Paroxetine in pregnancy?
FDA advisory flunks as evidence-based medicine

Lawson Wulsin, MD, and Michael Ignatowski, BA

Mrs. J, age 24, has a history of recurrent major depression, for which you have prescribed paroxetine. Newly pregnant, she brings you Internet articles with headlines such as “Depression drugs can raise birth defect risks.” Particularly, the articles mention congenital cardiac defects with paroxetine use during pregnancy. She adds that Web sites offer legal support and invite her to join class-action lawsuits. How would you respond?

Psychiatrists and patients such as Mrs. J face a dilemma since the FDA requested in December 2005 that GlaxoSmithKline (GSK) change paroxetine’s pregnancy warning from category C to category D (see Related resources, page 48, for the FDA advisory). Selective serotonin reuptake inhibitors (SSRIs) are the antidepressants prescribed most often during pregnancy, and all had been pregnancy class C.²

FDA says category D means controlled or observational studies in pregnant women have shown risk to the fetus, but benefits of therapy may outweigh the risk. Category C means adverse effects have been seen in animal studies when no controlled studies in women exist, or studies in women and animals are unavailable (see Do antidepressants’ benefits outweigh the risks?, page 31).

FDA recommends avoiding paroxetine in women of child-bearing age. How does this advisory change the way we manage depression in pregnancy? How strong is the evidence supporting it?

SSRIs and Birth Defect Risk

Eight prospective or case-control studies of SSRIs in >5,400 pregnant women have been published since 1993 (Table, page 47).³,⁴,⁵,⁶,⁷,⁸,⁹,¹⁰ Five included paroxetine.⁵,⁶,⁷,⁸,⁹ The studies ranged from small to large, and none showed a significant increase in major malformations with any SSRI. Even in a study of >2,500 women, no single malformation was overrepresented.⁶

In addition, a recent meta-analysis¹¹ of 7 prospective comparative cohort studies involving 1,774 pregnant women showed no increased risk of major birth defects from exposure to any of the 8 antidepressants studied, including 4 SSRIs used during the first trimester. The review identified no specific malformation or cluster of malformations associated with first-trimester antidepressant use.

Evidence Cited by FDA

FDA’s advisory Box, page 46 came 3 months after GSK notified health professionals that fetuses exposed to paroxetine during organogenesis may be at increased risk of developing malformations, particularly ventricular septal defect (see Related resources).
After adjustments were made for other antidepressants and known teratogenic drugs the women took while pregnant, the study showed:

- Major congenital defects occurred in 4% of 527 pregnancies during which women used paroxetine, (adjusted odds ratios [OR], 2.0; 95% CI, 1.34-3.63), compared with 3% prevalence in the general population.
- Cardiovascular malformations occurred at an adjusted rate of 2% (OR, 2.08; 95% CI, 1.03-4.23), compared with 1% in the general population.
- 10 of the 14 cardiovascular malformations were ventricular septal defects.

The cardiovascular malformation rate associated with paroxetine was significantly higher than the rates seen with other SSRIs examined in the databases.

The GSK investigation was an unpublished retrospective study without peer review when FDA issued its advisory about paroxetine.

Two abstracts. The FDA alert also cited two abstracts that were not peer-reviewed and whose findings were inconsistent with those of GSK.

In the first abstract, a U.S. case-control study showed an increased risk of major malformations in 5,357 infants of women who took SSRIs in the first trimester, compared with 3,366 normal controls. Specific birth defects included:

- 161 infants with omphalocele (bowel protrusion through an abdominal wall defect) (OR, 3.0; 95% CI, 1.4-6.1)
- 372 infants with craniosynostosis (deformities caused by premature closure of skull sutures) (OR, 1.8; 95% CI, 1.0-3.2).

Paroxetine was associated with an increased risk of omphalocele (OR, 6.3; CI, 2.0-19.6) but...
The authors stated that the associations need to be confirmed in other data sets, but this had not been done when FDA issued its warning.

In the second abstract, Wogeliu et al. examined a Danish prescription database and found a slightly increased risk for congenital malformation (OR, 1.4; 95% CI, 1.1-1.9) and specifically cardiac malformation (OR, 1.6; 95% CI, 1.0-2.6) with SSRIs during pregnancy. This study included 1,054 women who filled SSRI prescriptions within a window of 30 days before conception to the end of the first trimester. The authors compared these malformation rates with those in 150,908 controls (women who did not fill an SSRI prescription in this period before and during pregnancy).

This cohort study did not report specific data about paroxetine, nor whether the women took the SSRIs they acquired.

