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Psychotropics and Pregnancy: An Update

Every month seems to bring a new FDA advisory or an alarming research finding about the use of medications in pregnancy. In this article, we update you on what we consider to be the most important developments over the past couple of years.

Antipsychotics

A new study is reassuring on atypicals. That great engine of teratogen information, Toronto's Motherisk Program, recently published an informative study of exposure to atypical antipsychotics. Researchers identified 151 pregnant women who were taking atypical antipsychotics and compared them to a matched control group of 151 unexposed pregnant women. Atypicals represented included the following medications: Zyprexa (N = 60), Risperdal (N = 49), Seroquel (N = 36), and clozapine (N = 6). The group reported that rates of major malformations were not different between the two groups (0.9% in the exposed group versus 1.5% in the nonexposed group). There were also no significant differences in premature birth, weight at birth, or obstetrical complications (McKenna et al., *J Clin Psychiatry* 2005;66:444-449).

Experts have generally considered conventional antipsychotics, particularly Haldol (haloperidol), Prolixin (fluphenazine), and Thorazine (chlorpromazine),

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Focus of the Month:
Pregnancy and Menopause in Psychiatry

Prescribing Medications during Pregnancy and Breastfeeding

By Leslie Hartley Gise, M.D.

Clinical Professor of Psychiatry, John A. Burns School of Medicine, University of Hawaii, and Staff Psychiatrist, Maui Community Mental Health Center

Over the last several years, we've all seen many FDA warnings and cautionary letters from drug companies about the effects of psychotropics in pregnancy. As a result, it's easy to become a little skittish about prescribing any medication for pregnant women.

I have worked in the field of women's mental health for more than 25 years, and over this time I have developed certain common-sense practices that have served most of my patients well.

Assess the possibility that your patient is pregnant. When presented with a distressed patient, we don't always think of the risk of pregnancy. But half of pregnancies are unintended, so we must assess the risk of pregnancy for all women of childbearing age. For example: Is she trying to get pregnant? Is she doing anything not to get pregnant? Did she have her tubes tied? This gives us the opportunity to discuss psychotropics before pregnancy or when psychotropics are first prescribed.

Every patient requires an individual risk/benefit analysis. No psychotropics are safe in pregnancy, so I never use the word "safe." None have been tested or approved by the Food and Drug Administration for use during pregnancy, and the FDA ratings are not useful because they are based on missing data. What I talk about is which medications we have more experience with and the rates of problems that have been reported. I also inform my patients that untreated psychiatric problems pose their own risks to fetal well-being, and that this must be balanced against the risks of medications.

Try to avoid any medications during the first trimester of pregnancy. During

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Dr. Gise has disclosed that she is on the medical advisory board of Medco Health Solutions, a pharmacy benefits manager. She has no significant relationships with or financial interests in any pharmaceutical company pertaining to this educational activity.

Learning objectives for this issue: 1. Cite the most important recent developments in the safety of psychotropics in pregnancy. 2. Outline a practical approach for prescribing in pregnancy. 3. Describe the data regarding depression during perimenopause.

This CME activity is intended for psychiatrists, psychiatric nurses, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Psychotropics and Pregnancy: An Update

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to be relatively safe, based largely on older studies of pregnant women who took these meds for the treatment of hyperemesis gravidarum (for a good review of this data, see *Psychiatry* 2005;2(8):36-44). This new data implies that Zyprexa, Seroquel, and Risperdal are relatively safe. We have less data on Abilify and Geodon.

Antidepressants

Neonatal SSRI syndrome. SSRIs are associated with a "neonatal SSRI syndrome" of jitteriness, irritability, increased muscle tone, and respiratory distress. Nobody knows for sure whether this represents SSRI withdrawal or toxicity. A meta-analysis of studies indicated that 30% of infants exposed to SSRIs in the third trimester get this syndrome, vs. about 8% of infants with no third-trimester exposure (Moses-Kolko et al., *JAMA* 2005;293:2372-2383). Neonatal syndrome does not appear to be a medically serious problem; none of the studied infants died, and all of them ended up going home with their mothers within a few days of birth, with no apparent long-term problems.

