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Dear Readers,

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

This Winter 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. The newsletter addresses how new findings from these investigations may inform clinical care of patients.

Our newsletter attempts to bridge the gap between data emerging from new investigation and the clinical implications of such studies. 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.

Sincerely,
Lee S. Cohen, MD

Reviewing the Safety of SSRI's in Pregnancy

Over the past 15 years, multiple studies have addressed the reproductive safety of the selective serotonin reuptake inhibitors (SSRIs). Data on the overall teratogenicity of SSRIs come from relatively small cohort studies and larger international programs, and they have cumulatively supported the reproductive safety of fluoxetine (Prozac) and certain other SSRIs. However, several recent studies have raised concerns regarding the use of SSRIs during pregnancy.

In a study presented at the annual meeting of the Teratology Society in June, investigators from the University of British Columbia, Vancouver analyzed data from the National Birth Defects Prevention study (Alwan et al, 2005). In this case control study 5,357 infants with selected major birth defects were compared with 3,366 normal controls, and their mothers were interviewed regarding exposures during pregnancy and other possible risk factors for major malformations. The investigators found an association between exposure to an SSRI during the first trimester and a three-fold increased risk of omphalocele. The strongest effect was observed with paroxetine, which accounted for 36% of all SSRI exposures and was

associated with a 6.4-fold increase in risk for omphalocele. (Omphalocele, an abnormality in which the infant's intestines or other abdominal organs protrude from the navel, occurs in approximately 1 out of every 4,000 births.) For women who used SSRIs during the first trimester, the risk of giving birth to an infant with craniosynostosis was 1.8 times higher. (Craniosynostosis occurs when the bones in an infant's skull fuse prematurely, resulting in a malformation of the skull; its prevalence in the general population has been estimated to be 1 per 2,200 births.) No association was noted between SSRI use and any of the other classes of major malformations studied.

In an unpublished report from GlaxoSmithKline, the manufacturer of paroxetine as Paxil, data derived from an HMO claims database were used to estimate risk of major malformations in children exposed to SSRIs and bupropion (Wellbutrin). A preliminary analysis was recently conducted which demonstrated a 2.2-fold increase in risk for congenital malformations as a whole and a 2.08-fold increase in risk for cardiovascular malformations in infants exposed to paroxetine, as compared to children exposed to the other antidepressants in the database. The majority of cardiovascular malformations observed in paroxetine-exposed children were ventral septal defects. When the study was updated to include a larger sample, now including 5956 infants born to 5791 women, the risk of major malformation appeared to be somewhat lower than originally calculated. The updated analysis demonstrated a 1.8-fold increase in overall risk of malformations and showed a trend toward an increased risk for cardiovascular malformation (odds ratio of 1.54) in paroxetine-exposed infants. The prevalence of congenital malformations as a whole and cardiovascular malformation alone were approximately 4% and 1.5%, respectively (see communication, [GlaxoSmithKline](#), December 2005).

In another preliminary report, presented at the 21st International Conference of Pharmacoepidemiology and Therapeutic Risk Management, Wogelius and colleagues (2005) studied pregnancy outcome in women (n=1054) who filled a prescription for SSRIs from 30 days before conception to the end of the first trimester, as compared with women with no SSRI prescriptions during this period (n=150,908). The investigators observed a 1.4 fold increase in risk for major malformations as a whole and a 1.6 fold increase for cardiovascular malformations among the infants born to women who filled a prescription for SSRIs, as compared to women who did not. (Paroxetine-specific data were not presented in this report.)

While an earlier report from the Swedish Medical Birth Registry, including 709 children exposed to paroxetine, did not demonstrate an increased risk of major malformations among children exposed *in utero* to paroxetine or other SSRIs (Hallberg & Sjoblom, 2005), the most recent analysis of this registry has suggested an increased risk of cardiovascular malformation in infants exposed to paroxetine (see communication, [GlaxoSmithKline](#), December 2005). This analysis assessed outcomes in 5,175 infants born to mothers taking SSRIs in early pregnancy and included 822 exposed to paroxetine. The overall prevalence of major malformations in the paroxetine-exposed infant was 4.9%, which did not differ significantly from the rate (4.8%) observed in unexposed infants. There was, however, a 1.78-fold increased risk of cardiovascular malformation in paroxetine-exposed children; the majority of these defects were ventricular or atrial septal defects. Infants exposed to other SSRIs did not have an increased risk of cardiac defects.

