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MGH Center for Women's Mental Health

Reproductive Psychiatry Resource and Information Center

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Dear Readers,

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

This Summer issue describes important new research findings and reports in the field of women's mental health, with particular focus on new developments in the area of psychotropic drug use during pregnancy. These new studies have significant implications for women who suffer from bipolar disorder and who are either planning to conceive or who are pregnant.

Part of the mission 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 attempts to bridge the gap between data emerging from new investigations across reproductive psychiatry and the clinical implications of such studies.

Sincerely,

Lee S. Cohen, MD

New Research from the CWMH: Neurobehavioral Outcomes in Children Exposed to Lithium in Utero

Driven by concerns regarding fetal exposure to psychotropic medications, many women with psychiatric illness attempt to discontinue their pharmacologic treatment during pregnancy; however, recent studies indicate that this approach may not be appropriate for all women. Dr. Adele Viguera and her colleagues at the Center for Women's Mental Health have reported that among pregnant women with bipolar disorder, relapse rates were very high (58%) in women who discontinued maintenance treatment with lithium during pregnancy ([Viguera et al 2000](#)). Given this risk of recurrent illness, many women may consider continuing lithium treatment during pregnancy. While the teratogenic effects of first trimester exposure to lithium have been well studied, data on the long-term outcome of children exposed to lithium during pregnancy are sparse. At the 61st Annual Meeting of

the Society of Biological Psychiatry in Toronto, Dr. Viguera presented preliminary data on the neurobehavioral outcomes of children exposed to lithium in utero.

In this study, 61 mothers with bipolar disorder and their children were recruited. The final analysis included children exposed to lithium at any point during pregnancy (n=32) and children not exposed to lithium or any other mood stabilizer during pregnancy (n=24). Five subjects were excluded from the analysis due to missing data. Information on maternal demographic, obstetrical, and psychiatric history was collected, as well as information about the medical/developmental history of the child. Early childhood development was assessed by a blinded rater using the Bayley Scales of Infant Development-II (BSID-II) and the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R). Children were assessed at 2.5 to 3.5 years for the BSID-II and from 3.5 to 7.3 years of age for the WPPSI-R.

There were no significant differences in the mean or range of global IQ scores of children exposed to lithium in utero versus non-exposed children. However, it is notable that the average developmental score for the lithium exposed group was 7-8 points lower than the control group. Despite this point-difference between exposed and non-exposed children, the average score for the exposed group remained well within the average range. Exposed children were more likely to be born early (37.8 vs. 39.3 weeks), have slightly lower Apgar scores at birth (8.6 vs. 9.1), weigh slightly less (3240 vs. 3550 grams), and were more likely to be admitted to the NICU.

Though preliminary, these findings suggest no gross developmental deficits associated with lithium exposure. While lithium appeared to have a statistically significant impact on certain outcomes (i.e., gestational age, birth weight, Apgar scores, Bayley scores); the effect was relatively small and appeared to have little clinical relevance. In fact, the two groups behaved similarly with respect to meeting developmental milestones. Furthermore, all scores for the lithium-exposed children were within the normal range.

It should also be noted that differences in outcomes between the exposed and non-exposed groups may stem from unidentified differences between the two groups of women recruited for the study. More specifically, women were not randomly assigned to the two groups but made their decisions regarding their treatment based on their clinical histories and personal preferences. Thus, it could be hypothesized that the women who chose to maintain treatment with lithium were more severely ill than those who chose to discontinue lithium, and it is the illness itself - not the medication-that has a negative impact on outcomes. Similarly, other studies in women with unipolar illness have demonstrated that more severe depressive symptoms during pregnancy have been associated with shorter gestation, lower birth weight, and lower Apgar scores, absent exposure to any medication ([Bonari et al, 2004](#)). Clearly there is need for more systematic study in larger samples of women in order to better understand the impact of lithium on neurobehavioral outcomes; nonetheless, the observed absence of clinically significant cognitive deficits is reassuring.

Ruta Nonacs, MD PhD

[Viguera AC et al. Risk of recurrence of bipolar disorder in pregnant vs. nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000; 157: 174-184. \[PDF\]](#)

[Bonari L et al. Perinatal Risk of untreated depression during pregnancy. Can J Psychiatry 2004; 49 \(11\): 726- 735. \[PDF\]](#)

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New Research from the CWMH: Duloxetine for the Treatment of Menopausal Symptoms and Mood in Postmenopausal Women

Depression is common in postmenopausal women suffering from menopausal vasomotor symptoms (hot flushes, night sweats) and insomnia. While estrogen replacement therapy may alleviate these symptoms and may also have a positive impact on mood, the use of estrogen has declined over recent years. There has been great interest in finding alternative strategies for the management of menopausal symptoms, and recent data suggest that selective serotonin reuptake inhibitor antidepressants (SSRIs) and the serotonin norepinephrine reuptake inhibitor (SNRI), venlafaxine, may be effective for the treatment of depression and vasomotor symptoms in peri- and postmenopausal women. In a study presented at the annual meeting of the American Psychiatric Association, Dr. Hadine Joffe and her colleagues at the Center of Women's Mental Health presented data on the use of duloxetine (Cymbalta), a new SNRI, for the treatment of mood, vasomotor symptoms, and insomnia in postmenopausal women.