SSRIs and persistent pulmonary hypertension of the newborn. Every ten years, the epidemiologist Christina Chambers publishes bad news about SSRIs and pregnancy in the *New England Journal of Medicine*. It was her *NEJM* study in 1996 that first suggested that SSRIs (in that case, fluoxetine) may lead to perinatal complications (Chambers et al., *NEJM* 1996;335:1010-1015). Her latest salvo is a study linking SSRI exposure to persistent pulmonary hypertension of the newborn (PPHN) (Chambers et al., *NEJM* 2006;354:579-587). What is PPHN? It's a condition leading to significant shunting of blood flow away from the lungs; about 10% of infants with this condition die and half end up with major cognitive and neurological problems.

The Chambers PPHN study was a well-done case-control study. She and her colleagues identified 377 women across the United States and Canada whose infants had PPHN and matched them with a comparison group of 836 women with normal infants. They discovered that infants with PPHN were six times more likely than unaffected infants to have been exposed to SSRIs in the second half of the gestation. What does this mean in absolute numbers? The baseline population risk of PPHN is about 1.5 out of 1,000 births. Thus, if Chambers' estimate of a sixfold relative risk is accurate, about one out of a hundred, or 1%, of SSRI-exposed babies would be expected to develop PPHN. These are not reassuring odds!

However, this is the only study that has shown such an association. While statistically significant, it was based on only 14 infants who developed PPHN after late gestational SSRI exposure. Furthermore, the study did not control for maternal depression, which many authorities believe is a risk factor for birth defects in itself.

Thus, most experts are not advocating a huge change in your prescribing practices based on this data. As always, prudence dictates avoiding any medication in pregnancy if possible. But sometimes, the risk of a serious psychiatric relapse outweighs the risk of medication.

Teratogen Hotlines

Need teratogen info *now*? These two free hotlines are available. (I thank Michael Delollis, M.D., for telling me about these resources.)

1. Lactation Study Line—585-275-0088, Mon-Fri 10 AM-3:30 PM, EST. Operated and funded by the University of Rochester Medical Center in New York, this line is specifically for health care professionals. I called and spoke to a very knowledgeable Pharm.D. who gave me accurate information immediately.

2. OTIS (Organization of Teratology Information Services)—866-626-6847, hours Mon-Fri 9 AM-4 PM, MST. Web site: http://otispregnancy.org/. An excellent free service for patients as well as clinicians. The site provides dozens of fact sheets on the risks of various possible exposures during pregnancy. The hotline service faxed me helpful information within 48 hours.

Paxil is now *the* SSRI to avoid. Recently, two large databases reported risks of congenital heart defects with Paxil (paroxetine). In a Swedish birth registry, Paxil use was associated with double the risk of an atrial or septal cardiac birth defect. In a U.S. insurance claims database, Paxil incurred 1.5 times the risk of cardiac defects and 1.8 times the risk of overall birth defects. In response to these data, an advisory committee of the American College of Obstetricians and Gynecologists advised against use of Paxil in pregnancy (Committee Opinion No. 354, *Obstetrics & Gynecology* 2006; 108:1601-1604), and the FDA downgraded Paxil's pregnancy risk category to category D, the most risky category short of X (the FDA advisory, which summarizes this data, can be found by visiting: http://www.fda.gov/cder/drug/advisory/paroxetine200512.htm).

