Maternal Sertraline Treatment and Serotonin Transport in Breast-Feeding Mother-Infant Pairs

Neill Epperson, M.D.
Kathryn A. Czarkowski, M.A.
Deborah Ward-O’Brien, M.S.N., A.P.R.N.
Erica Weiss, M.D.
Ralitza Gueorguieva, Ph.D.
Peter Jatlow, M.D.
George M. Anderson, Ph.D.

Objective: Pharmacological treatment of postpartum depression is frequently complicated by the mother’s desire to breast-feed. Although breast milk levels of several selective serotonin reuptake inhibitors (SSRIs) have been reported to be relatively low, a critical question is whether SSRI exposure during nursing results in clinically significant blockade of serotonin (5-HT) reuptake in infants. This study determined the degree of transporter blockade in infants exposed to sertraline through maternal breast milk.

Method: The extent of maternal and infant transporter blockade was assessed by measurement of platelet levels of 5-HT in 14 breast-feeding mother-infant pairs before and after 6–16 weeks of maternal treatment with sertraline for major depression with postpartum onset. Plasma sertraline and desmethylsertraline levels were obtained in 13 of these mothers and 11 of their infants.

Results: Marked declines in platelet 5-HT levels of 70%–96% were observed in mothers after sertraline treatment, 25–200 mg/day. In contrast, infants showed little or no change in platelet 5-HT levels after exposure through breast-feeding. Mean levels of maternal plasma sertraline and its major metabolite, desmethylsertraline, were 30.7 ng/ml and 45.3 ng/ml, respectively. Drug and drug metabolite concentrations in the infants were at or below the lower limit of quantitation.

Conclusions: The data indicate that while mothers receiving clinical doses of sertraline experience substantial blockade of the platelet 5-HT transporter, platelet 5-HT uptake in nursing infants of treated mothers is unaltered. The observations suggest that mothers taking sertraline can breast-feed without appreciably affecting peripheral or central 5-HT transport in their infants.

Postpartum major depression occurs in approximately 10% of childbearing women (1) and is associated with significant morbidity in mothers and their children (2). For many women, the optimum treatment may be an antidepressant alone or in addition to psychotherapy. However, the decision to institute antidepressant therapy is often complicated by the mother’s desire to breast-feed. All selective serotonin reuptake inhibitors (SSRIs) are categorized by the Food and Drug Administration as category C drugs (“benefits must outweigh risks”) for pregnancy. Classification regarding the safety of SSRIs in breast-feeding varies from “safe” to “unknown” in the numerous pharmacology compendia online and in print. Therefore, women and their health care providers are presented with a difficult choice: whether to breast-feed and expose the infant to antidepressant medication or to wean and deprive the infant of the proven benefits of breast milk. On the basis of recent estimates of the percentage of women breast-feeding at the time of discharge from the hospital (59%) (3), the rate of postpartum depression (10%) (1), and the birth rate in the United States (approximately 4 million per year) (4), it is estimated that each year in the United States alone approximately a quarter of a million women may consider nursing while receiving antidepressant medication.

Benefits of Breast-Feeding

In its policy statement (5), the American Academy of Pediatrics recommended exclusive breast-feeding during the first 6 months of life to promote “optimal” growth and development. Extensive research has provided compelling evidence that breast-feeding reduces the risk of respiratory (6) and urinary tract infections (7), otitis media (8), bacteremia and bacterial meningitis (9), allergic diseases (10), sudden infant death syndrome (11), and insulin-dependent diabetes mellitus (12). Exclusive breast-feeding may also enhance neurodevelopment (13, 14). As a result of the Academy’s policy statement and improved public awareness of the benefits of breast-feeding, an increasing proportion of women are opting to breast-feed instead of bottle-feed.

