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ORIGINAL ARTICLE

# Poor Neonatal Adaptation After Antidepressant Exposure During the Third Trimester in a Geographically Defined Cohort

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## Abstract

**Objective:** To examine the associations between antidepressant exposure during the third trimester of pregnancy, including individual drugs, drug doses, and antidepressant combinations, and the risk of poor neonatal adaptation (PNA).

**Patients and Methods:** The Rochester Epidemiology Project medical records-linkage system was used to study infants exposed to selective serotonin reuptake inhibitors (SSRIs; n=1014), bupropion, (n=118), serotonin-norepinephrine reuptake inhibitors (n=80), antidepressant combinations (n=20), or other antidepressants (n=22) during the third trimester (April 11, 2000-December 31, 2013). Poor neonatal adaptation was defined based on a review of medical records. Poisson regression was used to examine the risk of PNA with serotonergic antidepressant and drug combinations compared with that with bupropion monotherapy as well as with high- vs standard-dose antidepressants. When possible, analyses were performed using propensity score (PS) weighting.

**Results:** Forty-four infants were confirmed cases of PNA. Serotonin-norepinephrine reuptake inhibitor monotherapy, antidepressant combinations, and paroxetine monotherapy were associated with a significantly higher risk of PNA than bupropion monotherapy in unweighted analyses. High-dose SSRI exposure was associated with a significantly increased risk of PNA in unadjusted (relative risk, 2.61; 95% confidence interval, 1.35-5.04) and PS-weighted models (relative risk, 2.29; 95% confidence interval, 1.17-4.48) compared with standard-dose SSRI exposure. The risk of PNA was significantly higher with high-dose paroxetine and sertraline than with standard doses in the PS-weighted analyses. The other risk factors for PNA included maternal anxiety disorders.

**Conclusion:** Although the frequency of PNA in this cohort was low (3%-4%), the risk of PNA was increased in infants exposed to serotonergic antidepressants, particularly with SSRIs at higher doses, during the third trimester of pregnancy compared with that in infants exposed to standard doses. Potential risk factors for PNA also included third-trimester use of paroxetine (especially at higher doses) and maternal anxiety.

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Maternal use of antidepressants during the third trimester of pregnancy has been associated with poor neonatal adaptation (PNA), defined as the occurrence of feeding or gastrointestinal disturbances, respiratory distress, motor tone abnormalities, other neurologic signs, or body temperature instability in exposed infants.[1-3] Although estimates vary, PNA is thought to occur in 30% of neonates exposed to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) during the third trimester,[4] reflecting neonatal serotonin toxicity or serotonergic rebound similar to that observed in adults.[5,6]

Most cases of PNA are mild and transient; however, some affected infants require prolonged hospitalization or neonatal intensive care.[7,8] Moreover, PNA can persist through the first 30 days of neonatal life and may be

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associated with more enduring adverse neurodevelopmental effects[9-13] and negative impacts on attachment and caregiving experiences.[14,15] These concerns—and the increasingly prevalent use of antidepressants by women of reproductive age[16]—highlight the importance of identification of risk factors for PNA.[17-20]

Some antidepressants may be associated with a higher risk of PNA than others based on a variety of pharmacologic properties.[21,22] However, questions remain about whether the risk of PNA varies by individual drugs, drug doses,[23-29] or exposure to antidepressant combinations that are often used to address inadequate clinical responses to monotherapy.[30]

## METHODS

### Data Source and Study Sample

We conducted a historical cohort study of the risk of PNA according to antidepressant exposure using the medical records-linkage system of the Rochester Epidemiology Project (REP).[31,32] Rochester Epidemiology Project electronic indices were used to identify live deliveries (April 11, 2000-December 31, 2013) by mothers (aged 15-49 years during the study period) residing in Olmsted County, Minnesota, during pregnancy and through the first 90 days of neonatal life with evidence of at least 1 antidepressant prescription during the third trimester. The REP includes computerized electronic health records (EHRs) and paper records that capture nearly the entire population of Olmsted County compared with US census estimates.[33] The underlying population is considered to be representative of the Upper Midwest region of the United States.[34] We excluded mothers who did not give permission to use their medical records for research (<3.0% of the overall population). The study cohort included liveborn deliveries at more than 34 weeks of gestation; however, during a manual review of potential PNA cases, infants born at 34-36 weeks had disqualifying conditions or diagnoses that made discernment of PNA unfeasible, resulting in the final cohort consisting of mother-infant dyads who delivered at or after 37 weeks of gestation. Infants with disqualifying conditions, electronically identified using International Classification of Diseases, Ninth Revision, diagnostic codes (Supplemental Table 1, available online at http://www.mcpiqojournal.org/), were excluded based on the likelihood of PNA unrelated to maternal use of medication. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies and was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