Mood stabilizers

Lithium may be safer than previously thought. The most serious risk of first-trimester lithium exposure is a cardiac valve defect called Ebstein's anomaly, a condition that carries a mortality rate of up to 50%. The baseline frequency of Ebstein's anomaly is one in 20,000. The most recent good review of all relevant studies pertaining to lithium in pregnancy was published a full 13 years ago (Cohen et al., *JAMA* 1994;271:146-150), but no further relevant exposure data has been generated since then. That review estimated that first trimester lithium use increases the risk of Ebstein's anomaly about tenfold, meaning that the absolute risk of lithium causing the defect is about one in 2,000. This is a very low risk, so most experts in the field of perinatal psychiatry will counsel patients to stay on lithium if a serious relapse is likely to occur off the drug. As usual, this is a judgment call.

Valproic acid is even more hazardous than previously thought. A recent study indicates that valproic acid (VPA; Depakote and others) is an even worse teratogen than previously thought. Researchers determined the Antiepileptic Drug

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Prescribing Medications during Pregnancy and Breastfeeding

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the first 13 weeks of pregnancy, the major organs systems are actively growing and differentiating, and the risk of malformations is highest. So I try to avoid prescribing any medication during this period. If insomnia is a problem, I discuss sleep hygiene with my patients and hand them a list of practices such as using the bed only for sleep, going to sleep at the same time each night, avoiding stimulating foods and beverages before bedtime, using relaxation exercises, etc. For depression or anxiety, I recommend psychotherapy, especially problem-focused techniques such as cognitive behavioral therapy or interpersonal therapy.

My favorite medication for depression or anxiety in pregnancy is sertraline (Zoloft). But pregnancy is not a time to experiment. So if a woman is stable on an antidepressant, I consider keeping her on it. We have the most data on sertraline, in both pregnancy and breastfeeding, and for this reason it is often my first choice when medication is needed (for an excellent review, see Wisner KL et al., *Am J Psychiatry* 2000;157(12)1933-1940). Fluoxetine (Prozac) has been taken by more women in pregnancy, but fluoxetine's long half-life is a disadvantage. First, with unintended pregnancy, if a woman decides to discontinue fluoxetine, the drug and its active metabolites will stay in the bloodstream for up to five weeks, while sertraline will be gone within 5 days. Second, for planned pregnancies, if we decide to taper before delivery to avoid neonatal withdrawal (see below), fluoxetine presents the same long half-life difficulty.

Nortriptyline is also on my short list of preferred medications, simply because we have 50 years of experience with it with no reports of teratogenicity. I prescribe it in low doses of 12.5 mg to 25 mg QHS for sleep or in higher doses (50 mg to 75 mg QD) for anxiety and depression.

If a patient on medication discovers that she is pregnant, I always try to reduce the dose of the medication. While I acknowledge that lowering the dose of medication risks triggering relapse, I would prefer to expose the fetus to the lowest level of a medication that is consistent with keeping my patient well. Often, over the course of this taper, we find that the patient can discontinue medication entirely, which is the best possible outcome.

I recommend continuing SSRIs until delivery. In 2005, the FDA required that all antidepressant makers insert a warning about the risk of a neonatal withdrawal syndrome of respiratory distress, jitteriness, and irritability. Since then, many patients have asked me if they should discontinue their medications one to two weeks before their due dates. I don't recommend this. I point out to patients that the symptoms are rarely serious, and that affected babies inevitably do fine once they go home. On the other hand, if the mother suffers a depressive relapse around delivery, she may develop full-blown postpartum depression, which can have drastic consequences for the baby's earliest experiences.

My Plan A for all patients on medications is to *not* breastfeed; Plan B is to use sertraline (Zoloft) over other antidepressants. Yes, breastfeeding is valuable, in terms of both optimal nutrition and mother-child bonding. But, particularly during the first month of life, medications in breast milk can pose unknown risks to an immature and developing brain. Furthermore, an immature liver and kidneys are poorer at eliminating even tiny amounts of medication. I believe these risks outweigh the benefits. For mothers on antidepressants who insist on breastfeeding, sertraline (Zoloft) has the most published data during breastfeeding (Altshuler L et al., *J Clin Psychiatry* 1995;56:243-245).

