MASSACHUSETTS GENERAL HOSPITAL
55 Fruit Street
Boston, MA 02114
617.726.2000

MGH Center for Women's Mental Health

Reproductive Psychiatry Resource and Information Center

In This Issue

Dear Readers:

We are very pleased to bring you this November issue of our newsletter from the Center for Women's Mental Health. Previous issues are available on our website at www.womensmentalhealth.org/.

This newsletter addresses issues including 1) the use of oral contraceptives for the treatment of PMDD and 2) the management of insomnia during pregnancy. We also discuss a recent ACOG report on SSRI use during pregnancy.

One of the goals of the Center is to provide critical current information for patients and care providers in the rapidly changing field of women's mental health. This newsletter describes new findings across studies in women's mental health and represents an effort to bridge the gap between data emerging from new investigations across reproductive psychiatry and the clinical implications of such studies.

Keeping with this mission, we are happy to announce that the Center has launched a new blog at http://cwmh.wordpress.com that will be updated frequently in order to provide you with the most current information from the field. We encourage you to visit our blog, and please feel free to write comments.

Sincerely,

Lee S. Cohen, MD

Oral Contraceptives for the Treatment of Premenstrual Mood Symptoms

Oral contraceptives are commonly prescribed for the treatment of premenstrual symptoms and premenstrual dysphoric disorder (PMDD); however, the evidence supporting the use of oral contraceptives in this setting is limited. While most studies have shown that oral contraceptives are not effective for the treatment of premenstrual symptoms, there is preliminary evidence that a new oral contraceptive pill, Yaz, which contains low-dose estrogen and a novel progestin called drospirenone, may alleviate the symptoms of PMDD.

In a multicenter, double-blind, placebo-controlled study, participants (n=450) were randomized to receive treatment with Yaz, an oral contraceptive formulation containing drospirenone 3 mg and ethinyl estradiol (EE) 20 mcg, or placebo for three cycles after a washout period of two treatment-free cycles. Hormones were administered for 24 days, followed by 4 days of inactive pills.

Scores on the total Daily Record of Severity of Problems decreased by -37.49 in the active treatment group and by -29.99 in the placebo group (adjusted mean difference -7.5; $p < 0.001$). Response, defined as a 50% reduction in the severity of daily symptoms, occurred in 48% of the treatment group and in 36% of the placebo group.

In comparing the current study to previous studies assessing the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in women with PMDD, the authors noted that the overall effect size observed in the Yaz study was similar to that found for SSRIs. In both the Yaz and the SSRI studies, placebo response rates tended to be high. In addition, the authors noted that physical symptoms responded well to Yaz. In contrast, these symptoms were less likely to respond to SSRIs or required higher doses for response.

The authors speculated that the efficacy of Yaz may be related to the addition of the novel progestin, drospirenone. Drospirenone is distinct from the progestins used in other oral contraceptives and is chemically related to spironolactone, a diuretic that is sometimes used to treat fluid retention in women with premenstrual symptoms.

Ruta Nonacs, MD PhD

Yonkers KA, Brown C, Pearlstein TB, et al. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstet Gynecol. 2005; 106: 492-501.

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Paroxetine CR May Be Helpful for Menopausal Women Discontinuing Hormone Therapy

Estrogen was first approved by the FDA for the treatment of menopausal symptoms in 1942, and for many decades estrogen replacement therapy had been widely prescribed for peri- and post-menopausal women. In 2002, however, data from the Women's Health Initiative (WHI) suggested that hormonal therapy may be associated with an increased risk of breast cancer and cardiovascular disease. These findings have led to a dramatic decrease in the use of hormone replacement therapy (HRT), with many women abruptly discontinuing its use.

After discontinuing hormone therapy, many women experience recurrent menopausal symptoms, including hot flushes, night sweats and sleep disturbance (Ness et al, 2006). Even when HRT is tapered gradually, these symptoms may recur. Women may also experience mood symptoms and other symptoms including anxiety, agitation, and irritability subsequent to hormone discontinuation. Although there is limited data regarding the prevalence of mood symptoms among women who discontinue HRT, it is likely that women who have a history of perimenopausal mood changes may be particularly vulnerable to depression in the setting of HRT discontinuation (Stewart et al, 2004).