Study data were abstracted manually from maternal and infant EHRs by trained nurses using a structured abstract form. The REP electronic indices included links to birth certificates that, in addition to information in EHRs, enabled the identification of live deliveries as well as maternal and infant factors, including delivery dates, maternal age at delivery, infant sex, and self-reported maternal race. Additional information abstracted from the health records included mode of delivery, maternal education level, number of previous pregnancies, substance use during pregnancy (alcohol, smoking, illicit drugs, and medications with known withdrawal syndromes such as psychostimulants, opioids, and benzodiazepines), and specific information used to identify cases of PNA.

### Exposure

Information on prescribed antidepressants was abstracted from EHRs and linked electronic records for all inpatient (at the time of discharge) and outpatient drug prescriptions. Electronic prescriptions were converted into RxNorm codes and grouped using the National Drug File-Reference Terminology classification system.[35,36] Rochester Epidemiology Project prescription records have been shown to have high rates of concordance with manual EHR review.[37] The drug exposure data elements included drug name, form, dosage, frequency, quantity prescribed, date prescribed, and number of refills. The study drugs included SSRIs and SNRIs. Bupropion, a norepinephrine-dopamine reuptake inhibitor antidepressant, was used as an active control given the absence of serotonergic activity. Other antidepressants were prescribed too infrequently to permit meaningful comparisons and were not considered further.

This study focused on antidepressant exposure during the third trimester and the

risk of PNA. The third trimester was defined as the first 181 days after the estimated first day of pregnancy (defined according to the best dating criteria for gestational age, comparing the estimated due date based on the last menstrual period, with the earliest estimated due date based on fetal ultrasound in obstetric records) and ending on the delivery date.

The study drugs were classified into broad groups (SSRIs, SNRIs, etc) and individual drugs. Antidepressant combinations were identified based on overlapping exposure windows with verification of prescriber intent (by reviewing maternal records). Combination therapy was classified according to categories of combined agents or individual agents combined with a member of the broad class (eg, bupropion + SSRI).

The peak third-trimester dose (mg/d) of the study drugs was standardized using World Health Organization defined daily doses (Supplemental Table 2, available online at http://www.mcpiqojournal.org/).[38] For each study drug, the highest daily dose prescribed in the third trimester was converted to a standardized dose using the following formula:

$$\text{Standardized dose} = \frac{\text{Observed daily dose } \left(\frac{mg}{day}\right)}{\text{WHO defined daily dose } \left(\frac{mg}{day}\right)}$$

Standardized doses of 2 or more were considered high-dose exposures, and the remainder doses were considered standard-dose exposures, analogous to other approaches.[27,39]

## Outcome

The primary outcome was antidepressant-associated PNA, defined as the occurrence of at least 1 of the neonatal signs listed in Supplemental Table 3 (available online at http://www.mcpiqojournal.org/), as documented in neonatal EHRs.[4] Any neonatal Finnegan scale score of 4 or more before discharge (31-item or 19-item versions) was also considered as evidence of PNA[40,41] given the absence of a validated PNA screening instrument.[42]

The record abstractors reviewed the infant medical records using structured abstraction forms. Potential cases of PNA were then confirmed by 2 primary adjudicators (including 1 neonatologist), who verified accurate documentation of neonatal signs and examined the medical records for causes of neonatal signs other than exposure to the study drug (eg, neonatal infections, metabolic derangements, neurologic disorders, and circulatory illnesses, etc). A third adjudicator (a pediatric intensivist) was consulted in cases of disagreement between the primary adjudicators. Adjudication was performed for records that were not flagged as potential PNA cases to minimize false negatives.

## Risk Factors

Information on risk factors for PNA was abstracted from the maternal and neonatal EHRs. The main risk factor included third-trimester exposure to the study drugs. Other potential risk factors included maternal sociodemographic characteristics; gravidity; maternal depression or anxiety as recorded in EHRs or 2 or more International Classification of Diseases, Ninth Revision, diagnostic codes (Supplemental Table 4, available online at http://www.mcpiqojournal.org/) separated by 30 days or more during pregnancy; maternal substance use during pregnancy (alcohol, smoking, use of drugs); number of maternal medications during the third trimester; use of health care during pregnancy and the first postpartum month (outpatient, emergency room, and hospitalization visits); delivery complications (postpartum hemorrhage, congenital infections, maternal coagulopathies, gestational hypertension, pre-eclampsia, eclampsia, multiple gestation, fetal malpresentation, and spontaneous premature rupture of membranes); delivery method; and the use of assisted reproductive technology.