Breastfeeding should be discussed as soon as pregnancy is discovered, and the decision is whether or not to breastfeed, not whether or not to take medication. If the woman needs medication, she should take it.

Document. Psychotropic medications are both over-prescribed and under-prescribed in pregnancy. Many psychiatrists fear lawsuits and won't prescribe to pregnant women on that basis alone, although I have never heard of a successful lawsuit over an adverse pregnancy outcome related to psychotropics. The best defense against lawsuits is to have a risks-benefits discussion with the woman and her partner and to document this in the chart.

TCPR VERDICT: Avoid meds if possible; Zoloft may be safest.

Q&A With the Expert

This Month's Expert:

Louann Brizendine, M.D.

Treating Depression in Perimenopause

Founder, UCSF Women's Mood and Hormone Clinic
Lynne and Marc Benioff Clinical Professor of Psychiatry
Author, *The Female Brain*

Dr. Brizendine has disclosed that she has no significant relationships with or financial interests in any commercial companies pertaining to this educational activity. The author has disclosed that the estradiol patch has not been approved by the U.S. Food and Drug Administration for use in the treatment of depression. Please consult product labeling for the approved usage of this drug.

TCPR: Dr. Brizendine, as the director of the UCSF Women's Mood and Hormone Clinic, you receive many referrals of women who are having difficulty with menopause. What are the typical problems that women have during this period?

Dr. Brizendine: First, it's important to be clear about some definitions, because many people think of menopause as encompassing a several-year time span. In actuality, menopause lasts for one single day – the day 12 months after a woman has had her last period. After this, we use the term "postmenopausal." Perimenopause, which is also termed "the menopausal transition," refers to the several-year period leading up to menopause and usually begins in the mid 40s. Most of the troubling physical and psychological symptoms occur during perimenopause.

TCPR: Clinically, how do we determine if a woman is in perimenopause?

Dr. Brizendine: The first clue is a change in the menstrual cycle. Early in perimenopause, the menstrual cycle begins to shorten; and later, it lengthens progressively until there are no more periods. Physiologically, the ovaries are becoming progressively less responsive to gonadotrophic hormones such as FSH (follicular stimulating hormone). Estrogen levels go down, and this leads to the menstrual irregularities, as well as a host of perimenopausal symptoms such as hot flashes, night sweats, insomnia, vaginal dryness, and lowered libido.

TCPR: What is the connection between perimenopause and depression?

Dr. Brizendine: A number of studies have suggested that perimenopause is a trigger for depression in some women, even women who have had no prior history of depression at all. Most recently, for example, researchers from Harvard published a study in which they enrolled 460 premenopausal women who had no history of depression (Cohen L et al., *Arch Gen Psychiatry* 2006;63:385-390). These women were interviewed by researchers periodically for the next several years, allowing them to ascertain correlations between onset of perimenopause and onset of psychiatric symptoms.

"Up to 50% of women who have a depression during perimenopause never had depression before. Therefore, we believe that hormonal treatments are appropriate, and I usually prescribe the estradiol patch, either with or without antidepressants."

– Louann Brizendine, M.D.

TCPR: And what did they find?

Dr. Brizendine: They found that women who entered perimenopause during the study were twice as likely to develop significant depressive symptoms than women who remained premenopausal. The odds of becoming depressed were even higher for women who also reported hot flashes. This study, combined with others, is pretty strong evidence that perimenopause is a high-risk time for depression.

TCPR: Is this consistent with your clinical experience?

Dr. Brizendine: Yes. In the UCSF Mood and Hormone Clinic, we see two different types of depressed perimenopausal women: those with no prior history of depression, and those with a depressive history. And we tend to treat these two categories of women differently.

TCPR: In what ways?

Dr. Brizendine: Women who have a perimenopausal worsening of depression do well on antidepressants, which is no surprise. One comment that I will add, however, is that these women tend to be very sensitive to possible sexual side effects of meds, because they are already suffering lowered sex drive due to perimenopause. So we very often start with Wellbutrin (bupropion) rather than SSRIs.

