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## MGH Center for Women's Mental Health

Reproductive Psychiatry Resource and Information Center

### Dear Readers,

We are pleased to send you our second newsletter from the **Center for Women's Mental Health**. Previous issues are available on our website at <http://www.womensmentalhealth.org/>.

The current issue addresses new findings in the area of women's mental health and a perspective on these results which can help the clinician understand how these investigations and reports inform the care of patients. The field of reproductive psychiatry continues to grow and more data are now available across a range of areas. The newsletter extends the mission of the Center which is to provide the best information to clinicians and patients and a context for understanding how new findings help us to chart a clinical course with respect to treatment of patients.

Sincerely,

Lee S. Cohen, MD

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## Mission Statement

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The mission of **The Center for Women's Mental Health** is to provide state-of-the-art evaluation and treatment to women who suffer from a spectrum of psychiatric disorders, including premenstrual dysphoric disorder, mood and anxiety disorders during pregnancy and the postpartum period, and peri- and post-menopausal depression. At the Center, internationally renowned clinician-researchers focus on the diagnosis, treatment and prevention of psychiatric disorders affecting women. Providing accurate information to patients and caregivers informs and improves care.

The **Reproductive Psychiatry Resource and Information Center** was developed as a means of providing up-to-date information to patients and caregivers in the rapidly evolving field of women's mental health. The primary goals of this internet-based resource are to disseminate current research findings in this field, to help women make informed decisions regarding their care, and to facilitate collaborative decision-making between patients and their caregivers.

## The Use of Lamotrigine During Pregnancy

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Early reports suggest that women with bipolar disorder may be at lower risk for onset or relapse of this disorder during pregnancy and that some women are able to remain well during pregnancy despite medication discontinuation. However, more recent studies suggest that persistence of affective illness during pregnancy is relatively common among women with bipolar disorder. Dr. Adele Viguera and her colleagues at the Center for Women's Mental Health report that among pregnant bipolar women, relapse rates were very high (58%) in those women who discontinued maintenance treatment with lithium during pregnancy ([Viguera et al 2000](#)).

Maintenance treatment with a mood stabilizer during pregnancy can significantly reduce the risk of relapse; however, many of the medications commonly used in this setting, including lithium and valproic acid, carry some degree of teratogenic risk. First trimester exposure to lithium has been associated with an increased risk of cardiovascular malformation estimated to be between 1 in 2000 (0.05%) and 1 in 1000 (0.1%) ([Cohen et al, 1994](#)). The anticonvulsant valproic acid carries a much higher risk of teratogenesis, with rates of neural tube defect ranging from 1 to 8%. Prenatal exposure to valproic acid has also been associated with characteristic craniofacial abnormalities, cardiovascular malformation, limb defects and genital anomalies, as well as other central nervous system structural abnormalities. While other anticonvulsants are being used with increasing regularity for the treatment of bipolar disorder, i.e. tiagabine, oxcarbazepine, there is limited information with respect to the reproductive safety of these agents.

Recently information has been published that suggests that lamotrigine (Lamictal) may be another option for women with bipolar disorder who are planning pregnancies. The International Lamotrigine Pregnancy Registry was created by GlaxoSmithKline (GSK) in 1992 to monitor pregnancies exposed to lamotrigine for the occurrence of major birth

defects. A preliminary report from the registry included data from 334 pregnancies exposed to lamotrigine monotherapy (n=168) or polytherapy (n=166) during the first trimester ([Tennis et al, 2002](#)). Data were collected prospectively, and health care providers voluntarily reported exposures to the registry before pregnancy outcomes were known. (The majority of women included in this study were treated for epilepsy.) Data on outcomes were obtained through subsequent follow-up with the reporting health care provider. This preliminary study reported no increase in risk for major malformation in the children exposed to lamotrigine monotherapy.