## Statistical Analysis

The risk of PNA with third-trimester exposure to serotonergic antidepressant monotherapy (SSRIs and SNRIs) compared with that with third-trimester exposure to bupropion monotherapy was estimated using the Zou modified Poisson regression approach with robust sandwich estimators to generate 95% confidence intervals (CIs)[43] and propensity score (PS) weighting using the matching weight approach.[44] Propensity scores were estimated using multivariable logistic regression, with third-trimester exposure to

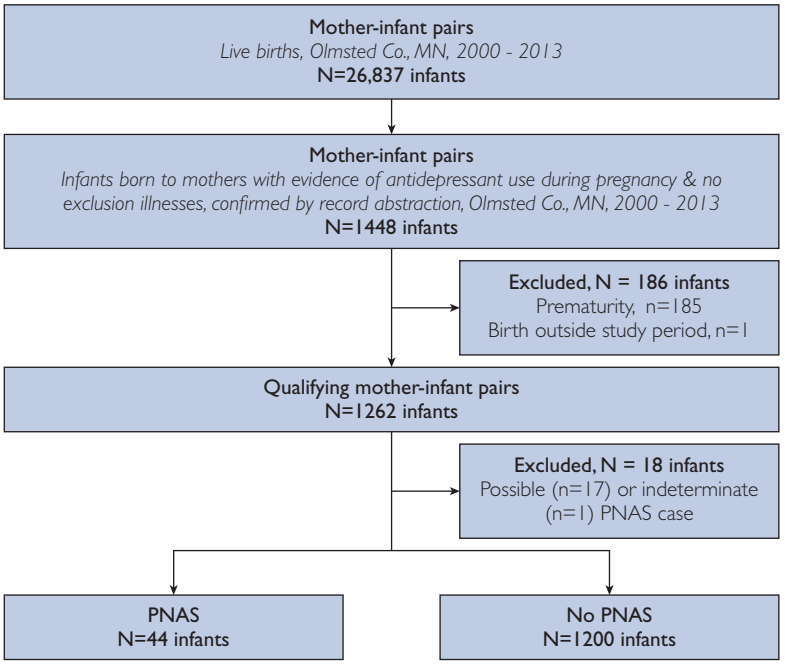


**FIGURE.** Selection of the study cohort. The study cohort consisted of mother-infant pairs for which there was electronic evidence of antidepressant use by mothers during the third trimester of pregnancy, term delivery in Olmsted County (Minnesota) during the study period, and absence of infant exclusionary illnesses (Supplemental Table 2). The records of qualifying mother-infant pairs were reviewed, and information from these records was abstracted to yield study data. Abstracted records were adjudicated to classify infants as having poor neonatal adaptation (PNA), no PNA, or possible or indeterminate PNA. For the main data analyses, only PNA and no-PNA records were included. Sensitivity analyses included possible or indeterminate records as also having PNA.

serotonergic antidepressant monotherapy as the dependent variable and maternal sociodemographic characteristics, primiparity, maternal mood and anxiety disorders (diagnosed during pregnancy or in the year before the estimated onset of pregnancy), and current pregnancy information variables (use of assisted reproductive technology, maternal drug use, infant sex, multiple gestation, and maternal gestational hypertension) as covariates. Balancing success was assessed by examining weighted summaries and standardized mean differences. Imbalance among antidepressant types was considered negligible when the standardized mean differences were less than 0.100. As shown in Supplemental Tables 5a-5r (available online at http://www.mcpiqojournal.org/), PS weighting improved the balance of baseline characteristics across exposure groups.

Additional analyses focused on the risk of PNA associated with antidepressant combinations during the third trimester (vs that associated with bupropion monotherapy) and within subgroups defined by the relative dose of serotonergic antidepressants (standard- and high-dose serotonergic antidepressants vs bupropion monotherapy and high-dose serotonergic antidepressants vs standard-dose serotonergic antidepressants). Analyses of high-dose paroxetine were performed using the overlap weighting approach[45] instead of matching weights because of large imbalances in the baseline characteristics.