TCPR: Are women at higher risk for perimenopausal depression if they have a history of either PMDD (premenstrual dysphoric disorder) or postpartum depression?

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Dr. Brizendine: That's still very much an open question in the field. While it would make sense that having had one hormonally related mood disorder would predict another, thus far the data have not been clear on this, and it is being intensively researched.

TCPR: What about the women with no prior depression history? How do you treat them in your clinic?

Dr. Brizendine: These women make up about half of those we see in the clinic and we think of their depression as hormonally induced. Up to 50% of women who have a depression during perimenopause will have never had a depression in their life before. Therefore, we believe that hormonal treatments are appropriate, and I usually prescribe the estradiol patch, either with or without antidepressants.

TCPR: But isn't hormone replacement therapy thought to be quite risky in light of the results from the Women's Health Initiative study?

Dr. Brizendine: Yes, but it's important to be clear about what these risks actually are, and to what extent these risks actually apply to a given patient. First of all, the WHI study did not enroll any women in perimenopause at all. Instead, the study followed 16,000 postmenopausal women between the ages of 50 and 79; the average age was 63 at study enrollment. These women were randomized to either Prempro (estrogen + progestin) or placebo, and were followed for an average of about five years before the study was halted in 2002.

TCPR: And why was the study halted?

Dr. Brizendine: Because a preliminary analysis of the data showed that women in the Prempro arm of the study (who were taking both progesterone and estrogen) had increased risks of breast cancer, heart disease, stroke, and pulmonary embolism. But this group actually showed a decreased risk of colon cancer and hip fracture (Rossouw J et al., *JAMA* 2002;288:321-333). And for those women who were less than five years postmenopausal, this group actually reduced the heart disease risk. It's also important to note that in another part of the WHI study, women who were assigned to estrogen alone showed a reduced breast cancer risk.

TCPR: Are these results generalizable to the younger perimenopausal women whom we have been discussing?

Dr. Brizendine: We don't know for sure, but most of us believe that these health risks are much lower when estrogen-only preparations are taken for a relatively short period (less than five years) by younger women. That's not to say that there is no risk, and before I start any woman on estrogen, I establish that she is not a smoker, that she doesn't have a personal or family history of breast cancer, and that she has not had a stroke, clotting disorder, or significant heart disease.

TCPR: As a "psychiatrists", do you feel comfortable starting these women on estrogen yourself, or do you refer them to their OB-GYN for that decision?

Dr. Brizendine: After having worked with this group of women for 15 years along with OB-GYNs at UCSF, I feel comfortable handling the discussion of risks versus benefits, but I do comanage these women with their OB-GYN.

TCPR: Has estrogen been tested specifically for the treatment of depression?

Dr. Brizendine: Yes, one placebo-controlled trial of the estradiol patch for perimenopausal women reported a 68% remission rate of depressive symptoms vs. a 20% remission rate on placebo (Soares C et al., *Arch Gen Psychiatry* 2001;58:529-534). This was a small trial that enrolled only 50 women, but the results were statistically significant. On the other hand, one controlled trial of the estrogen patch for postmenopausal women showed no effect (Morrison M et al., *Biol Psychiatry* 2004;55(4):406-12), so I view it as helpful primarily in perimenopause.

TCPR: Is there any particular brand that you favor?

Dr. Brizendine: We usually prescribe the Vivelle-Dot patch (estradiol transdermal system), because it is small and women don't experience as much skin irritation with it. Vivelle-Dot comes in several strengths, ranging from 0.025 mg to 0.1 mg, and we usually start with the 0.1 mg/day version. Patients change the patch twice a week, and I tell them that we are going to do this for the next 12 to 24 months to try to get a hold of their mood, irritability, and insomnia.

TCPR: And what sort of results do you see?