SSRIs and Breast-Feeding

Findings from case reports, case series, and larger studies examining the safety of using fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram during lactation...
SERTRALINE AND BREAST-FEEDING

(15–26) have suggested that infants exposed to SSRIs from maternal breast milk receive 0.5% to 10% (depending on the SSRI) of the maternal weight-adjusted daily dose. Direct measurement of infant plasma/serum levels of SSRIs has demonstrated that most infants exposed to sertraline (18, 27–29) and paroxetine (22, 26, 30) through maternal breast milk developed blood levels of the drugs that are below assay limits of detection (1–3 ng/ml), whereas data from studies of fluoxetine (16, 31–33), fluvoxamine (34), and citalopram (23, 25) have been less consistent or sparse. We know of no reports of adverse effects in breast-fed infants exposed to sertraline, paroxetine, or fluvoxamine. Although infant plasma concentrations of SSRIs are low in most cases compared to maternal levels, it is not clear to what extent serotonin (5-HT) transport is affected in infants exposed to SSRIs through breast milk.

5-HT in Neurodevelopment

In addition to general reservations about exposing infants to medications of any type, there are specific concerns regarding the potential adverse effects of serotonergic agents on neurodevelopment and behavior. Preclinical data have demonstrated that 5-HT influences neurogenesis and morphogenesis during gestation (35, 36) and modulates synaptogenesis during early infancy (37). 5-HT receptors are present in the prenatal rat brain and can be modulated by serotonergic agents (38). Although long-term treatment of cultured neurons from the rat fetal cortex with the SSRI citalopram did not result in changes in neuronal morphology and fine structure, changes were seen in mitochondria and vesicular aggregation that were suggestive of increased synaptic activity (39). In contrast, Vorhees et al. (40) failed to demonstrate any consistent adverse effect on several neurodevelopmental tests in rat pups exposed in utero to fluoxetine.

These findings are difficult to interpret with respect to human exposure to SSRIs in utero. Maternal use of cocaine, a drug shown to affect 5-HT functioning in studies of fetal rats (41), has been associated with adverse effects on infant habituation performance (42). These data suggest that serotonergic agents administered prenatally may affect neurodevelopment in humans. Although failure to find adverse effects on measures of infant cognitive and psychomotor development with prenatal exposure (43) or breast-feeding exposure (44) to fluoxetine is reassuring, group sizes have been small, and the measures used examined limited aspects of infant neurodevelopment.

Assessing 5-HT Transport

The neuronal 5-HT transporter or reuptake site is the principle route of clearance of 5-HT after neuronal release; it plays, therefore, a critical role in the modulation of extracellular 5-HT concentration and serotonergic neural transmission. Platelet and neuronal 5-HT transporters are encoded on the same gene (44) and appear identical with respect to ionic and pharmacologic sensitivities (45). There is no known age-dependent change in transporter structure or sensitivity to inhibition. Because platelet 5-HT is exogenously derived (taken up through the membrane transporter), measurement of platelet 5-HT provides an opportunity to assess the extent of transporter blockade or inhibition after SSRI administration (46–53). A critical question is whether the degree of transporter inhibition occurring in the platelets corresponds to that occurring centrally. As mentioned, the brain and platelet transporters appear to be identical, and a number of studies (46–53) have used platelet 5-HT levels to assess the extent of central blockade. In addition, animal studies (47, 53, 54) examining the effects of reuptake inhibitors on brain and platelet uptake have indicated that most agents bring about similar declines in central and peripheral transport. The special utility of platelet 5-HT, when used in this manner, is underlined by a study showing a significant effect of long-term low-dose paroxetine on mean levels of monkey platelet 5-HT (30% reduction), despite the absence of a detectable (<2 ng/ml) plasma drug level (55).

We measured platelet 5-HT levels in 14 breast-feeding mother-infant pairs before and after maternal treatment with sertraline. The data reported here extend our previous report (28) of four infants (numbers 2, 4, 8, and 11) exposed to sertraline through breast-feeding and permit a reasonably definitive determination of sertraline’s effect on 5-HT transport in both mothers and their nursing infants.

Method

Subjects

The 19 breast-feeding mothers and infants who took part in the study were referred to the Yale Postpartum Mood Disorders Clinic by their psychiatrist, obstetrician-gynecologist, or midwife for the evaluation and treatment of postpartum depression or for consultation regarding the use of antidepressants during lactation. In all cases, the women were counseled regarding the known risks and benefits of receiving antidepressants during lactation; nonpharmacologic treatments for their depression were also discussed. All of the mothers were married or in a stable cohabiting relationship. Each mother’s significant other had knowledge of her decision to breast-feed while taking sertraline, and a concerted effort was made to include each partner in this discussion. The women were instructed to inform their infant’s pediatrician of their decision to take sertraline during lactation. Written informed consent was obtained from the mothers (mean age=32.2 years, SD=4.5) who agreed to participate in this study, which was approved by the Human Investigation Committee of Yale University School of Medicine.

