

- 973 A Cross-Sectional Evaluation of Perimenopausal Depression
- 981 Relevance of the 5-HTTLPR Polymorphism and Childhood Abuse to Increased Psychiatric Comorbidity in Women With Bulimia-Spectrum Disorders
- 991 Luteal Phase Administration of Paroxetine for the Treatment of Premenstrual Dysphoric Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial in Canadian Women
- 999 Olanzapine Plus Dialectical Behavior Therapy for Women With High Irritability Who Meet Criteria for Borderline Personality Disorder: A Double-Blind, Placebo-Controlled Pilot Study

Reproductive Neuroscience: Biology, Environment, and Clinical Implications in Women's Mental Health

Two of the articles in this issue's Focus on Women's Mental Health section provide data on phenomenology and risk of psychiatric disorders in women, while 2 articles report findings from treatment trial results.

The perimenopause has been identified as a high-risk time for major depressive disorder in women, as reviewed by Steinberg et al. in the introduction section of their article. The authors generously provide an accompanying editorial following this introduction, in which they put their results into a historical and clinical context. Better understanding of perimenopausal depression will allow for a stronger foundation for its identification, treatment, and prevention. As the authors discuss in their article, "Many assumptions are made about the cause and characteristics of depression occurring during the menopause transition, but little is actually known."

The investigators conducted a cross-sectional study of 116 women between 40 and 55 years of age in the perimenopausal transition who presented to a mood disorders clinic. The authors found that first-onset depression did not present with a different clinical picture than recurrent episodes during perimenopause, and depression that was accompanied by hot flushes did not appear distinct from depressive disorders without hot flushes. Hot flushes were not found to be a predictable determinant of new-onset perimenopausal depression. Also, postpartum depression did not predict perimenopausal depression, although premenstrual dysphoria was common in the sample. Importantly, the investigators documented a high prevalence of depressive symptoms with significant impairment and clustering in the later perimenopausal transition. These factors may suggest future research directions.

Gender, childhood abuse, and comorbidity are important topics regarding the manifestation of psychiatric disorders and treatment response. Richardson et al. present a study in which the serotonin transporter promoter polymorphism 5-HTTLPR is assessed with regard to bulimia-spectrum eating disorders, psychiatric comorbidity, and histories of abuse. Eighty-nine women participated in the study, which included diagnostic assessments, interviews, and genotyping. The complex interplay between genetic predisposition, environmental impact, and expression of psychiatric disorders deserves sophisticated consideration. Richardson et al. found that greater psychiatric comorbidity in an eating-disordered population was associated with the S allele and exposure to abuse. The impact of a more sophisticated understanding of genetic influences on the expression and course of psychiatric disorders remains unclear and full of potential. In this article, the investigators add to the literature that demonstrates the important interactions between environment and biology. These types of studies are exciting overall for psychiatry and will likely contribute to our understanding of the biopsychosocial elements that lead to gender differences in disease prevalence and course.

Steiner et al. assess paroxetine in a double-blind, placebo-controlled trial of 2 doses (10 mg and 20 mg) for premenstrual dysphoric disorder (PMDD), with intermittent (luteal only) dosing. The higher dose was significantly more effective than the 10-mg dose and placebo. Luteal phase dosing was demonstrated at the higher dose to be an effective and well-tolerated option for women with PMDD without other Axis I comorbidity. Interestingly, the investigators encountered a high protocol violation rate (30%), with many patients missing an excessive number of doses. It is unclear if a high rate of missed doses could be due to the intermittent dosing regimen

or the temporal nature of PMDD symptoms. This finding suggests that a better understanding of the factors influencing adherence may guide future research focused on improving adherence to treatments, especially in the context of more complicated medication regimens.

Linehan and colleagues provide treatment data on a study of dialectical behavior therapy (DBT) and olanzapine. They include women who met criteria for borderline personality disorder with substantial irritability and anger symptoms. Patients (N = 24) were randomly assigned to olanzapine (up to 15 mg/day) or placebo. All subjects received DBT during this 6-month study. Eight patients (33%) dropped out of the study for reasons detailed in the article before completing the protocol, demonstrating the challenges involved in a treatment study of this length. Measures of aggression and irritability demonstrated benefit for both groups. There was

a trend for a more rapid improvement with olanzapine that did not reach statistical significance. Interestingly, the occurrence of self-harm decreased more rapidly in the placebo group. It is difficult to make definitive conclusions based on the small sample size and a design in which an adjunctive assessment of a pharmacologic intervention was provided in addition to a well-established and effective psychotherapy.

We thank the contributing authors for their work in the area of women's mental health research and hope that these articles encourage further interest in these important topics.

For feedback and suggestions about the Focus on Women's Mental Health section, please contact me at mfreeman@psychiatrist.com.

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Vice–Editor in Chief

IN THE AUTHORS' OWN WORDS

Why Study Reproductive Neuroscience? A Clinical Perspective

The relationship between disturbances in mood and a woman's reproductive function has been, and continues to be, a source of controversy. The 19th century medical literature contains numerous reports suggesting that changes in reproductive endocrine function accompanying reproductive senescence could sufficiently alter central nervous system function so as to change behavior.

In the last 30 years, an enhanced understanding of reproductive physiology in women has facilitated efforts to systematically evaluate the nature of these otherwise anecdotal reports. Although the endocrinology of the menopause transition remains to be fully characterized, recent community-based and clinic-based studies provide evidence that a subgroup of women are at an increased risk for depression and anxiety disorders during this phase of reproductive life. Thus, clinicians are no longer arguing about the existence of these phenomena. Furthermore, it is clear that for a subgroup of women, changes in reproductive function are critical regulators of behavior. However, much more needs to be learned about these relationships.

Our next step will be to characterize the substrates of susceptibility to this differential behavioral sensitivity—one in which ostensibly identical hormonal events provoke alterations in affective adaptation in a subgroup of women but not in the majority. The importance of context in determining this differential response has been documented repeatedly in the basic science literature. In humans, an understanding of the roles of contextual variables such as age, sex, past experience, and genotypic variation will inform our future studies of these important phenomena.

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