In a subsequent report released by GlaxoSmithKline in March 2004, data on 599 pregnancy outcomes was presented. (A copy of this report can be obtained from GlaxoSmithKline at 800-336-2176.) The registry identified 684 pregnancy outcomes exposed to lamotrigine monotherapy (n=414) or polytherapy (n=270) during the first trimester. The percentage of infants with major birth defects exposed to lamotrigine monotherapy was 2.9%. In the 88 children exposed to lamotrigine polytherapy with valproic acid, 11 children (12.5%) presented with major birth defects. In contrast, of the 182 children exposed to lamotrigine polytherapy with an anticonvulsant other than valproic acid, 5 children (2.7%) presented with major birth defects. No specific patterns of major birth defects in any treatment subgroup or within the registry as a whole were observed.

As the sample sizes for individual treatment groups were small, it is not possible to rule out a small increase in the overall rate of major malformations. Even significant increases in the frequency of a rare major birth defect may not be detected with this sample size. However, the percentage of infants with major birth defects after exposure to lamotrigine monotherapy in this study did not differ significantly from the reported incidence of major malformations among women with no known exposure to a teratogen (estimated to be between 2 and 3% in the United States). However, the frequency of major malformations after fetal exposure to lamotrigine and valproic acid was significantly higher than in children exposed to lamotrigine monotherapy or lamotrigine polytherapy with an anticonvulsant other than valproic acid. This increase in risk may be a result of exposure to valproic acid which is a known teratogen. Alternately, this finding may be attributed to the use of multiple anticonvulsants, as anticonvulsant polytherapy has been observed to increase the overall incidence of major malformations.

Although more data are essential to better understand the reproductive safety of lamotrigine, these preliminary data are encouraging. This agent may prove to be an attractive alternative to other mood stabilizers for women who are planning a pregnancy. Data on other anticonvulsants remains sparse. The North American Anti-Epileptic Drug Pregnancy Registry (<http://www.aedpregnancyregistry.org>) is currently collecting data on pregnancy outcomes in children exposed to anticonvulsants. Pregnant patients who are currently taking an anticonvulsant for any reason, can enroll in the Registry by calling TOLL FREE 1-888-233-2334.

Ruta M. Nonacs, MD PhD

[Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk of in utero exposure to lithium. JAMA. 1994 Jun 15;271\(23\):1828-9.](#)

[Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry. 2001 Oct;158\(10\):1741-2.](#)

[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.](#)

## Recent Antidepressant Label Changes

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In October, the Food and Drug Administration (FDA) ordered drug manufacturers to include warnings in the packaging inserts regarding the use of certain antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) and venlafaxine (Effexor), during pregnancy. The labels now describe a spectrum of adverse events in newborns exposed to these drugs late in the third trimester, including jitteriness, irritability, hypoglycemia (low blood sugar), feeding difficulties, respiratory distress, abnormal muscle tone, and constant crying. Complications requiring "prolonged hospitalization, respiratory support and tube feeding" are also mentioned.

What prompted these label changes were post-marketing adverse event reports submitted to the FDA over the past several years, suggesting a constellation of symptoms associated with third trimester exposure to antidepressants. Because these reports do not come from controlled studies, it is impossible to know with certainty 1) how common they are or 2) whether they are secondary to exposure to the medicine. Some of the symptoms—such as jitteriness, irritability, and feeding difficulties—are consistent with anecdotal reports and case series reported in the literature. More recently, several controlled studies have demonstrated lower APGAR scores and higher rates of jitteriness and tremulousness in children exposed to SSRIs in utero ([Casper 2003](#), [Laine et al. 2003](#), [Simon et al. 2002](#), [Zeskind and Stephens 2004](#)). But more serious problems such as prolonged hospitalization and the need for respiratory support are not well supported by any objective data in the medical literature. Listing these purported treatment emergent adverse events in the medication label may cause alarm to patients and physicians and may limit use of these agents not only during the peripartum period but during other times across pregnancy.

The package label also now advises physicians to "carefully consider the potential risks and benefits of treatment" in patients and suggests that clinicians should consider tapering or discontinuing the medicine late in the third trimester before labor and delivery. The wisdom of taper or discontinuation of an antidepressant during this critical time may be lacking when risk for relapse among women who discontinue antidepressants during pregnancy is high and when it appears that depression during pregnancy is one of the strongest predictors of postpartum depression. Furthermore, there are no data to suggest that drug taper near term attenuates risk for the symptoms described in the newborn.