Postmenopausal women (age 40-60) were recruited for this study. Women receiving hormonal therapy or antidepressants were excluded. Preliminary analysis of the data included 26 postmenopausal women (mean age: 51.5 + 4.3 years) diagnosed with depression (Montgomery-Asberg Depression Rating Scale [MADRS] scores > 20). Subjects had significant menopausal symptoms, with a Green Climacteric Scale (GCS) total score of > 20 and a GCS vasomotor subscale score of > 3. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.

Following a 2-week single-blind placebo run-in phase, subjects were treated for 8 weeks with open-label duloxetine with flexible dosing (60-120 mg/day). For the 11 women who had completed the study at the time this work was presented, MADRS scores declined from a mean of 22.6 + 2.9 to 6.0 + 4.9 ($p < 0.001$). 82% of the women had a full remission of their symptoms (MADRS < 10). GCS vasomotor scores declined from a mean of 4.8 + 1.4 to 2.5 + 1.1 ($p < 0.001$), reflecting improvement of hot flushes. Sleep quality also improved significantly, with PSQI scores declining from 11.8 + 3.7 to 7.1 + 3.3 ($p < 0.001$). The final mean dosage of duloxetine used was 79.1 + 20.2 mg/day.

These preliminary data suggest that duloxetine is effective for the treatment of depressive symptoms in postmenopausal women with prominent vasomotor symptoms. Duloxetine also appears to alleviate hot flushes and improve sleep quality in this population and thus may be an attractive alternative to hormonal therapy for women with significant menopausal symptoms.

Ruta Nonacs, MD PhD

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Evaluating the Safety of First-Trimester Exposure to Lamotrigine (Lamictal)

Women with bipolar disorder are at high risk for relapse during pregnancy ([Viguera et al 2000](#)). While maintenance treatment with a mood stabilizer during pregnancy can significantly reduce the risk for relapse, many of the medications commonly used in this setting, including lithium and valproic acid, carry some degree of teratogenic risk. Anticonvulsants are being used with increasing regularity for the treatment of women with bipolar disorder; however, data regarding the reproductive safety of many of the newer anticonvulsants (i.e., gabapentin, tiagabine, oxcarbazepine) is limited. Several recent studies have evaluated the safety of lamotrigine (Lamictal) use in pregnancy.

Data from the International Lamotrigine Pregnancy Registry recently presented at the meeting of the American Academy of Neurology did not show an elevated risk of malformations associated with lamotrigine exposure (Messenheimer and Wiel, 2006). In a total of 680 first-trimester exposures to

lamotrigine monotherapy, the frequency of major congenital malformations was 2.8% (n=19). These findings are consistent with previous reports which observed rates of malformation in lamotrigine-exposed infants similar to those observed in the general population ([Tennis et al, 2002](#); [Cunnington et al, 2005](#)).

Other data presented at the Annual Meeting of the Teratology Society and included in a "Dear Health Care Professional" letter sent out by GlaxoSmithKline, the manufacturer of Lamictal, comes from the North-American Anti-Epileptic Drug Registry. In this study, the prevalence of major malformations in a total of 564 children exposed to lamotrigine monotherapy was observed to be 2.7%; however, five infants had oral clefts, indicating a prevalence rate of 8.9 per 1000 births ([Holmes et al, 2006](#)). In a comparison group of 221,746 unexposed births, the prevalence rate for oral clefts was 0.37/1000, indicating a 24-fold increase in risk of oral cleft in infants exposed to lamotrigine. However, other registries have not demonstrated such a significant increase in risk for oral clefts. Among a total of 1,623 lamotrigine-exposed infants surveyed in five other anticonvulsant registries, four infants with oral clefts were identified, indicating a frequency of 1:405 or 2.5/1,000.

Although numerous studies have linked older anticonvulsants, including valproate and carbamazepine, to an increased risk of malformations, this study is the first to report an increase in the frequency of a specific major malformation among infants exposed to one of the newer anticonvulsant drugs. Clearly more data are essential to better evaluate the reproductive safety of lamotrigine; important questions regarding the safety of lamotrigine and other anticonvulsants might be best addressed by collaboration between multiple registries, including EURAP and the North-American Anti-Epileptic Drug Registry.