These recent findings of increased risk with prenatal paroxetine exposure are inconsistent with earlier findings. Ericson and colleagues published a study which included 122 paroxetine-exposed infants and demonstrated no difference in the rates of major malformations between paroxetine-exposed infants and controls (Ericson et al, 1999).

Similarly, another report including 97 paroxetine-exposed infants did not show an association between paroxetine exposure *in utero* and an increased risk of malformation (Kulin et al, 1998). These reports are complemented by a recent meta-analysis conducted by researchers at the [Motherisk Program](#) in Toronto; an analysis of seven prospective studies including a total of 1774 infants exposed to newer antidepressants *in utero* suggests that the newer antidepressants are not associated with an increased risk of major malformations above the baseline risk (Einarson et al, 2005).

This volley of conflicting reports has left many clinicians confused and uncertain about how to counsel their patients regarding the use of SSRIs during pregnancy. The differences in the results from the available studies and the diversity in the types of abnormalities reported make it difficult to definitively draw a causal link between paroxetine exposure and any particular congenital abnormality. While the recent studies raise concerns, it is important to note their limitations. Several of these studies use data from prescription databases, where it is not known whether the mothers actually took the medication in question. Furthermore, the data may be confounded by the use of other medications during pregnancy. Also complicating the matter is the fact that these data are preliminary; re-analysis of these data has often yielded findings that are significantly different from the original reports.

While there is clearly a need for more thorough analysis of the existing data, these reports, taken together, may signal an increase in risk of malformations in children exposed to paroxetine. However, it is important to put this risk in perspective. Even if we assume the associations from the new case-control study are true, a 6.4-fold increase in risk for omphalocele translates into an absolute risk of only 0.16% (approximately 2 out of every 1,200 births). Absolute risk is of far greater clinical value than relative risk and should be taken into consideration before patients are arbitrarily counseled to discontinue antidepressants during pregnancy.

The new findings are not necessarily cause for alarm. Patients who are planning to conceive and are at significant risk for depressive relapse in the setting of antidepressant discontinuation may benefit from using an antidepressant for which there are more data supporting reproductive safety. These include fluoxetine and citalopram, as well as the older tricyclic antidepressants. However, for women who present when pregnant and are still taking paroxetine, discontinuation should not be arbitrarily pursued. Abrupt discontinuation of antidepressants can threaten maternal affective well-being and may increase the likelihood of postpartum depression. If, after having a discussion with her physician, a woman does decide that she wants to discontinue paroxetine, the drug should be slowly tapered off over a number of weeks.

Lee S. Cohen, MD
Ruta Nonacs, MD PhD

"Dear Doctor" Letter to Canadian practitioners from GlaxoSmithKline and Health Canada:
[December 16, 2005](#)

"Dear Doctor" Letters from GlaxoSmithKline: [September 2005](#) and [December 2005](#)

New [FDA Guidelines](#) concerning paroxetine during pregnancy (Issued September 2005)

[Einarson TR, Einarson A. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. Pharmacoepidemiol Drug Saf 2005; 14\(12 \): 823-827.](#)

Alwan S, Reefhuis J, Rasmussen S, et al. Maternal use of selective serotonin re-uptake inhibitors and risk for birth defects, (abstract). Birth Defects Research (Part A): Clinical and Molecular Teratology 2005;73:291.

[Hallberg P, Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. Journal of Clinical Psychopharmacology 2005; 25 \(1\): 59-73.](#)
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Wogelius P, Norgaard M, Muff Munk E, et al. Maternal use of selective serotonin reuptake inhibitors and risk of adverse pregnancy outcomes, (abstract). Pharmacoepidemiology and Drug Safety 2005;14:S143.