The labeling changes will likely create alarm about a potential clinical syndrome that has an extremely low incidence and modest clinical significance. While it is possible that some children may experience adverse events subsequent to delivery, it is important to put these concerns into a larger context. Reassuringly, the reported adverse events appear to be relatively short-lived and rarely require any type of medical intervention. Furthermore, there is no indication of longer-term problems in children exposed to SSRIs during pregnancy ([Casper 2003](#), [Laine et al. 2003](#), [Nulman et al. 2002](#), [Nulman et al. 1997](#), [Simon et al. 2002](#)).

Clinicians faced with the clinical decision of whether or not to treat depression during pregnancy should weigh the risks and benefits of antidepressant use versus the risks of untreated psychiatric disorder. At this point, no psychotropic drug is approved for use in pregnancy, and decisions about using these medicines are made on a case-by-case basis.

For women who have experienced depression during pregnancy, particularly those who have had residual symptoms of depression, discontinuing antidepressant therapy proximate to delivery may lead to significant worsening or relapse of depression. These risks should be discussed with patients in the context of the patient's individual clinical situation. Only in that context can truly thoughtful treatment decisions be made pending better controlled data.

Lee S. Cohen, MD  
Ruta M. Nonacs, MD, PhD

[Casper RC et al. 2003. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. J Pediatrics 142: 402-8.](#)

[Laine K, Heikkinen T, Ekblad U, Kero P. 2003. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. Arch Gen Psychiatry 60: 720-6.](#)

[Nulman I, Rovet J, Stewart DE, Wolpin J, Pace-Asciak P, Shuhaiber S, Koren G. 2002. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 159: 1889-95.](#)

[Nulman I, Rovet J, Stewart D, Wolpin J, Gardner HA, et al. 1997. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 336: 258-62.](#)

[Simon GE, Cunningham ML, Davis RL. 2002. Outcomes of prenatal antidepressant exposure. Am J Psychiatry 159: 2055-61.](#)

[Zeskind P, Stephens L. 2004. Maternal Selective Serotonin Reuptake Inhibitor Use During Pregnancy and Newborn Neurobehavior. Pediatrics 113: 368-75.](#)

## **New Research at the CWMH: Polycystic Ovarian Syndrome Associated with Valproate Use**

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Polycystic ovarian syndrome (PCOS) occurs in 4-7% of women and is characterized by irregular menstrual cycles and hyperandrogenism (facial hair, male-pattern hair loss, acne, or elevated male hormone levels). The majority of women with PCOS also suffer from obesity and insulin resistance. PCOS has been associated with a spectrum of health problems including infertility, diabetes, and possibly heart disease and endometrial cancer. Recently there has been concern that women with bipolar disorder who are treated with the mood stabilizer valproate (VPA), marketed as Depakote, may be at higher risk for PCOS, although the data have been somewhat conflicting.

In a recent study from Dr. Hadine Joffe at the Center of Women's Mental Health, the incidence of PCOS was studied in a group of women with bipolar disorder (ages 18-45) who had received treatment with a mood stabilizer (valproate, carbamazepine, lithium, lamotrigine, topiramate, gabapentin, or oxcarbazepine) for at least 3 months. 229 women were evaluated for treatment-emergent PCOS, which included retrospective assessment of menstrual cycle patterns and menstrually timed assays of serum hormone levels.

Of the 86 VPA users, 9 (10.5%) developed PCOS, as compared to 2 of the 144 (1.4%) VPA non-users. This represents a 7.5-fold increase in risk for PCOS among VPA users. Menstrual irregularity emerged early, developing within 3 months in half of the women. At higher risk for PCOS were women who started treatment with VPA at an earlier age. Ultrasound examination of the ovaries revealed that valproate use was not associated with

typical polycystic ovarian morphology.

PCOS appears to be more common among bipolar women treated with valproate, occurring in approximately one out of every 10 women. Symptoms of PCOS tended to emerge early, often within the first three months of treatment. Given the spectrum of health problems associated with PCOS and the unclear reversibility of this syndrome, the use of valproate in women with bipolar disorder must be considered carefully. Women treated with valproate must be informed of their risk for PCOS and should be monitored for signs of PCOS, especially during the first year of valproate use. Weight change, menstrual irregularity, excess facial hair, male-pattern hair loss and acne are signs that should alert the clinician to the possibility of treatment-emergent PCOS.

