**Health and Drug Alerts**

**Paroxetine (Paxil) and congenital malformations**

**Reason for posting:** Selective serotonin reuptake inhibitors (SSRIs) have not previously been demonstrated, as a group, to be teratogenic. However, the results of an unpublished study by GlaxoSmithKline (GSK) has led the US Food and Drug Administration and Health Canada to warn that one SSRI, paroxetine, may increase the risk of major congenital malformations.

**The drug:** Antidepressants, including paroxetine, are used to treat major depression, anxiety, obsessive–compulsive disorder and premenstrual dysphoria, all common disorders during the childbearing years. GSK, the manufacturer of paroxetine and another antidepressant, bupropion, recently completed an unpublished retrospective study of data from 2 US managed-care insurance databases. Pregnancy outcomes among 3581 expectant mothers aged 12–49 years who were taking antidepressants were studied.

Initially, the study sought to investigate whether women prescribed bupropion had infants with higher rates of cardiovascular malformations than women either taking other antidepressants or taking the drug in the third trimester only. Any cardiac or serious congenital malformation was recorded for users of bupropion in the first or third trimester and users of any other antidepressants. The analysis excluded women with concurrent first-trimester use of known teratogens, including lithium, valproic acid and carbamazepine.

Children exposed to bupropion in the first or third trimester did not have increased rates of malformations relative to those taking any antidepressant. The FDA, however, requested a secondary analysis of specific rates of malformations among infants of users of all other antidepressants. There were 18 used in total, including SSRIs, tricyclics, serotonin-norepinephrine-reuptake inhibitors and other new antidepressants.

Only users of paroxetine had an increased risk of malformations higher than those of other antidepressants (Table 1). Various organ systems (gastrointestinal, genitourinary and central nervous system) were affected in roughly equal proportions. The most common cardiovascular malformations seen were ventricular septal defects.

The absolute rate of major congenital seen in the first trimester for paroxetine users was 4%; of cardiovascular malformations, 2%. This study did not include controls of women not taking an antidepressant; however, the prevalence of major congenital and cardiovascular malformations for all births in the United States, regardless of drug exposure, are 3% and 1%, respectively.

**What to do:** This study is limited by its retrospective design, its post hoc secondary analyses, the limited clinical details available in an insurance database, and its lack of controls. However, it is one of the first reasonably large epidemiologic studies to suggest possible teratogenicity of an SSRI. Why paroxetine may have this effect is not clear, and the results conflict with other epidemiologic studies performed to date. Although the relative risk increase of malformations is about twofold, the absolute risk increase over baseline malformation rates appears to be about 1% (i.e., about 100 pregnant users would be needed before additional harm would come to one infant). Any woman of childbearing age being treated with paroxetine should be counselled on these absolute and relative risks. If pregnancy is a real possibility, consideration should be given to switching medications.

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**Table 1:** Risk of major congenital malformation in infants according to the antidepressant medication used maternally during the first trimester

| Drug             | Maternal users | Infant malformations | Malformations per 1000 live births | Adjusted odds ratio (95% CI)† |
|------------------|----------------|----------------------|------------------------------------|-------------------------------|
| Amitriptyline    | 146            | 1                    | 6.8                                | 0.27 (0.04-1.96)              |
| Bupropion        | 248            | 6                    | 24.2                               | 0.99 (0.42-2.30)              |
| Citalopram       | 188            | 7                    | 37.2                               | 1.39 (0.62-3.11)              |
| Fluoxetine       | 820            | 18                   | 22.0                               | 0.82 (0.48-1.39)              |
| Nefazodone       | 41             | 1                    | 24.4                               | 0.94 (0.13-6.96)              |
| Paroxetine       | 527            | 23                   | 43.6                               | 2.20 (1.34-3.63)              |
| Sertraline       | 507            | 7                    | 13.8                               | 0.48 (0.22-1.05)              |
| Trazodone        | 49             | 2                    | 40.8                               | 1.98 (0.47-8.39)              |
| Venlafaxine      | 129            | 2                    | 15.5                               | 0.59 (0.14-2.42)              |

>1 type of antidepressant: 406 14 3.42 (0.79-2.55)

*CATEGORIES OF SPECIFIC ANTIDEPRESSANTS ARE MUTUALLY EXCLUSIVE. DATA WERE TAKEN FROM A GLAXOSMITHKLINE REPORT (AVAILABLE AT HTTP://CTR.GSK.CO.UK/SUMMARY/PAROXETINE/EIP083.PDF [ACCESSED 2005 OCT 26] AND ALSO AT WWW.CMAJ.CA/CGI/CONTENT/173/11/1320/DC1). BECAUSE NO MAJOR CONGENITAL MALFORMATIONS WERE OBSERVED AMONG THE OFFSPRING OF PARTICIPANTS EXPOSED TO CLOMIPRAMINE, DESIPRAMINE, DOXEPIN, FLUOXAMINE, IMIPRAMINE, MITRAZAPINE, NORTRIPTYLINE OR PROTRIPTYLINE, DATA FOR THESE ANTIDEPRESSANTS ARE NOT SHOWN. ADJUSTED FOR AGE AND SEX OF INFANT, CALENDAR YEAR OF DELIVERY AND A MATERNAL DIAGNOSIS OF PRE-ECLAMPSIA OR ECLAMPSIA. THE COMPARATOR GROUP IS THE RATE OF MALFORMATIONS AMONG INFANTS OF ANY OTHER ANTIDEPRESSANT IN THE FIRST TRIMESTER. CI = CONFIDENCE INTERVAL.
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Early release
All Health and Drug Alerts are posted online ahead of print and are available at www.cmaj.ca. This article was posted on Nov. 4, 2005.

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