[Kulin NA, Pastuszak A, Sage S, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors - A prospective controlled multicenter study. JAMA 1998;279:609-610.](#)

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Atypical Antipsychotics during Pregnancy: What are the Risks?

Although primarily used to treat schizophrenia and other psychotic disorders, the newer "atypical" antipsychotic agents are now used widely to treat a spectrum of psychiatric disorders, including major depression, bipolar disorder, PTSD and other anxiety disorders. While the reproductive safety of the older typical antipsychotic drugs, such as haloperidol (Haldol) and perphenazine (Trilafon), is supported by data accumulated over the past 40 years, we have far less data on the newer atypical agents: olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), and clozapine (Clozaril).

Thus far, most of the data on the reproductive safety of atypical agents has been limited to manufacturers' accumulated case series and spontaneous reports, which are inherently biased: people who experience a poor outcome or an adverse event are much more likely to report having used a particular medication than people who have not experienced any problems. Among the 242 reports of olanzapine-exposed pregnancies collected by the manufacturer, there was no increase in risk of major malformations above baseline. Of 523 clozapine-exposed pregnancies, there were reported 22 "unspecified malformations." In 151 reported quetiapine-exposed pregnancies, 8 infants were observed to have congenital anomalies. Eight malformations were reported among the infants born to approximately 250 women taking risperidone; however, pregnancy outcomes were not known in many of these cases reported to the manufacturer. Taken together, these reports do not suggest an increase in the risk of major malformation above the baseline 2% to 4% risk of malformations seen in the general population, nor do they indicate any specific pattern of abnormalities among drug-exposed infants. While this information has not suggested any particular concerns regarding the use of atypical antipsychotic drugs in pregnancy, we can make only limited conclusions based on this type of information.

The first published prospective study on the reproductive safety of the atypical agents comes from the [Motherisk Program](#) in Toronto and provides some reassuring data regarding the risk of malformations in infants exposed to these drugs. (McKenna et al, 2005) In this study, investigators prospectively followed a group of women taking olanzapine (n=60), risperidone (n=49), quetiapine (n=36), or clozapine (n=6) during pregnancy. All of the 151 women completing the study had taken one of these agents during the first trimester, and 48 were exposed to drug throughout the pregnancy. A comparison group of 151 healthy pregnant women who had been exposed to non-teratogenic agents (including hair dyes, cold medications, antacids, antibiotics, acetaminophen, and antacids) were also followed.

More women in the exposed group elected to terminate their pregnancy (9.9%) than in the comparison group (1.3%); rates of spontaneous abortion were also higher in the exposed group (14.5%) than in the comparison group (8.6%), although this finding was not statistically significant. The rates of major malformations were not statistically different in the two groups; one child in the exposed group was born with a malformation (0.9%) versus two (1.5%) in the comparison group. There were no differences between the two groups in terms of mean gestational age or birth weight; however, 10% of the exposed infants were low birth weight, as compared to only 2% of the comparison group. (This finding may be attributed to differences in lifestyle characteristics between the two groups; the exposed women were more likely to smoke and to use alcohol and were less likely to take vitamins.) There were no differences between the two groups in rates of complications at labor or neonatal complications.

This study did not evaluate the long-term neurobehavioral effects of exposure to these agents. The study is also limited by its small sample size; the authors estimate that approximately 800 pregnancies would be required in each group in order to detect a two-fold increase in the risk of relatively common malformations. Still, this is the first prospective study that complements existing reports from the manufacturers. Although this study is encouraging, given the prevalence of reproductive-age women taking these agents, it would be ideal if the industry carried out post-marketing studies to provide the number of cases needed to reliably estimate risk. Such studies may soon be mandated by the Food and Drug Administration.

Decisions regarding the use of these and other psychotropic drugs must be made on a case-by-case basis. Given the limited data regarding the reproductive safety of the atypical agents, patients taking an antipsychotic drug may choose to discontinue their medication or to switch to a better characterized conventional anti-psychotic agent, like perphenazine or haloperidol. However, many women do not respond as well to the typical agents or have such severe illness that making any change in their regimen may place them at significant risk. While the Motherisk data are not a guarantee of safety, they do provide information in combination with the manufacturers' data that is moderately reassuring. Thus, women and their clinicians may choose to use atypical agents during pregnancy in order to sustain functioning, while acknowledging information regarding their reproductive safety remains incomplete.