For sensitivity analysis, we used an alternative definition of PNA that included both indeterminate and confirmed cases. Statistical analyses were performed using R, version 4.0.3. All statistical tests were 2 sided. *P* values


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**TABLE 1. Distribution of Maternal and Infant Characteristics, Overall and According to the Presence or Absence of Poor Neonatal Adaptation[a,b]**

| Maternal characteristics | PNA (n=44) n (%) | No PNA (n=1200) n (%) | PNA vs no PNA *P* value |
|---|---|---|---|
| Advanced maternal age | 10 (23.0) | 174 (14.0) | .13 |
| Race | | | .24 |
| Caucasian | 38 (86) | 1069 (89) | |
| African American | 0 (0) | 41 (3) | |
| Asian or Pacific Islander | 1 (2) | 15 (1) | |
| Hispanic or non-Caucasian | 0 (0) | 0 (0) | |
| Other or unknown | 5 (11) | 75 (6) | |
| Level of education | | | .29 |
| Less than high school | 0 (0) | 69 (6) | |
| HS graduate or GED | 6 (14) | 207 (17) | |
| Some college | 10 (23) | 338 (28) | |
| College degree | 12 (27) | 280 (23) | |
| Graduate or professional degree | 14 (32) | 243 (20) | |
| Missing or unknown | 2 (5) | 63 (5) | |
| Urban residence[c] | 32 (73) | 968 (81) | .18 |
| Primiparous | 21 (48) | 311 (26) | .008 |
| Any maternal mood disorder[d] | 25 (57) | 515 (43) | .09 |
| Any maternal anxiety disorder[e] | 18 (41) | 269 (22) | .009 |
| **Pregnancy and delivery information** | **n (%)** | **n (%)** | ***P* value** |
| Method of delivery (current pregnancy) | | | .16 |
| Spontaneous vaginal | 23 (52) | 790 (66) | |
| Cesarean | 14 (32) | 273 (23) | |
| Other or unknown | 7 (16) | 137 (11) | |
| Any pregnancy or delivery complication[f] | 19 (43) | 438 (36) | .43 |
| Assisted reproductive technology used | 3 (7) | 38 (3) | .17 |
| Maternal drug use during pregnancy | | | |
| Smoking | 12 (27) | 259 (22) | .36 |
| Alcohol | 5 (11) | 101 (8) | .42 |
| Opioids | 7 (16) | 143 (12) | .48 |
| Benzodiazepines | 2 (5) | 51 (4) | .71 |
| Psychostimulants | 0 (0) | 13 (1) | 1.00 |
| Cannabis | 3 (7) | 51 (4) | .44 |
| Major congenital malformation, if any[g] | 1 (2.3) | 23 (2) | .58 |
| **Maternal characteristics** | **Median (IQR)** | **Median (IQR)** | ***P* value** |
| Maternal age at delivery (y) | 30 (26-34) | 29 (26-33) | .13 |
| N medications taken during the third trimester | 3.5 (2.0-5.0) | 3.0 (2.0-5.0) | .13 |
| **Infant characteristics** | **Median (IQR)** | **Median (IQR)** | ***P* value** |
| Male sex | 28 (64) | 593 (49) | .07 |
| NICU admission, first 24 h of life | 8 (18) | 54 (4) | .001 |

*Continued on next page*

**TABLE 1. Continued**

| Infant characteristics | Median (IQR) | Median (IQR) | *P* value |
|---|---|---|---|
| Gestational length (d) | 273 (269-278) | 274 (270-280) | .22 |
| Birth weight (g) | 3378 (3058-3611) | 3420 (3120-3740) | .26 |
| Head circumference (cm) | 34.2 (33.0-35.0) | 34.5 (33.5-35.5) | .53 |
| APGAR scores (min) | | | |
| 1 | 8 (6-9) | 8 (7-9) | .02 |
| 5 | 9 (8-9) | 9 (9-9) | .07 |

[a]APGAR,; GED, general education degree; HS, high school; IQR, interquartile range; NICU, neonatal intensive care unit; PNA, poor neonatal adaptation.

[b]The sample median (IQR) is shown for continuous variables, whereas the number (percentage of infants) is shown for categorical variables. *P* values for the comparison of PNA with no-PNA result from Wilcoxon rank sum tests or Fisher exact tests. For categorical maternal characteristics, the data shown are n (%)infants with the specified maternal characteristics.

[c]Urban residence was defined as residing in a US census-defined urbanized area of 50,000 or more people.

[d]Maternal mood disorder was defined as evidence of diagnosed major depressive disorder, persistent depressive disorder, dysthymic disorder, other depressive disorder (depressive disorder, not otherwise specified; other specified depressive disorder; or other unspecified depressive disorder), bipolar I or II disorder, cyclothymic disorder, or other bipolar disorder (bipolar disorder, not otherwise specified; other specified bipolar spectrum disorder; other unspecified bipolar spectrum disorder), as identified in maternal electronic health records during pregnancy or in the year preceding the estimated onset of pregnancy.