Study Group

Before the mothers began taking sertraline, 19 breast-feeding mothers and their infants had blood drawn for determination of whole blood 5-HT levels. The mothers of four infants decided soon after the preexposure blood sampling to wean their infants or to abstain from taking medication out of concern that even low levels of sertraline might harm their infants. When the mothers decided not to take medication, they were counseled regarding the risks of untreated maternal depression and offered a referral for appropriate nonpharmacologic treatment. A fifth mother...
started sertraline treatment but was determined to be noncompliant on the basis of an absence of plasma sertraline. All 19 pre-exposure infant blood samples were included in an analysis of possible age-related changes in whole blood 5-HT levels over the first year of life.

Thirteen of the remaining mothers then began taking sertraline, 50 mg/day, while one began taking 25 mg/day. Each mother was instructed to breast-feed her infant according to their preferred schedule. Postexposure blood sampling occurred 6 to 16 weeks after the mothers had started taking sertraline. The timing of postexposure testing was dictated by whether the mother's clinical status required an increase in her sertraline dose. All postexposure testing occurred at least 10 days after a change in sertraline dose in order to allow maternal plasma sertraline concentrations to reach a steady state. All blood samples were obtained between 10:00 a.m. and 2:00 p.m., approximately 4–8 hours after the mothers had taken their daily sertraline dose and 2–4 hours after they had last nursed their infants.

At the mothers' pre- and postexposure blood draws, approximately 5 ml of blood was collected into a tube containing dipotassium EDTA by means of standard venipuncture techniques. At the infants' preexposure blood draws, approximately 150 μl of blood was obtained with a heel or finger stick by means of a lancet with a 2.2-mm puncture depth. Blood samples were collected into capillary tubes containing dipotassium EDTA and transferred to an associated capped vial. Three ml of blood was obtained for the infants' postexposure 5-HT and drug level determinations by using a 23-gauge winged infusion set and collected into a tube containing dipotassium EDTA. Blood was kept at room temperature and immediately transported to the research laboratory in which duplicate or triplicate whole blood samples were removed for storage at −70°C; portions were also sent for automated platelet count (Hematology Laboratory, Yale–New Haven Hospital, New Haven, Conn.).

5-HT and Sertraline Concentrations

Whole blood 5-HT levels were determined by means of high-performance liquid chromatography with fluorometric detection (56). Blood was prepared as previously described: antioxidants and the internal standard N-methylserotonin were added to the samples while they were thawing, perchloric acid was added after thawing, and the sample was vigorously vortex mixed. After centrifugation, the supernate was directly injected into the high-performance liquid chromatography system. Specimens from given mother-infant pairs were always examined in a single batch. Whole blood 5-HT levels were determined for 250-μl samples obtained by venipuncture with within-day and day-to-day coefficients of variation of 3.0%–4.6% and 3.0%–5.9%, respectively. In replicate heel stick or finger stick blood specimens (of 25 μl), 5-HT levels were determined with within-day coefficients of variation of 1.2%–8.8%. In a comparison of venipuncture and finger stick blood sampling in three adult comparison subjects, similar results were seen (mean absolute difference=3.5%, group mean difference=0.4%). It should be noted that since more than 99% of results were seen (mean absolute difference=3.5%, group mean difference=0.4%). It should be noted that since more than 99% of results were seen (mean absolute difference=3.5%, group mean difference=0.4%).

Statistical Analysis

To compare changes in pre- and postexposure 5-HT levels between mothers and infants, a mixed-effects repeated measures analysis with unstructured variance-covariance was performed by using PROC MIXED in SAS (58). A cluster in that analysis consisted of the pre- and postmeasurements for a mother-infant pair. This design allowed simultaneous tests of mother and infant effects, of pre- and posteffects, and of the interaction between time (pre- and postexposure) and group (mother and infant). A significant interaction meant that the change in pre- versus postexposure 5-HT levels was significantly different in mothers compared to the change in infants. Individual comparisons could then be performed for mothers and for infants to test whether the mean change was significantly different from zero in either group. Pearson's correlations were performed to explore possible relationships between the variables of interest.