Dr. Brizendine: We often see improvements in all of the psychiatric symptoms I already mentioned, as well as improvements in hot flashes and vaginal dryness.

TCPR: And why do you prefer to use the patch over oral estrogen?

Dr. Brizendine: Because oral estrogen undergoes first pass metabolism in the liver, and this stimulates the production of sex hormone binding globulin (SHBG). SHBG's favorite victim is free testosterone, and within 30 days of going on an oral estrogen the free testosterone level plummets. This, in turn, causes the sex drive to go into the basement. It may take up to six months after stopping oral estrogen for the SHBG level to normalize.

TCPR: Dr. Brizendine, thank you for this whirlwind course in perimenopause, and I also have found your new book, *The Female Brain*, very helpful clinically.

Dr. Brizendine: It was my pleasure. And if your readers would like more information on some of these issues, they can contact me through my Web site, www.thefemalebrain.com.

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Research Updates IN PSYCHIATRY

STIMULANTS

Provigil for the Masses?

Provigil (modafinil) is FDA approved for excessive sleepiness due to various causes. An ADHD indication was rejected because of its possible association with a single case of Stevens-Johnson syndrome. Nonetheless, Provigil enjoys wide use for off-label indications, including medication-associated fatigue, augmentation of antidepressants, and as a pick-me-up for the frazzled and exhausted 21st-century human. A group of researchers at Vanderbilt University has recently reported on the effects of Provigil on 12 healthy male volunteers aged 30 to 44. Patients were randomized to either three days of Provigil 400 mg/day or placebo. Provigil made subjects feel more energized, alert, and quick-witted than did placebo, but it also produced more anxiety and tension (Taneja I et al., *J Clin Psychopharm* Feb 2007;27(1):76-78). In a separate report on the same subjects, Provigil was associated with a nine-beat increase in heart rate, a seven-point increase in systolic blood pressure, and a five-point increase in diastolic blood pressure (Taneja I et al., *Hypertension* 2005;45:612).

TCPR's Take: Provigil energizes but causes autonomic activation when given to non-fatigued volunteers. This could be hazardous for people with cardiac disease. Let patients know that there are hazards associated with sharing their Provigil with family or friends who seek a quick boost. Caffeine is probably safer.

ANTIDEPRESSANTS

Does "California Rocket Fuel" Work?

The combination of Effexor (venlafaxine) and Remeron (mirtazapine) has been dubbed "California Rocket Fuel" by Stephen Stahl (see page 290 of his *Essential Psychopharmacology*, 2nd Edition) because of the multiple ways the combination boosts various neurotransmitter systems. The STAR-D study found that this combination outperformed the MAOI Parnate (tranylcypromine), though the difference was not statistically significant (McGrath PJ et al., *Am J Psychiatry* 2006; 163(9): 1531-1541). Psychiatrists in Ireland recently reported on a series of 32 patients with refractory depression who were given this combination. The response rate, based on the Clinical Global Impression Scale, was 44% at four weeks and 50% at eight weeks. Most patients who responded were on Effexor XR at 225 mg/day or higher and Remeron 30 mg to 45 mg HS. In terms of side effects, 12% of patients reported moderate to severe weight gain and another 12% reported at least moderate sedation (Hannan N et al., *J Psychopharm* 2007;21(2):161-164).

TCPR's Take: Since this is only a case series, it doesn't prove the value of Effexor/Remeron, but the combination is fairly well tolerated and certainly worth trying in patients who have not responded to anything else.

BEREAVEMENT

What Are the Stages of Grief?

A widely cited sequence of reactions following the death of a loved one includes: disbelief, yearning (for the loved one's return), anger, depression/mourning, and acceptance. Researchers conducted a study aimed at empirically assessing whether these stages actually occur and, if so, in what order. A total of 233 bereaved individuals were interviewed over a 24-month period after a loved one's death. Subjects were limited to those whose loved ones died of natural causes; the majority were widowed women in their 60s. The study found that the predominant initial reaction was not disbelief, but rather acceptance and yearning. Nonetheless, when researchers looked at when each reaction reached its peak, they found that the data fit the theory exactly, with reactions peaking in the sequence disbelief, yearning, anger, depression, and acceptance. All the negative grief reactions (i.e., all those other than acceptance) peaked at six months post-loss and declined steadily thereafter (Maciejewski PK et al., *JAMA* 2007;297(7)716-723).