[e]Maternal anxiety disorder was defined as evidence of diagnosed generalized anxiety disorder, panic disorder (with or without agoraphobia), specific phobia, social phobia (or social anxiety disorder), posttraumatic stress disorder, acute stress disorder, or other anxiety disorder (anxiety disorder, not otherwise specified; other specified anxiety disorder; other unspecified anxiety disorder), as identified in maternal electronic health records during pregnancy or in the year preceding the estimated onset of pregnancy.

[f]Pregnancy or delivery complications included evidence of diagnosed postpartum hemorrhage, congenital infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, group B streptococcus, group A streptococcus), coagulopathy during pregnancy, hypertensive complications during pregnancy (gestational hypertension, pre-eclampsia, eclampsia, Hemolysis, Elevated Liver enzymes, and Low Platelets [HELLP] syndrome), fetal malpresentation, or premature rupture of membranes complicating the current pregnancy or delivery, as identified in maternal or infant electronic health records.

[g]Major congenital malformation was defined as a diagnosed major structural congenital malformation not caused by a chromosomal defect or a clinical genetic syndrome, as identified in maternal or infant electronic health records.

less than .05 were considered statistically significant, without adjustment for multiplicity.

## RESULTS

The cohort initially included 1448 mother-infant pairs with evidence of maternal antidepressant use during the third trimester. Exclusions because of preterm delivery (n=185) and birth outside the study period (n=1) resulted in 1262 mother-infant pairs (Figure), the characteristics of which are summarized in Table 1. Most exposures were to antidepressant monotherapy, mainly with SSRIs (n=1014), SNRIs (n=70), or bupropion (n=118). Twenty exposures were to antidepressant combinations, mainly SSRIs with bupropion (n=14). Exposures to individual study drugs did not differ greatly according to study year, with the exceptions of exposures to fluoxetine and paroxetine decreasing from 2002 and 2006 onward, respectively (Table 2).

There were 44 confirmed cases of PNA, the majority of which were exposed to SSRI monotherapy (n=35), followed by SNRI monotherapy (n=6), bupropion monotherapy (n=1), and antidepressant combinations (n=2). The most common signs of PNA among the 44 confirmed cases were jitteriness, respiratory problems, poor feeding, and hypoglycemia (Supplemental Table 3). One of the 44 cases of confirmed PNA was based only on Finnegan scale scores.

Infants with confirmed PNA had significantly higher frequencies of the diagnosis of maternal anxiety disorders during pregnancy, primiparity, and admission to the neonatal intensive care unit during the first 24 hours of life than infants without PNA (Table 1). The association between the diagnosis of maternal anxiety disorders and PNA was significant in an unadjusted analysis and analyses that were adjusted for exposure to benzodiazepines, antipsychotic drugs, and both benzodiazepines and antipsychotics (Supplemental


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TABLE 2. Frequencies of Serotonergic Antidepressant Exposure, Bupropion Exposure, and Poor Neonatal Adaptation by Delivery Year[a]

| | 2000 (n=18) | 2001 (n=28) | 2002 (n=45) | 2003 (n=48) | 2004 (n=73) | 2005 (n=101) | 2006 (n=93) | 2007 (n=102) | 2008 (n=98) | 2009 (n=137) | 2010 (n=128) | 2011 (n=140) | 2012 (n=118) | 2013 (n=133) | Total (n=1262) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Citalopram | 3 (17) | 1 (4) | 11 (24) | 8 (17) | 19 (26) | 29 (29) | 27 (29) | 28 (27) | 24 (24) | 32 (23) | 29 (23) | 38 (27) | 31 (26) | 32 (24) | 312 (25%) |
| Escitalopram | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (3) | 2 (2) | 4 (4) | 2 (2) | 4 (4) | 5 (4) | 3 (2) | 4 (3) | 7 (6) | 7 (5) | 40 (3%) |
| Fluoxetine | 5 (28) | 6 (21) | 6 (13) | 8 (17) | 12 (16) | 13 (13) | 11 (12) | 13 (13) | 11 (11) | 23 (17) | 15 (12) | 18 (13) | 11 (9) | 12 (9) | 164 (13%) |
| Fluvoxamine | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 1 (0%) |
| Paroxetine | 1 (6) | 2 (7) | 5 (11) | 8 (17) | 9 (12) | 9 (9) | 6 (6) | 0 (0) | 2 (2) | 4 (3) | 2 (2) | 2 (1) | 0 (0) | 0 (0) | 50 (4%) |
| Sertraline | 6 (33) | 16 (57) | 18 (40) | 20 (42) | 24 (33) | 33 (33) | 34 (37) | 35 (34) | 38 (39) | 39 (28) | 55 (43) | 59 (42) | 42 (36) | 58 (44) | 477 (38%) |
| Duloxetine | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 2 (2) | 2 (1) | 2 (2) | 5 (4) | 3 (3) | 2 (2) | 17 (1%) |
| Venlafaxine | 0 (0) | 1 (4) | 3 (7) | 2 (4) | 3 (4) | 4 (4) | 3 (3) | 6 (6) | 5 (5) | 7 (5) | 8 (6) | 3 (2) | 8 (7) | 6 (5) | 59 (5%) |
| Poor neonatal adaptation | 0 (0) | 1 (4) | 0 (0) | 1 (2) | 2 (3) | 2 (2) | 1 (1) | 5 (5) | 5 (5) | 5 (4) | 4 (3) | 7 (5) | 6 (5) | 5 (4) | 44 (3%) |