Results

Exposure data for 14 mother-infant pairs, including the mother's dose of sertraline, the frequency of breast-feeding, the infant's age at pre- and postexposure sampling, and maternal and infant plasma sertraline and desmethylsertraline levels are given in Table 1. In all but one case, the mothers began taking sertraline within 24 hours of the preexposure blood sampling. One mother (number 1) did not begin taking sertraline until 7 weeks after the preexposure blood sampling. At the time of postexposure sampling, the mothers were receiving 25 mg (N=1), 50 mg (N=6), 100 mg (N=5), 150 mg (N=1), and 200 mg (N=1) of sertraline per day. The mean ages for the infants at the times of preexposure and postexposure sampling were 17.3 weeks (SD=15.8) and 26.3 weeks (SD=14.7), respectively. Six infants (numbers 4–7, 11, 12) were less than 3 months of age and exclusively breast-fed when their mothers began taking sertraline. These infants remained exclusively breast-fed throughout the course of the study. No infant experienced any adverse effects or behavioral changes that appeared to be related to sertraline exposure.

Plasma sertraline and desmethylsertraline levels were obtained for 13 of 14 mothers and 11 of 14 infants. Mean maternal plasma concentrations of sertraline and desmethylsertraline were 30.7 ng/ml (SD=15.3) and 45.3 ng/ml (SD=19.6), respectively. All 11 infants had plasma sertraline and desmethylsertraline levels that were <2.5 ng/ml
SERTRALINE AND BREAST-FEEDING

Mean maternal pre- and postexposure 5-HT levels were 158.7 ng/ml (SD=63.8) and 18.7 ng/ml (SD=10.3), respectively (Table 1), whereas the mean infant postexposure 5-HT concentration was similar to the mean preexposure concentration (mean=227.0 ng/ml, SD=100.1, versus mean=223.7 ng/ml, SD=93.0). Repeated measures analysis using PROC MIXED (58) with two within-cluster factors of group (mother versus infant) and time (pre- versus post-exposure) revealed a significant decrease in maternal whole blood 5-HT levels (F=84.2, df=1, 13, p<0.0001), no significant change in infant whole blood 5-HT levels (F=0.1, df=1, 13, p=0.77), and a significant interaction of group and time (F=73.5, df=1, 13, p<0.0001) (Figure 1).

Individual declines in maternal 5-HT levels ranged from 70% to 96% (postexposure levels were 30% to 4% of baseline). Intraindividual changes in infant platelet 5-HT levels ranged from -22% to +25%; the absolute pre- to postexposure mean change was 11% (SD=9). Given the coefficient of variation for the analytical determination and the expected biological variability, the mean absolute change in the infant group is reasonable. Similar group mean changes were seen in both maternal and infant groups when the data were expressed as ng/10^9 platelets. There were no significant changes in platelet counts between pre- and postexposure samples in either the mother (t=0.49, df=13, p=0.63) or infant (t=-0.62, df=13, p=0.55) groups. When the relationship between infant ages and baseline 5-HT levels was examined in the 19 infants who had preexposure 5-HT level determinations, no correlation was seen (Pearson’s r=0.008, N=19, p=0.83).

Exploratory analysis of the data revealed few substantial correlations between the variables of infant age, frequency of nursing, length of exposure, maternal dose, maternal and infant plasma sertraline and desmethylsertraline levels, and maternal and infant postexposure 5-HT expressed as a percentage of 5-HT (postexposure/preexposure 5-

TABLE 1. Mother’s Sertraline Dose, Frequency of Nursing, Plasma Drug Levels, and Whole Blood Serotonin (5-HT) Levels in 14 Mother-Infant Pairs