These data may signal an increase in risk of malformations in children exposed to lamotrigine; however, it is important to put this risk into perspective. If we assume that the findings from the North American registry are true, the absolute risk of having a child with cleft lip or palate is about 0.9%. While some women may elect to discontinue treatment with lamotrigine given the magnitude of this risk, many women with more brittle bipolar illness may require treatment with some type of mood stabilizer during pregnancy. However, the alternatives to lamotrigine also carry some risk. Exposure to valproate during the first trimester carries an unacceptably high risk of major malformations (over 10% in some samples), including neural tube defects. Lithium usage during the first trimester has been associated with a 0.1% risk of cardiovascular malformation. At this point, data regarding the reproductive safety of atypical anti-psychotic agents is sparse. Thus, some women may elect to continue treatment with lamotrigine, acknowledging that, while there may be risks associated with this exposure, other treatment options are not risk-free.

Ruta M. Nonacs, MD PhD

[Tennis P, Eldridge RR; International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. *Epilepsia*. 2002 Oct;43\(10\):1161-7. \[PDF\]](#)

[Cunnington M and Tennis P; International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005; 64: 955-960 \[PDF\]](#)

Holmes LB, Wyszynski DF, Baldwin EJ, Habecker E, et al. Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy. 46th Annual Meeting of the Teratology Society, June 24-29, 2006, Tucson, AZ.

Messenheimer JA, Wiel J. Thirteen year interim results from an International Observational Study of Pregnancy Outcomes Following Exposure to Lamotrigine. 58th Annual Meeting of the American Academy of Neurology, April 1-8, 2006, San Diego, CA.

[Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarni RJ. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. *Am J Psychiatry* Feb 2000; 157: 179-184 \[PDF\]](#)

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Patient Corner: Use of SSRIs During Pregnancy

Q. I have been taking antidepressants on and off for the last ten years, and I am now planning a pregnancy. I am now on Effexor, and my psychiatrist recommended switching to Prozac and staying on it up until the end of the second trimester. He said that antidepressants should be avoided later on in pregnancy because they may cause problems for the baby at the time of delivery. I am concerned about having to come off my medication for such a long time. In the past, every time I have tried to stop the medication, my depression has come back within a month or so.

A. Over the last decade, research has supported the use of certain selective serotonin reuptake inhibitors (SSRIs) and the older tricyclic antidepressants during pregnancy, indicating no increase in risk for congenital malformations in children exposed to these medications in utero. More recent studies, however, have raised questions regarding the risk for adverse events in newborns exposed to antidepressants around the time of labor and delivery (see Fall 2004 , Spring 2005, and Spring 2006 Newsletters). Most commonly these studies have reported symptoms of jitteriness, irritability, sleep disturbance, feeding problems, and excessive crying in infants shortly after delivery. There have also been reports of respiratory distress (usually tachypnea or rapid breathing). In general, the symptoms observed have been brief, in most cases resolving within 1-4 days without any specific medical intervention. While the majority of these studies have observed relatively benign symptoms in antidepressant-exposed infants, one study has suggested that infants exposed to antidepressants late in pregnancy may be susceptible to a more serious form of respiratory distress associated with persistent pulmonary hypertension of the newborn or PPHN ([Chambers et al, 2006](#)).

Given the concerns that antidepressants taken late in pregnancy may cause a spectrum of adverse events in the newborn, some experts in the field have suggested that women discontinue antidepressants several months before delivery. While this approach may potentially reduce the incidence of toxicity in the newborn, it carries certain risks. Most women who make the decision to use antidepressants during pregnancy have histories of recurrent or severe depression, and their decision to maintain treatment with a medication has been driven by their inability to remain well without it. For these women, withholding medication is likely to increase the risk of depressive illness in the mother.

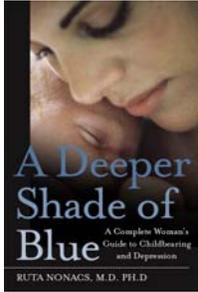
Depression is never a benign event. Pregnant women who are depressed are more likely to receive inadequate prenatal care and are more likely to use tobacco, alcohol, and recreational drugs, behaviors that may place the pregnancy at risk. Depression during pregnancy has also been associated with increased risk of preterm labor, lower birth weight, smaller head circumference, and lower Apgar scores ([Bonari et al, 2004](#)). Keeping these risks in mind, some women with depression may make the decision to continue treatment with an antidepressant, acknowledging that while there may be some risks associated with exposure to the medication, there are also significant risks associated with untreated depression.