[a]Data are presented as n (%).

Table 6, available online at http://www.mcpiqojournal.org/). Infants with confirmed PNA were more likely to have lower APGAR scores at 1 minute but not 5 minutes than infants without PNA. There were no significant differences in any of the other characteristics between infants with PNA and those without PNA.

Neither serotonergic antidepressant monotherapy (SSRI or SNRI) nor SSRI monotherapy was associated with a significantly increased risk of PNA compared with bupropion monotherapy (Table 3). Serotonin-norepinephrine reuptake inhibitor monotherapy was associated with a significantly higher risk of PNA than bupropion in the unweighted analyses (relative risk [RR], 9.65; 95% CI, 1.19-78.56) but not in the PS-weighted analyses. For individual SSRIs, paroxetine was associated with a significantly increased risk of PNA compared with bupropion (RR, 9.52; 95% CI, 1.09-83.07) but only in the unweighted analyses (Table 3).

In the analyses of the risk of PNA with high- vs standard-dose exposure, high-dose monotherapy with any SSRI and sertraline was associated with an increased risk of PNA compared with standard-dose exposures in both the unweighted and PS-weighted analyses (Table 4). High-dose paroxetine monotherapy was also associated with a significantly higher risk of PNA than standard-dose paroxetine monotherapy after PS weighting.

Sensitivity analyses that included 18 indeterminate cases of PNA supported the main findings for monotherapy with any SNRI and the risk of PNA in both the unweighted and PS-weighted analyses (Supplemental Table 7a, available online at http://www.mcpiqojournal.org/); however, the relationship between paroxetine monotherapy and PNA was no longer statistically significant in the unweighted analyses. The sensitivity analyses were also consistent with the main findings for high- vs standard-dose monotherapy with any SSRI and paroxetine. High-dose sertraline was associated with an increased risk of PNA compared with standard-dose sertraline in both the unweighted and PS-weighted analyses (Supplemental Table 7b).

Combination therapy with serotonergic antidepressants (SSRIs or SNRIs) and bupropion was associated with a higher risk of

**TABLE 3. Risk of Poor Neonatal Adaptation Among Study Infants According to Fetal Exposure to Serotonergic Antidepressants or Bupropion During the Third Trimester**

| Exposure groups | Fraction with poor neonatal adaptation (%) | Unadjusted analysis | | PS-weighted analysis | |
|---|---|---|---|---|---|
| | | RR for poor neonatal adaptation (95% CI) | *P* value | RR for poor neonatal adaptation (95% CI) | *P* value |
| Serotonergic antidepressant monotherapy vs bupropion monotherapy | | | | | |
| SSRI or SNRI | 41/1101 (3.7%) | 4.43 (0.62-31.93) | .14 | 4.20 (0.58-30.56) | .16 |
| SSRI | 35/1027 (3.4%) | 4.06 (0.56-29.33) | .17 | 3.94 (0.54-28.88) | .18 |
| SNRI | 6/74 (8.1%) | 9.65 (1.19-78.56) | .034 | 9.43 (0.93-95.90) | .058 |
| Bupropion | 1/119 (0.8%) | 1.00 (Reference) | | 1.00 (Reference) | |
| Individual SSRI monotherapy vs bupropion monotherapy | | | | | |
| Sertraline | 15/471 (3.2%) | 3.79 (0.51-28.40) | .19 | 2.98 (0.39-22.95) | .29 |
| Citalopram or escitalopram | 11/341 (3.2%) | 3.84 (0.50-29.42) | .20 | 4.83 (0.61-37.88) | .13 |
| Fluoxetine | 5/164 (3.0%) | 3.63 (0.43-30.65) | .24 | 5.32 (0.58-49.19) | .14 |
| Paroxetine | 4/50 (8.0%) | 9.52 (1.09-83.07) | .041 | 9.03 (0.79-103.24) | .077 |
| Bupropion | 1/119 (0.8%) | 1.00 (Reference) | | 1.00 (Reference) | |