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

[McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, et al. \(2005\). Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J. Clin. Psychiatry 2005;66\(4\):444-9](#)

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New Research from the CWMH

Escitalopram for Menopause-Related Depression and Vasomotor Symptoms

Every year more than 1.7 million women in the United States enter into menopause. During this time of hormonal fluctuations it is typical for women to experience hot flashes, night sweats and sleep disturbance. More recently, studies have identified an association between menopausal transition and an increased risk for developing depressive symptoms (Harlow et al., 2003; Freeman et al., 2004). It is not clear how physicians and patients should deal with menopause-related physical and emotional symptoms. While hormone therapy effectively treats insomnia and hot flashes, the results have been mixed in treating mood and anxiety symptoms. Moreover, the safety of long-term use of hormone therapy is not known.

In a recent study from Dr. Claudio Soares at the Center for Women's Mental Health, preliminary data suggest that antidepressants may effectively treat menopause-related depressive symptoms as well as vasomotor symptoms (Soares et al., 2005). In this study, 38 women between the ages of 40 and 60 (15 peri-menopausal and 23 post-menopausal) with depressive disorders were randomized to receive open treatment with either escitalopram (flexible dosing of 10-20mg) or hormone therapy (norethindrone acetate and ethinyl estradiol). The Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess the severity of depressive symptoms. Improvement in quality of life was also measured in both treatment groups.

After 8 weeks, full remission of depression (defined as MADRS score < 10) was observed in 75%(12/16) of subjects treated with escitalopram versus 25% (4/16) treated with hormone therapy. Both treatment groups showed significant improvement of vasomotor symptoms, sleep and quality of life. Ten of the 12 non-responders to hormone therapy received a trial of hormone therapy plus escitalopram. After this 8-week extension phase, 60% (6/10) of the women achieved remission of depression with the addition of escitalopram.

As significant improvements in depressive symptoms, quality of life and vasomotor symptoms were noted in both treatment groups, escitalopram may constitute an interesting treatment option for symptomatic menopausal women who are unable or unwilling to receive treatment with hormone therapy. Further research will examine the characteristics of symptomatic menopausal women who could better benefit from hormonal or non-hormonal interventions.

Maria Houghton, BA
Claudio Soares, MD, PhD

These data were presented as a poster at the
2004 Annual Meeting of the American Psychiatric Association.
Click here to view the [poster](#) presented by Dr. Claudio Soares.

[Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. \(2004\). Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 61\(1\): 62-70.](#)

[Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. \(2003\). Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry 60\(1\): 29-36.](#)

[Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL, Cohen LS. \(2003\). Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. J Clin Psychiatry 64\(4\): 473-9.](#)

[Soares CN, Joffe H, Steiner M. \(2004\). Menopause and mood. Clin Obstet Gynecol 47\(3\): 576-91.](#)

[Soares CN, Prouty J, Born L, Steiner M. \(2005\). Treatment of menopause-related mood disturbances. CNS Spectr 10\(6\): 489-97.](#)

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Patient Corner: Breastfeeding and Lamotrigine

Q. I have bipolar disorder and am now about 24 weeks pregnant. I tried to go off my medications during the first trimester but had a severe episode of depression and had to restart my medications. I am now taking Lamictal 300 mg/day and am doing well. I would very much like to breastfeed after delivery, and I was wondering what information you have regarding Lamictal and breastfeeding.

A. Because rates of postpartum illness are very high in women with bipolar disorder, it is generally recommended that mothers continue treatment with a mood stabilizer throughout the postpartum period to reduce their risk of relapse; however, the use of medications during the postpartum period is complicated by the issue of breastfeeding. All medications are secreted into the breast milk, although their concentrations appear to vary (Chaudron and Jefferson, 2000).