Ruta Nonacs, MD PhD

[Bonari L et al. Perinatal Risk of untreated depression during pregnancy. Can J Psychiatry 2004; 49 \(11\): 726- 735.\[PDF\]](#)
[Chambers et al. Selective Serotonin Reuptake Inhibitors and risk of persistent pulmonary hypertension of newborns. New Eng J Med 2006; 354: 579- 587. \[PDF\]](#)

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New Book: *A Deeper Shade of Blue: A Women's Guide to Recognizing and Treating Depression in Her Childbearing Years*, by Ruta Nonacs, MD. (Simon and Schuster, 2006)



Depression affects women almost twice as often as men, with about one in four women suffering from it in her lifetime. While depression may strike at any time, studies show that women are particularly vulnerable during their childbearing years.

Despite the increasing awareness of this deeply concerning issue, many studies and health professionals still continue to focus almost solely on postpartum depression, ignoring the fact that depression is just as likely to affect women while they're trying to conceive and during pregnancy. Now, in this comprehensive, empathetic, and candid book, Dr. Ruta Nonacs, a senior member of the Center for Women's Mental Health at Massachusetts General Hospital and mother of two children herself, confronts the seldom talked-about issues of pregnancy-related depression, including:

- *Becoming pregnant while being treated for depression
- *Infertility-related depression and the effects of fertility treatments
- *Understanding the effects of maternal depression on spouses and family
- *Postpartum depression and anxiety

Nonacs also addresses the many complicated issues in a woman's life during the span of her childbearing years -- education, career, marriage, childbearing, and child rearing -- and discusses the ways in which depression often takes hold during potentially stressful times. Nonacs identifies many of the symptoms of depression associated with pregnancy and discusses treatments and cures, as well as ways to minimize effects of depression on family and friends.

Straightforward and honest, as well as emotionally sensitive and deeply moving, *A Deeper Shade of Blue* gives every woman who has suffered from pregnancy-related depression the information she needs to get the best care for herself, during pregnancy and beyond.

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

Premenstrual Dysphoric Disorder (PMDD)

The Center for Women's Mental Health is seeking women, between the ages of 18-49, who regularly experience symptoms of moodiness, sadness, irritability and/or anxiety before getting their menstrual period each month. Eligible women will be enrolled in a clinical research study of an investigational medication to possibly alleviate severe premenstrual symptoms.

Contact: Kate Silver-Heilman at (617) 643-3083 or ksilver-heilman@partners.org

Bipolar Disorder in Pregnancy

Do you have questions about bipolar disorder and anti-depressants or mood stabilizers during

pregnancy? If you are pregnant 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: Marisa Johnson at (617) 726-2912 or mjohnson33@partners.org

Postpartum Depression

Are you a pregnant woman with a history of depression who is less than 36 weeks pregnant?

Contact: Viveka Prakash at (617) 724-6540 or vprakash@partners.org

Breastfeeding and Psychiatric Medications

Are you breastfeeding and taking psychiatric medications?

Contact: Viveka Prakash at (617) 724-6540 or vprakash@partners.org

Neurobehavioral Outcome of Children Exposed to Psychotropics During Pregnancy

Are you a mother with a history of bipolar disorder who has young children?

Contact: Viveka Prakash at (617) 724-6540 or vprakash@partners.org

Menopause and Recent Discontinuation of Hormone Replacement Therapy

Do you have hot flashes? Have you tried Hormone Replacement Therapy and recently stopped it?

Are your menopause-related symptoms still bothering you?

Contact: Brittny Somley at (617) 724-1181 or bsomley@partners.org

Menopause, Mood, Sleeplessness, and Hot Flashes

Are you menopausal? Do hot flashes keep you awake at night? Do you have mood swings? If you are a 40-60 year-old menopausal woman who has hot flashes, mood swings, and difficulty sleeping, you may be eligible for an 8-week research study at Massachusetts General Hospital evaluating how estrogen and a sleep medication treat your menopausal symptoms. You will receive study medication and evaluations of your mood, hormone levels, hot flashes, and sleep at no cost.

Contact: Brittny Somley at (617) 724-1181 or bsomley@partners.org

Menopause, Mood and Insomnia

The Center for Women's Mental Health is seeking menopausal women, 40 or older, with irregular or no menstrual periods in the past year, and have trouble sleeping at night, you may be eligible for a research study at Massachusetts General Hospital that evaluates the effectiveness of a sleeping medication for the treatment of your insomnia. You will receive study medications and evaluations of your sleep at no cost.

Contact: Kate Silver-Heilman at (617) 643-3083 or ksilver-heilman@partners.org

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