written permission, except if necessary to protect your rights and welfare (for example, if you are injured and need emergency care or if required by law). If you choose to allow the research staff to discuss your progress and treatment with your primary care physician or psychiatrist, we will contact that individual.

When results of research are published or discussed in conferences, no information will be included which will reveal your identity. Test results will be kept in a computerized database without your name. Only a coded identification number will be in the database. The principal investigator will be the only person able to find out the name associated with a particular identification number. All research data collected from you will be labeled with a coded identification number.

PARTICIPATION AND WITHDRAWAL

Your participation in this research is VOLUNTARY. If you decide not to participate, that will not affect your relationship with UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at UCLA.

WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience adverse side effects or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, Melinda Morgan, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research policy that people who develop certain conditions may not continue to participate. If you must drop out because the investigator asks you to (rather than because you have decided on your own to withdraw), you will be paid \$50.00 for each QEEG that you have completed.

NEW FINDINGS

During the course of the study, you will be notified of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might cause you to change your mind about continuing in the study. If significant new information is provided to you, your consent to continue participating in this study will be re-obtained.

IDENTIFICATION OF INVESTIGATORS

In the event of a research related injury or if you experience an adverse reaction, please contact the investigators listed below. If you have any questions about the research, please feel free to contact Melinda Morgan, Ph.D.

UCLA IRB# 01-06-063-02a
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Melinda L. Morgan, Ph.D. (310) 825-5028, Andrew Leuchter, M.D. (310) 825-0207 or Ian Cook, M.D. (210) 825-0304. Mailing address: UCLA Neuropsychiatric Institute and Hospital, Room 37-418, 760 Westwood Plaza, Los Angeles, CA 90024-1759

or

Andrea Rapkin, M.D. (310) 825-6963. Mailing address: Department of Obstetrics and Gynecology, UCLA School of Medicine, Room 27-162, CHS
10833 Le Conte Avenue, Los Angeles, CA 90095-1740
In case of emergency after hours, page Dr. Morgan at (310) 724-9655.

RIGHT OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research subject, you may contact the Office for Protection of Research Subjects, 2107 Ueberroth Building, UCLA, Box 951694, Los Angeles, CA 90095-1740.

SIGNATURE OF RESEARCH SUBJECT

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions, and all of my questions have been answered to my satisfaction. I have been given a copy of this form as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

Name of subject

Subject's signature

Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject and answered all of her questions. I believe that she understands the information described in this document and freely consents to participate.

Name of Investigator

Investigator's signature

Date (must be the same as the subject's)