TCPR's Take: This is an extraordinary study that will help us to inform our patients (and ourselves) about what to expect after a loved one dies. This also confirms the validity of the concept of "prolonged grief disorder," defined as symptoms of grief lasting longer than six months post-loss.

NEW MEDICATION

Vyvanse Approved for ADHD

On February 23, the FDA approved Shire and New River's Vyvanse (lisdexamfetamine dimesylate) for the treatment of ADHD in children. Vyvanse is the molecule dextroamphetamine (trade names Dexedrine and Dextrostat) attached to the amino acid lysine. After this inactive "pro-drug" is absorbed through the GI tract into the bloodstream, the liver hydrolyzes the molecule, cleaving off the lysine and producing the active drug d-amphetamine. This delivery system slows the release of d-amphetamine, so that the concentration peaks at 3.5 hours instead of 3 hours, which is when plain d-amphetamine reaches its maximum concentration (see Dexedrine prescribing information, accessed at http://www.fda.gov/cder/foi/label/2006/017078s040lbl.pdf). While classified as a Schedule II controlled substance as existing stimulants, Vyvanse produces no high if snorted, and a 100 mg dose made drug abusers less buzzed than a 40 mg dose of Dexedrine. However, at 150 mg of Vyvanse there were no differences between the two on the "drug likeability scale." (See the manufacturer's Web site at www.vyvanse.com.)

TCPR's Take: Vyvanse is not in pharmacies yet, so it is too early to judge whether there are any clinical advantages. If it is truly less abusable, this would be its primary advantage. The cynic in *TCPR* notes that Vyvanse is timed to be marketed shortly before Adderall XR goes off patent. Since Shire makes both drugs, watch for shenanigans such as "shortages" of Adderall XR just as Vyvanse hits the shelves.

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CME Post-Test

To earn CME credit, you must read the articles and complete the quiz below, answering at least four of the questions correctly. Mail a photocopy or fax the completed page (no cover sheet required) to **Clearview CME Institute, P.O. Box 626, Newburyport, MA 01950**; **fax (978) 499-2278**. For customer service, please call (978) 499-0583. Only the first entry will be considered for credit and must be received by Clearview CME Institute by March 31, 2008. Acknowledgment will be sent to you within six to eight weeks of participation.

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Please identify your answer by placing a check mark or an X in the box accompanying the appropriate letter.

1. A recent study on the use of atypical antipsychotics during pregnancy showed that
- [ ] a. Haldol is safer than atypicals.
- [ ] b. Zyprexa, Risperdal, and Seroquel did not increase the risk of birth defects.
- [ ] c. Geodon and Abilify are the safest of all atypicals.
- [ ] d. Atypicals can cause diabetes in infants.

2. The Chambers et al. study on persistent pulmonary hypertension of the newborn (PPHN) concluded that
- [ ] a. SSRIs are associated with six times the baseline risk.
- [ ] b. About 0.1% of SSRI-exposed infants will be affected.
- [ ] c. Paxil is the only SSRI to show an association with PPHN.
- [ ] d. The risk of PPHN is greatest with exposure during the *first* half of pregnancy.

3. The absolute risk of lithium causing Ebstein's anomaly is about one in 2,000.
- [ ] a. True [ ] b. False

4. The data on Omega-3 fatty acids indicates that
- [ ] a. It is more teratogenic than Paxil.
- [ ] b. It is associated with neonatal withdrawal.
- [ ] c. It may pose some risk in breastfeeding.
- [ ] d. It may lead to improved intelligence in exposed infants.