PS, propensity score; RR, relative risk; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

PNA than SSRIs alone (RR>2.0). However, the associations were not statistically significant in the PS-weighted analyses. Combination therapy with serotonergic antidepressants and bupropion was associated with a significantly higher risk of PNA than bupropion monotherapy but only in the unweighted analyses (RR, 11.90; 95% CI, 1.13-125.19).

## DISCUSSION

This study documented a higher risk of PNA with SNRI monotherapy and antidepressant combination therapy than with bupropion monotherapy during the third trimester in the unweighted statistical analyses. Propensity score weighting resulted in attenuation of these associations, resulting in a null finding for both the exposures. However, in the analyses of the relative dose of the study drugs and the risk of PNA, high-dose SSRI monotherapy was associated with a significantly higher risk of PNA than standard-dose SSRI monotherapy. For individual SSRIs, high-dose paroxetine and high-dose sertraline were associated with an increased risk of PNA compared with standard-dose exposures.

The increased risk of PNA with SNRIs compared with that with bupropion is consistent with the absence of serotonergic activity with bupropion[46,47] and is broadly consistent with previous studies of the risk of PNA that mainly used antidepressant nonuser controls.[4,48] Although positive associations were found (RR>1), monotherapy with any SSRI was not associated with a significantly greater risk of PNA than bupropion monotherapy. This unanticipated finding may have been due to the low frequency of confirmed PNA (approximately 4% of exposed infants) in our study, which is at the low end of the frequency range (3%-85%) reported in other studies of antidepressant-associated PNA.[4,49] Although our case definition of PNA included a broad range of neonatal signs, we excluded preterm deliveries and specific congenital or neonatal illnesses and subjected potential PNA cases to further review to reduce misclassification of PNA because of factors other than exposure to the study drugs.[50,51] Collectively, these procedures may have resulted in the identification of fewer cases of PNA than would have been otherwise permitted.

In our study, the risk of PNA was higher with high-dose SSRIs than with standard-dose SSRIs using a standardized dose cutoff of 2, analogous to that in other studies in which high doses were above those considered minimally effective.[27,39] Our approach to dose categorization is valid given that the dose-response curve is flat for most antidepressants within their approved range.[52,53] However, we did not include a low-dose category, and the


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**TABLE 4. Association of Fetal Exposure to High-Dose Antidepressants During the Third Trimester With the Risk of Poor Neonatal Adaptation[a]**

| Exposure groups | Fraction with poor neonatal adaptation (%) | Unadjusted analysis | | PS-weighted analysis | |
|---|---|---|---|---|---|
| | | RR for poor neonatal adaptation (95% CI) | *P* value | RR for poor neonatal adaptation (95% CI) | *P* value |
| SSRI monotherapy | | | | | |
| High dose | 20/347 (5.8%) | 2.61 (1.35-5.04) | .004 | 2.29 (1.17-4.48) | .015 |
| Standard dose | 15/680 (2.2%) | 1.00 (Reference) | | 1.00 (Reference) | |
| Sertraline monotherapy | | | | | |
| High dose | 10/167 (6.0%) | 3.64 (1.27-10.47) | .017 | 3.31 (1.05-10.39) | .041 |
| Standard dose | 5/304 (1.6%) | 1.00 (Reference) | | 1.00 (Reference) | |
| Citalopram or escitalopram monotherapy | | | | | |
| High dose | 6/118 (5.1%) | 2.27 (0.71-7.28) | .17 | 2.06 (0.59-7.19) | .26 |
| Standard dose | 5/223 (2.2%) | 1.00 (Reference) | | 1.00 (Reference) | |
| Fluoxetine monotherapy | | | | | |
| High dose | 2/51 (3.9%) | 1.48 (0.25-8.57) | .66 | 1.12 (0.16-7.98) | .91 |
| Standard dose | 3/113 (2.7%) | 1.00 (Reference) | | 1.00 (Reference) | |
| Paroxetine monotherapy[b] | | | | | |
| High dose | 2/11 (18.2%) | 3.55 (0.56-22.37) | .18 | 113.14 (2.86-4478.31) | .012 |
| Standard dose | 2/39 (5.1%) | 1.00 (Reference) | | 1.00 (Reference) | |
| SNRI monotherapy[c] | | | | | |
| High dose | 0/12 (0.0%) | | .58 | | |
| Standard dose | 6/62 (9.7%) | | | | |

[a]PS, propensity score; RR, relative risk; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

[b]PS-weighted standardized mean differences in some maternal characteristics between those exposed to high-dose paroxetine and those exposed to standard-dose paroxetine were not comparable after using matching weights, Therefore, the PS-weighted analysis used overlap weights.