<table>
<thead>
<tr>
<th>Mother/Infant Pair</th>
<th>Maternal Daily Dose (mg/day)</th>
<th>Frequency of Nursing (times/day)</th>
<th>Infant Age (weeks)</th>
<th>Maternal Plasma Sertraline Level (ng/ml)</th>
<th>Sertraline</th>
<th>Desmethylsertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>3–4</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>4–5</td>
<td>27</td>
<td>36</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>5–6</td>
<td>45</td>
<td>53</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>7–8</td>
<td>11</td>
<td>19</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>7–8</td>
<td>4</td>
<td>13</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>7–8</td>
<td>3</td>
<td>13</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>7–8</td>
<td>2</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>3–4</td>
<td>49</td>
<td>56</td>
<td>21</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>3–4</td>
<td>20</td>
<td>26</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>6–7</td>
<td>13</td>
<td>20</td>
<td>27</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>7–8</td>
<td>2</td>
<td>14</td>
<td>31</td>
<td>46</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>7–8</td>
<td>6</td>
<td>22</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>13</td>
<td>150</td>
<td>5–6</td>
<td>22</td>
<td>30</td>
<td>39</td>
<td>74</td>
</tr>
<tr>
<td>14</td>
<td>200</td>
<td>1–2</td>
<td>31</td>
<td>37</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Mean</td>
<td>83.9</td>
<td>5.6</td>
<td>17.3</td>
<td>26.3</td>
<td>30.7</td>
<td>45.3</td>
</tr>
<tr>
<td>SD</td>
<td>47.6</td>
<td>2.0</td>
<td>15.8</td>
<td>14.7</td>
<td>15.3</td>
<td>19.6</td>
</tr>
</tbody>
</table>

*p Mother started taking sertraline 7 weeks after preexposure 5-HT measurement.

Infant was breast-fed exclusively.

 Obtained from a commercial laboratory (coefficient of variation=7%–8%).

 Not available owing to an inferring peak.

 No blood sample obtained.

 Significant interaction of group and time [repeated measures analysis: F=73.5, df=1, 13, p<0.0001].

FIGURE 1. Infant and Maternal Serotonin (5-HT) Levels-Before and After Exposure to Sertraline

and <5.0 ng/ml, respectively. Desmethylsertraline and sertraline levels in the mothers were highly intercorrelated (Pearson’s r=0.72, N=12, p=0.008).

The mothers were taking sertraline doses of 25–200 mg/day. The infants were exposed to sertraline through maternal breast milk but did not experience a significant blockade of 5-HT transport.

The mothers were taking sertraline 7 weeks after preexposure 5-HT measurement.
The correlative analyses were not corrected for the number (N=40) of correlations performed. Of the observed correlations, only those between infant age and frequency of nursing (r=−0.73, N=14, p=0.003) and between maternal plasma sertraline and desmethylsertraline concentrations (r=0.72, N=12, p=0.008) were significant with any degree of Bonferroni correction.

To follow up on a possible relationship between maternal sertraline dose and infant postexposure/preexposure 5-HT ratio (Pearson’s r=0.58, N=14, uncorrected p=0.03), the infants were dichotomized (N=7 and N=7) on the basis of maternal sertraline dose (25 or 50 mg/day versus ≥100 mg/day). A biserial Pearson’s correlation revealed a correlation (r=−0.50, N=14, p=0.07) with mean infant postexposure/preexposure 5-HT ratio of 9.4% (SD=13) and −4.4% (SD=12) in the lower dose and higher dose groups, respectively. A Student’s t test found no significant between-group difference in mean postexposure/preexposure 5-HT ratio (t=2.06, df=12, p=0.06). In addition, when the infants were dichotomized on the basis of those who were exclusively breast-fed (N=6), the postexposure/preexposure 5-HT ratio for the exclusively breast-fed infants (mean=107, SD=11) was similar to that of the eight infants who were receiving additional forms of nutrition (mean=100, SD=16).