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**Table 8 published studies: No significant increase in birth defects with SSRIs**

<table>
<thead>
<tr>
<th>Year/location</th>
<th>Authors</th>
<th>Study design</th>
<th>SSRI exposure (# of patients)</th>
<th>Risk of major malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993/USA, Canada</td>
<td>Pastuszak et al</td>
<td>Prospective, controlled</td>
<td>Fluoxetine (98)</td>
<td>SSRI: 2% Control: 1.8% (ns)</td>
</tr>
<tr>
<td>1996/USA</td>
<td>Chambers et al</td>
<td>Prospective, controlled</td>
<td>Fluoxetine (174)</td>
<td>SSRI: 3.4% Control: 2.7% (ns)</td>
</tr>
<tr>
<td>1997/worldwide</td>
<td>Goldstein et al</td>
<td>Clinical trial</td>
<td>Fluoxetine (28)</td>
<td>SSRI: 3.6% (ns)</td>
</tr>
<tr>
<td>1998/USA, Canada, Brazil</td>
<td>Kulin et al</td>
<td>Prospective, controlled</td>
<td>Paroxetine (97) Sertraline (147) Fluvoxamine (26)</td>
<td>Total SSRI: 4.1% Control: 3.8% (ns)</td>
</tr>
<tr>
<td>1999/Sweden</td>
<td>Ericson et al</td>
<td>Case-control</td>
<td>Citalopram (364) Paroxetine (118) Sertraline (32) Fluoxetine (15)</td>
<td>Citalopram: 3.9% Total risk of remaining SSRIs: 3.8% (ns)</td>
</tr>
<tr>
<td>2002/USA</td>
<td>Simon et al</td>
<td>Case-control</td>
<td>Fluoxetine (129) Sertraline (32) Paroxetine (28)</td>
<td>Total SSRI: 6.5% Control: 4.9% (ns)</td>
</tr>
<tr>
<td>2003/USA</td>
<td>Hendrick et al</td>
<td>Prospective, uncontrolled</td>
<td>Fluoxetine (13) Paroxetine (19) Sertraline (36)</td>
<td>Total SSRI: 1.4% (ns)</td>
</tr>
<tr>
<td>2005/Sweden</td>
<td>Hallberg et al</td>
<td>Case-control</td>
<td>Citalopram (1,696) Paroxetine (708) Sertraline (1,067) Fluoxetine (574)</td>
<td>Citalopram: 3.1% Paroxetine: 3.4% Sertraline: 2.0% Fluoxetine: 3.3% (ns)</td>
</tr>
</tbody>
</table>

ns: No statistically significant difference
Unfortunately, FDA has refused to release information about these studies beyond what it gave in the advisory, stating simply that the studies are unpublished. Evidence-based medicine can be difficult to practice if clinicians can’t access the evidence to assess its quality.

**IN CLINICAL PRACTICE**

Evidence from five peer-reviewed, published studies contradict the FDA advisory on increased risk for congenital cardiac malformations with paroxetine use during pregnancy. So, when prescribing antidepressants for depressed pregnant women, do we rely on the five negative studies or practice defensive medicine and choose SSRIs other than paroxetine?

We have good reasons to question the FDA advisory’s scientific validity, but our patients—and our lawyers—will be more comfortable if we avoid paroxetine in women of child-bearing potential for now. Excluding paroxetine and relying on other SSRIs when necessary to treat major depression during pregnancy is hardly evidence-based medicine, but it’s a legitimate practice of legally-defensive medicine.

This answers our question about how to respond to Mrs. J’s concerns:

- First, she and I would decide if she needs an antidepressant during pregnancy.
- Then, after reviewing with her the FDA warning on paroxetine and discussing its questionable scientific validity, I would recommend that she switch to another SSRI.
- If she chooses to continue paroxetine, I would ask her to sign the note that documents our discussion of the pros and cons of choosing paroxetine instead of alternatives.

**References**

Continued brief summary of prescribing information from previous page.

Fosamtra X (acetylsalicylic acid hydrochloride) extended-release capsules

Adverse Events or Clinical Studies with Fosamtra X—Adults
Adverse Events Associated with Discontinuation or Treatment: In the adult placebo-controlled study, 10.3% of the Fosamtra X-treated patients and 7.6% of the placebo-treated patients discontinued for adverse events. Among Fosamtra X-treated patients, nausea, dizziness, feeling “tired” or “sick,” or “nausea” (1.2%, 2%, and 2%, respectively) were the reasons for discontinuation reported by more than three patients.

Adverse Events Occurring at an Incidence of 5% or More Among Fosamtra X-Treated Patients: Table 1 summarizes treatment-emergent adverse events for the placebo-controlled, parallel group studies in adults with ADHD at Fosamtra X doses of 20, 30, and 40 mg/day. A notable inclusion is the events that occurred in 5% or more of patients in a Fosamtra X dose group and for which the incidence in patients treated with Fosamtra X appeared to be increase over the placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patients and other factors differ from those prevailing in the clinical trials. Adversely, the other frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigations. The cited figures, however, do provide the prescriber with the approximate contribution of drug and non-drug clinical factors to adverse events in the incidence of the adverse events listed in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Fosamtra X 20 mg</th>
<th>Fosamtra X 30 mg</th>
<th>Fosamtra X 40 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.3%</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3.2%</td>
<td>4.3%</td>
<td>4.5%</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.2%</td>
<td>4.3%</td>
<td>4.5%</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>1.2%</td>
<td>1.3%</td>
<td>1.4%</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.7%</td>
<td>1.1%</td>
<td>1.2%</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3.2%</td>
<td>4.3%</td>
<td>4.5%</td>
<td>4.9%</td>
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<td>3.2%</td>
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</table>

For legal reasons alone, in women avoiding paroxetine due to child-bearing potential unless their depressive symptoms respond exclusively to this medication. Document all risk-benefit discussions you have with patients about SSRI use during pregnancy.

continued from page 48