In a preliminary study conducted at the Center for Women's Mental Health, Drs. Claudio Soares and Hadine Joffe have examined the efficacy of paroxetine CR (controlled release) for the treatment of peri- and postmenopausal women who had recently discontinued hormone therapy. In this study, 64 peri- and postmenopausal women (age 40-60 years) who experienced the emergence of significant vasomotor symptoms (VMS) and other somatic complaints after the discontinuation of hormone

therapy were recruited. Most of the women had initiated hormone therapy to alleviate vasomotor symptoms and sleep disruption and had discontinued hormone therapy (median duration of use = 77 months) primarily because of concerns regarding the long-term safety of HRT. While subjects with mild depressive symptoms were considered eligible for the study, those with any Axis I psychiatric disorder (assessed with the Mini-International Neuropsychiatric Interview, MINI), moderate to severe symptoms of depression (MADRS scores > 19) and/or significant anxiety (HAM-A scores > 17) were excluded.

Subjects entered a one-week, single blind, placebo lead-in phase. Placebo non-responders (<30% decline in VMS, n=56) entered into a six-week, double-blind phase and were randomized to receive either paroxetine CR 12.5 mg/day (n=28) or placebo (n=28). Dosing was adjusted up to 25 mg/day after two weeks, based on treatment response and tolerability. Subjects were re-evaluated after 1, 2, and 6 weeks.

Treatment with paroxetine CR resulted in significant reduction of vasomotor and mood symptoms in peri- and postmenopausal women who became symptomatic after discontinuing hormone therapy. Treatment was well tolerated. These findings are consistent with previous studies that have demonstrated a significant reduction in the severity of vasomotor symptoms in non-depressed women treated with serotonergic antidepressants (Stearns et al, 2003; Evans et al, 2005) and demonstrate that therapy with paroxetine CR may be helpful for the treatment of both mood and physical symptoms following the discontinuation of hormone therapy.

Ruta Nonacs, MD PhD

Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB. Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. Obstet Gynecol 2005;105(1):161-6.

Ness J, Aronow WS, Beck G. Menopausal symptoms after cessation of hormone replacement therapy. Maturitas 2006;53(3):356-61.

Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA. 2003; 289(21):2827-34.

Stewart DE, Rolfe DE, Robertson E. Depression, Estrogen, and the Women's Health Initiative. Psychosomatics 2004; 45:445-447.

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ACOG Opinion on SSRI Use During Pregnancy

Recent reports have raised questions regarding the use of selective serotonin reuptake inhibitors (SSRI) during pregnancy. To date, no professional medical association has issued formal guidelines regarding the use of SSRIs during pregnancy. However, in December the American College of Obstetricians and Gynecologists ACOG published an opinion paper on this topic that is noteworthy for its clarity and balanced review of the existing data on the reproductive safety of SSRI antidepressants (Obstetrics and Gynecology 2006;108:1601-3). The ACOG report addressed the following issues:

Two unpublished reports have suggested a 1.5 to 2.0-fold increase in the risk of cardiovascular malformations (atrial and ventricular septal defects) among children exposed to paroxetine (Paxil)

during the first trimester of pregnancy. These findings prompted a change in Paxil's labeling from Pregnancy Category C to D (see April 2006 Newsletter). The ACOG Committee on Obstetric Practice notes that this increase in risk has not been observed with any other SSRIs and makes the following recommendation: "At this time, paroxetine use among pregnant women and women planning pregnancy should be avoided, if possible."

Also referenced in the opinion are multiple reports indicating that exposure to SSRIs late in pregnancy may be associated with neonatal complications, including jitteriness, mild respiratory distress, weak cry, poor muscle tone, and admission to a special care nursery (see December 2005 Newsletter). The report also commented on a single study documenting an increased risk of a more serious complication, persistent pulmonary hypertension of the newborn (PPHN), in infants exposed to SSRIs after 20 weeks of gestation (see April 2006 Newsletter).