**Discussion**

As expected, consistent marked declines in maternal platelet 5-HT concentrations were seen in the mothers treated with the SSRI sertraline. The observed individual reductions of 70%–96% were in the range typically seen (46–52). In contrast, mean infant platelet 5-HT levels showed little change (2.5%) after exposure to sertraline through breast milk; changes in individual infants ranged from −22% to +25%. There was some suggestion that the infants of the mothers receiving sertraline doses of 100 mg or more per day may have been more likely to show some decrease in platelet 5-HT levels. However, the absence of a relationship between maternal plasma sertraline levels and infant change in 5-HT with exposure and the small magnitude of the change (−4.4%) seen in the higher dose group indicates that this effect was negligible. In addition, our analysis of the infants who would be considered to have received the greatest sertraline exposure on the basis of the frequency of breast-feeding and their age at the start of the study (those who were exclusively breast-fed and youngest) actually had a slightly higher mean postexposure 5-HT level (expressed as percentage of preexposure level) than the other infants. (All but one of the exclusively breast-fed infants was 6 weeks old or younger at the start of the study; this is a period of relative immaturity of hepatic metabolism [59] and renal drug excretion [60].)

Thus, it appears that at typical clinical doses, sertraline administered to mothers usually has a negligible effect on platelet 5-HT transport even in young, exclusively breast-fed infants. The usual absence of a discernible effect on infant platelet 5-HT transport is consistent with the relatively low levels of sertraline observed in infant plasma. However, it should be noted that the maximum decline in platelet 5-HT of −22% seen in one infant (number 14) for whom we could not obtain a drug level is conceivably consistent with the drug effect caused by a 2–3 ng/ml infant plasma sertraline level (compare this 22% reduction in platelet 5-HT to the 70% decline in mother number 1, who had a plasma drug level of 7 ng/ml).
Several aspects of using platelet 5-HT levels as a measure of 5-HT transporter inhibition deserve comment. First, based on the absence of an interindividual correlation between age and 5-HT level, it is doubtful that much age-related intranidividual drift occurred in infant 5-HT levels over the 6-14-week period between pre- and postexposure sampling. Second, although 5-HT is taken up into platelets throughout its life in the plasma, little efflux occurs until the end of the platelet's lifespan (of ~10 days). The resulting long half-life of platelet 5-HT (estimated to be ~5 days) (61) leads to the measure's relatively slow response to changes in 5-HT uptake blockade. Thus, steady-state platelet 5-HT levels can be viewed as an integrated measure of transporter activity. The use of platelet 5-HT levels in this manner assumes that the mean platelet exposure to free plasma 5-HT does not change appreciably between conditions. Finally, although the relevant data are relatively sparse, animal studies (47, 53, 54) strongly suggest that equivalent levels of uptake blockade occur peripherally (in platelets) and centrally (at neuronal and glial uptake sites). Combining neuroimaging techniques for assessing central transporter availability (62) with platelet 5-HT measures may provide a route for better establishing the relationship between the peripheral and central blockade occurring during SSRI administration.

Although one cannot be certain that the absolute levels of inhibition seen peripherally can be extrapolated to central uptake inhibition, this seems likely. It appears quite probable that the relative amount of platelet blockade seen here in the mother and infant groups is highly related to the relative amounts of transporter inhibition occurring centrally in the two groups (47, 53, 54). In summary, it appears that mothers receiving sertraline who breast-feed do not typically subject their infants to drug levels that appreciably affect infant 5-HT transport. In most cases, the effects on infant uptake are negligible; the effects that may occur in infants appear substantially smaller than the effects seen on maternal uptake. Additional research is needed to more definitively establish the safety of sertraline during breast-feeding and to determine whether all SSRIs display a similar (usually negligible) effect on infant uptake.

References


Presented in part at a biennial meeting of the Marc Society, June 24–28, 1998, Iowa City, Iowa. Received Sept. 21, 2000; revision received April 4, 2001; accepted April 24, 2001. From Yale University School of Medicine. Address reprint requests to Dr. Epperson, Department of Psychiatry, Yale University School of Medicine, University Towers, Suite 2H, 100 York St., New Haven, CT 06511; neill.epperson@yale.edu (e-mail).

Supported by a Young Investigator Award from the National Alliance for Research in Schizophrenia and Depression, NIMH grant MH-30929, and Pfizer, Inc.

The authors thank Shani Osbourne, B.A., for help with the preparation of this article.
38. Whitaker-Azmitia PM, Azmitia EC: Astroglial 5-HT1A receptors and S-100 beta in development and plasticity. Perspect Dev Toxicol 1994; 23:194–205
43. Nulman I, Rovet J, Stewart D, Wolpin J, Gardner HA, Theis JGW, Kulmin N, Koren G: Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336:258–262