Title: Hormone Sensitivity and Stressful Life Events: Predictors of Estradiol Treatment Response in Perimenopausal Depression

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Abstract:

Approximately 40% of women in the menopause transition (perimenopause) exhibit affective impairment associated with fluctuations in estradiol (E2), and a 2-4 fold increase in major depression risk. Perimenopause is a reproductive stage characterized by substantial day-to-day variability in E2 and heightened psychosocial stress. Controlled research indicates that individual differences in vulnerability to normal changes in E2 is etiologically relevant to affective impairment in perimenopause. While the source of affective susceptibility to perimenopausal E2 fluctuations is not known, our research has identified that recent very stressful life events (SLEs) predict the emergence of affective symptoms in those women with greater variability in E2 over the menopause transition.

Our more recent work adds a dimensional approach to studying perimenopausal depression by focusing on symptoms of depression that are most clinically relevant to perimenopausal women, namely anxiety and irritability. Irritability is the predisposition towards anger and represents, along with anxiety, the most frequent affective symptoms of perimenopausal depression, with attendant distress and impairment. Irritability and anxiety are transdiagnostic symptoms evident across mental health disorders. Estradiol has anti-depressant and anti-anxiety effects and modulates the hypothalamic-pituitary-adrenal (HPA) stress axis as well as limbic neural networks important for affective processing.

Results will be presented from three, randomized, placebo controlled trials (RCTs) using transdermal estradiol (TE2) to investigate the role of E2 and stress exposure in perimenopausal depression, anxiety, and irritability. Our first RCT of TE2 (100ug/day vs. placebo) in 172 perimenopausal women followed for 12 months found that the antidepressant effects of TE2 were significantly greater in women with more SLEs. Moreover, the odds of women developing clinical depression over the 12 months was cut by 50% in those randomized to TE2, especially for women in the early menopause transition (STRAW+10 Stage -2). Our second study, in 82 perimenopausal women, established individual baseline hormone sensitivity strength scores (co-variation of

weekly urinary estrogen with weekly anxiety scores) and randomized each subject to TE2 (100 ug/day) or placebo for 16 weeks. Greater baseline hormone sensitivity predicted significantly lower post-treatment anxiety and somatic symptoms. Our third, on-going RCT uses electroencephalography (EEG) methods and relevant computer-based tasks to determine the role of baseline E2 fluctuation and responses to TE2 intervention in altering neural networks involved in threat and reward processing. Findings will advance our understanding of the role of E2 in the neural basis of perimenopausal irritability and anxiety symptomatology and have implications for treatment.

Biography

Dr. Susan Girdler, is Professor and Associate Vice Chair for Faculty Development in the Department of Psychiatry at the University of North Carolina at Chapel Hill. Dr. Girdler has a long history of research funding from the National Institutes of Health (NIH) for her clinical research in women's reproductive mood disorders, including premenstrual dysphoric disorder and perimenopausal depression. Dr. Girdler's recently funded work examines hormone sensitivity and exposure to stressful life events as predictors of depression risk during the menopause transition and the beneficial effects of transdermal estradiol on that risk. She is also committed to minority health research and is currently Principal Investigator on an NIH study to test best mentoring practices for racially and ethnically underrepresented biomedical researchers.