Several recent studies have suggested that lamotrigine reaches infants through breastmilk in relatively high doses. One study of four mother-infant pairs reported lamotrigine levels in infant serum that were 20-43% of levels found in the mothers' serum; in this study, infants were tested at 10 days of age and at two months (Liporace, 2004). Unpublished preliminary research from Dr. Adele Viguera at the Center for Women's Mental Health has found infant Lamictal levels ranging from 20-30% of the mothers' serum concentrations in a sample of three nursing infants. Another study, reporting on nine breastfeeding mother-infant pairs, yielded similar results; infant serum levels ranged from 23 to 50% of levels found in the mothers' serum (Ohman et al, 2000). These higher than expected levels of lamotrigine in the infants may be explained by poor neonatal metabolism of lamotrigine. It was also noted that maternal serum levels of lamotrigine increased significantly after delivery, and this may have also contributed to the high drug levels seen in the nursing infants. Despite the relatively high levels of medication found in these infants, none of these studies reported any adverse events in the breastfeeding newborns.

One worry shared by clinicians and new mothers is the risk for Stevens-Johnson syndrome (SJS). This is a severe, potentially life-threatening rash, most commonly resulting from a hypersensitivity reaction to a medication, which occurs in about 0.1% of bipolar patients treated with lamotrigine (Goldsmith et al, 2004). Thus far, there have been no reports of SJS in infants associated with exposure to lamotrigine. In fact, it appears that cases of drug-induced Stevens-Johnson syndrome are extremely rare in newborns. In a single case report, authors described a neonate developing the syndrome after exposure to the anticonvulsant phenobarbital (Oles and Gal, 1982).

More research is required to assess the safety of lamotrigine in nursing infants, and decisions regarding the use of this drug in breastfeeding women involves a careful consideration of the risks and benefits of using this medication. For women with bipolar disorder, breastfeeding raises concerns for another reason. Nursing a young infant requires multiple feedings during the night. Sleep deprivation is destabilizing for those with bipolar disorder and may help to precipitate a relapse during this vulnerable time. Thus for women with bipolar disorder, we recommend that somebody else take over the nighttime feedings in order to protect the mother's sleep and to increase her chances of staying well. For mothers who choose to breastfeed while taking lamotrigine (or any other mood stabilizer), the child should be monitored closely for signs of toxicity. Breastfeeding is usually avoided when the baby is premature or has signs of hepatic immaturity (hyperbilirubinemia), which may make it

more difficult for the infant to metabolize the medication to which he or she is exposed. Premature babies are also probably more vulnerable to the toxic effects of these medications. Measurement of the mother's and infant's serum drug levels may be helpful when evaluating the extent of drug exposure.

Juliana Mogielnicki, BA
Ruta Nonacs, MD, PhD

[Chaudron LH, Jefferson JW. Mood stabilizers during breastfeeding: a review. J Clin Psychiatry. 2000 Feb;61\(2\):79-90. Review.](#)

[Liporace J, Kao A, D'Abreu A. Concerns regarding lamotrigine and breast-feeding. Epilepsy & Behavior 2004; 5:102-5.](#)

[Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsia 2000; 41:709-13.](#)
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[Oles K, Gal P. Stevens-Johnson syndrome associated with anticonvulsant therapy in a neonate. Clin Pharm 1982; 1:565-7.](#)

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Current Research Studies

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: Kim Kelly at (617) 724-6540 or kkelly11@partners.org

Breastfeeding and Psychiatric Medications

Are you breastfeeding and taking psychiatric medications?

Contact: Juliana Mogielnicki at (617) 724-6989 or jmogielnicki@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 at (617) 724-6989 or jmogielnicki@partners.org

PMS and Bipolar Disorder

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

Contact: Maya Rydzewski at (617) 643-3078 or mrydzewski@partners.org.

Depression in Post-Menopausal Women

If you are a post-menopausal woman who is feeling depressed or down and has not had a menstrual period in the past year, you may be eligible to participate in a research study evaluating how a non-hormonal medication helps with depression and menopausal symptoms.

Contact: Brittany Somley at (617) 724-1181 or bsomley@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: Maya Rydzewski at (617) 643-3078 or mrydzewski@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: Brittany Somley at (617) 724-1181 or bsomley@partners.org.

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