Ruta M. Nonacs, MD PhD

These data were presented as a poster at the 2004 Annual Meeting of the American Psychiatric Association. The complete [poster](#) can be viewed here.

### Patient Corner: Is Wellbutrin Safe During Pregnancy?

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**Q. I have a long history of depression and have been taking Wellbutrin (bupropion SR) for several years now. Every time I try to come off the medication, the depression comes back. I am planning to get pregnant within the next year and was wondering if it is safe to use Wellbutrin.**

A. While there is information to support the reproductive safety of certain antidepressants, including fluoxetine, citalopram and the tricyclic antidepressants, during pregnancy, there are much less data on the reproductive safety of bupropion (Wellbutrin). Information from the manufacturer (GlaxoSmithKline) includes data from 426 pregnancies involving first trimester exposure to bupropion. In this sample, there were 12 outcomes that involved major malformations. This represents a 2.8% risk of congenital malformation, which is consistent with what is observed in women with no known history of medication exposure. While this information regarding the overall risk of malformation associated with fetal exposure to bupropion is reassuring, the most recent report revealed that 8 of the 12 cases reported involve malformations of the heart and great vessels. In addition, among the 16 retrospectively reported cases of malformations in bupropion-exposed infants, seven involved cardiac defects. While these reports may signal a potential risk, the manufacturers point out that the relatively small sample size and the high percentage of cases lost to follow-up (n=302) make it difficult to draw solid conclusions regarding the impact of bupropion on the developing cardiovascular system; further studies regarding the reproductive safety of this medication are warranted.

**Clinical Implications:** Given the incomplete nature of these findings, women may want to switch to the better characterized SSRIs or a tricyclic antidepressant during plans to conceive. However, there may be certain situations when it is appropriate to use this medication during pregnancy. If a woman has had a poor response to SSRIs in the past but has had a good response to bupropion, it may be clinically thoughtful to consider bupropion treatment during pregnancy. However, this is done, of course, in the context of an informed conversation between the patient and her doctor, acknowledging the lack of extensive information regarding the reproductive safety of this agent. It is important to remember that

untreated depression in the mother is not benign and may contribute to maternal psychiatric morbidity both during pregnancy and the postpartum period.

Ruta Nonacs, MD PhD

Information regarding the use of bupropion during pregnancy may be obtained from the manufacturer at 1-800-336-2176.

For other Frequently Asked Questions, please visit our [FAQ page](#).

## Research Studies

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### Postpartum Depression

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

Contact: Kim Kelly, (617) 724-6540 or [kkelly11@partners.org](mailto:kkelly11@partners.org)

### Breastfeeding and Psychiatric Medications

Are you breastfeeding and taking psychiatric medications?

Contact: Juliana Mogielnicki, (617) 724-6989 or [jmogielnicki@partners.org](mailto:jmogielnicki@partners.org)

### PMS and Depression

Do you experience symptoms such as depression, anxiety, and/or irritability before your period?

Contact: Hannah Gottschall, (617) 726-2912 or [hgottschall@partners.org](mailto:hgottschall@partners.org)

### PMS and Bipolar Disorder

Have you been diagnosed with bipolar disorder and have premenstrual worsening of mood symptoms?

Contact: Hannah Gottschall, (617) 726-2912 or [hgottschall@partners.org](mailto:hgottschall@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: Revital Yehezkel, (617) 724-1181 or [ryehezkel@partners.org](mailto:ryehezkel@partners.org)

### Perimenopause and Insomnia

Are you a perimenopausal woman with irregular periods? Are you having trouble falling asleep at night? Feeling tired?

Contact: Revital Yehezkel, (617) 724-1181 or [ryehezkel@partners.org](mailto:ryehezkel@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: Juliana Mogielnicki, (617) 724-6989 or [jmogielnicki@partners.org](mailto:jmogielnicki@partners.org)

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