5. According to Dr. Brizendine, the estrogen patch is effective for both peri- and postmenopausal depression.
- [ ] a. True [ ] b. False

Correction
for *TCPR* Volume 5, Number 2, page 8:

In the article, "Statistical Significance: What Does it Really Mean?" the two literature references in the last paragraph were reversed. The corrected sentence is: "In this case, it turns out that several other studies have compared rTMS and ECT; some have replicated the findings of this study (Grunhaus L, *Biol Psychiatry* 2000;47:314-324), while others have reported that rTMS is just as good as ECT (Janicak PG, et al, *Biol Psychiatry* 2002;51:659-667)."

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Your evaluation of this CME activity (i.e., this issue) will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives? [ ] Yes [ ] No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity? [ ] 5 [ ] 4 [ ] 3 [ ] 2 [ ] 1
3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? Please explain. [ ] Yes [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? Please explain. [ ] Yes [ ] No

5. How long did it take you to complete this CME activity? ___ hour(s) ___ minutes
6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

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Pregnancy Registry and compared 149 first-trimester VPA-exposed infants with two control groups: infants exposed to antiepileptic drugs (AEDs) other than VPA, and infants exposed to no teratogens at all. **Overall, 10.7% of VPA-exposed infants had major malformations,** versus 2.9% of the AED-exposed group, and 1.6 % of the unexposed group. There were three cases of neural tube defects in the VPA group which is a well-known risk, but there were various other anomalies, including cardiac and pulmonary defects (Wyszynski, D F, *Neurology* 2005; 64(6): 961-965). By the way, most of these women were taking prenatal folic acid supplements, which did not prevent the occurrence of neural tube defects. Bottom line: Avoid valproic acid in the first trimester!

Lamictal may cause cleft palate. Lamictal (lamotrigine) has been thought to be one of the safer treatments for bipolar disorder in pregnant women. However, the FDA recently reported data from the North American Antiepileptic Drug Registry indicating that, out of 564 pregnant women treated with Lamictal, there were five cases of cleft palate, a prevalence of 0.9%. This is about 10 times higher than the baseline prevalence of 0.1% (http://www.fda.gov/cder/drug/InfoSheets/HCP/lamotrigineHCP.pdf). However, the FDA also noted that other pregnancy registries have not replicated this finding, so it's not clear how real it is. Even if the finding is real, Lamictal is far safer than Depakote and somewhat safer than lithium, which causes a very low prevalence of a far more serious condition, Ebstein's anomaly.

Benzodiazepines

There is nothing new to report on benzos. Many studies have been conducted to examine possible teratogenic effects. While the results are conflicting, most authorities appear to have settled on the concept that benzodiazepines may double the risk of cleft palate from the baseline rate of one in 1,000 to about two in 1,000 (see a recent Medscape review at http://www.medscape.com/viewarticle/512650). Using relatively low doses of shorter half-life agents (e.g., 0.5 mg lorazepam or alprazolam) is likely to minimize this risk.

Natural Treatments

Omega-3 consumption and smarter babies. A recent article in *The Lancet* showed that pregnant women who consumed large amounts of seafood (more than three servings per week) gave birth to babies with higher IQs than women who ate less seafood (fewer than 3 servings per week). Because the researchers asked respondents about specific types of fish consumed (only certain fatty fish have lots of omega-3), they were able to ascertain that higher levels of dietary omega-3 were specifically associated with more intelligent kids. The researchers controlled for the possible confounding effects of maternal IQ in a number of ways, so these findings appear legitimate (Hibbeln JR et al., *The Lancet* 2007;369:578-585).

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Next Month in *The Carlat Psychiatry Report*: Topics in Geriatric Psychiatry, including a review of medications for dementia, a practical approach to distinguishing normal forgetfulness from pre-dementia, and an interview with James Ellison, M.D., Director of Geriatrics at McLean Hospital.