The report reminds us that while these reports have raised concerns regarding SSRI use during pregnancy, depression is common during pregnancy, affecting approximately 1 in 10 women. Furthermore, the ACOG Committee notes that women who discontinue treatment with an antidepressant are five times to experience a depressive relapse than women who maintain treatment. "The potential risk of SSRI use throughout pregnancy must be considered in the context of the risk of relapse of depression if maintenance treatment is discontinued," the report states. "Untreated depression may increase the risk of low weight gain, sexually transmitted diseases, and alcohol and substance abuse, all of which have maternal and fetal health implications."

Most importantly, the report recommends an individualized approach to treating women who are either pregnant or planning pregnancy while taking an SSRI or selective norepinephrine reuptake inhibitor: "Decisions about treatment of depression should incorporate the clinical expertise of the mental health clinician and obstetrician, and the process should actively engage the patient's values and perceptions when framing the discussion of the risks and benefits of treatment." When it comes to prescribing SSRIs during pregnancy, patients must collaborate with their treaters in order to make the best decision under circumstances in which we have imperfect estimates of risk on both sides of the risk-benefit equation. As in any other clinical situation, treatment must be individually tailored based on the patients' particular clinical scenario and her own personal wishes.

Ruta Nonacs, MD PhD
Lee S. Cohen, MD

Obstetrics and Gynecology 2006;108:1601-3

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Patient Corner: Treatment of Insomnia during Pregnancy

Q. I am now about 5 weeks pregnant, and I am having problems falling asleep. Even though I am totally exhausted, it may take up to two hours to fall asleep. Even when I do sleep, I wake up feeling tired. My obstetrician recommended Ambien. Is Ambien safe to take during pregnancy?

A. Most women experience some degree of sleep disturbance during pregnancy, and for a significant number of women sleep disruption may be quite severe. There are many different causes for sleep disturbance during pregnancy, and choosing the appropriate intervention relies on an accurate diagnosis of the problem.

Certain sleep disorders, such as restless leg syndrome and sleep apnea, are more common during pregnancy and may cause significant sleep disruption.

Sleep disturbance may also be a symptom of depression or an anxiety disorder, thus it is important to screen for these problems. Many women with depression or anxiety have difficulty falling asleep or they wake early and are unable to return to sleep. Treating the underlying disorder may improve sleep quality. (More information on the treatment of depression and anxiety during pregnancy can be found here.) Typically antidepressants, including fluoxetine (Prozac) and the older tricyclic agents (including nortriptyline and amitriptyline) are used in this setting.

While certain strategies may help to improve sleep quality, some women may require some type of pharmacologic intervention. Although Ambien (zolpidem) and other sedative-hypnotic agents, including Lunesta (eszopiclone) and Sonata (zalepion), are commonly prescribed to women with sleep disturbance, the data regarding their reproductive safety is limited and generally we try to avoid their use during pregnancy.

Sedating tricyclic antidepressants, such as amitriptyline or nortriptyline, may be a better choice for women with sleep disturbance and have not been associated been associated with an increase in risk of congenital malformation. Benzodiazepines, including Ativan (lorazepam) and Klonopin (clonazepam) may also be useful. There is some controversy regarding the use of benzodiazepines during pregnancy. Although initial reports suggested that there may be an increased risk of cleft lip and cleft palate, more recent reports have shown no association between exposure to benzodiazepines and risk for cleft lip or palate. Pooling the data suggests that this risk-- if it exists -- is estimated to be 0.7%. The risk of malformation is confined to the first trimester when lip and palate formation take place; thus, benzodiazepines when used later in pregnancy do not carry this tertogentic risk.

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Current Research Studies at the Center for Women's Mental Health

Bipolar Disorder in Pregnancy
Do you have questions about bipolar disorder and anti-depressants or mood stabilizers during pregnancy? If you are pregnant, or planning pregnancy, and diagnosed with bipolar disorder (or manic depression), you may be eligible for this research study. Participants meet with research coordinators and psychiatrists who specialize in bipolar illness during pregnancy.
Contact: Rachel VanderKruik (617) 726-2912 or rvanderkruik@partners.org

More research studies will be starting in 2008! Please check our website for updates.

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