[c]Relative risks were not estimated for the analysis evaluating the association of high-dose SNRI exposure with the risk of poor neonatal adaptation because of no infants developing poor neonatal adaptation in the group exposed to high-dose SNRI; the *P* value results from the Fisher exact test. The unadjusted difference (high- vs standard-dose SNRI) in the proportion of patients who developed poor neonatal adaptation was −9.7% (95% CI, −19.5% to 15.1%). The CI for the difference in independent proportions was estimated using the Wilson score method.

peak dose of a study drug may not have been the maintenance dose for some cohort members, which are acknowledged limitations. Furthermore, the doses of some antidepressants may need to be increased during pregnancy because of changes in the activity of drug-metabolizing isoenzymes.[22,54,55] Therefore, some high-dose exposures in our study may reflect the dose adjustments needed to maintain therapeutic efficacy. Finally, the thresholds defining high-dose exposures were at the maximum approved doses (nongeriatric adults) for some agents but not others. The extent to which this discrepancy may have led to drug-specific differences in the ability to detect the risk of PNA conditioned on the relative dose is unknown. Overall, our findings support existing recommendations for the maintenance of the lowest effective doses of antidepressants in pregnant women.[56-58]

High-dose paroxetine and high-dose sertraline were the only specific antidepressants associated with a significantly increased risk of PNA in this study compared with standard-dose exposures. Paroxetine has a number of properties that may confer a higher risk of PNA, including a short elimination half-life, lack of active metabolites, and anticholinergic properties.[21] Guidelines typically recommend against the use of paroxetine during early pregnancy to minimize the risk of congenital malformations.[59,60] Our results suggest that to minimize the risk of PNA, alternatives to paroxetine should be considered when antidepressants are needed during late

pregnancy, especially if higher doses may be needed. Our results also suggest that decisions about increasing the dose of sertraline beyond standard doses should account for a potential increase in the risk of PNA.

Very little is known about bupropion and the risk of neonatal complications when used during late pregnancy.[61] The few available studies have found no significant adverse relationship between bupropion and gestational age or birth weight,[62-64] although 1 study documented a potential increased risk of miscarriage.[64] We are not aware of any previous studies of bupropion-associated risk of PNA. In this study, 1 PNA case was observed in the bupropion group. The reasons for this finding may include nonserotonergic mechanisms underlying the risk of PNA and the occurrence of PNA because of exposures other than those to bupropion such as other maternal or obstetric factors or undiagnosed neonatal illness. Because bupropion is commonly used by women of reproductive age,[65] additional studies of the reproductive safety of bupropion are needed.

Our study also focused on antidepressant combinations, most commonly serotonergic antidepressants and bupropion. The increased risk of PNA with antidepressant combinations in the unweighted analyses but not in the PS-weighted analyses may be related to confounding by indication severity given that antidepressant combinations are used to manage more severe disorders and that increased levels of maternal depressive symptoms during late pregnancy are associated with a heightened risk of PNA.[26,30] In addition, bupropion is an inhibitor of CYP2D6 and can cause significant elevations in plasma concentrations of certain serotonergic antidepressants.[66,67] This may further increase the risk of PNA given positive correlations between the symptoms of PNA and the levels of antidepressant drugs.[10]

This study identified maternal anxiety as a potential risk factor for PNA. For many patients, the target doses of several antidepressants may be higher for anxiety disorders than for depression,[68] which may contribute to a heightened frequency of PNA associated with anxiety disorders. On the other hand, the importance of maternal anxiety as a modifiable risk factor for a variety of adverse neonatal outcomes is being increasingly recognized.[69] To our knowledge, the only study that examined maternal anxiety and the risk of antidepressant-associated PNA yielded negative findings.[70] More studies investigating maternal anxiety and the risk of PNA in antidepressant-exposed neonates are needed.

Our study has limitations in addition to those discussed above. Some potential risk factors for PNA were not assessed in this study, including type of infant feeding, maternal obesity, adequacy of prenatal care, and level of psychosocial support. The low number of PNA cases in our cohort likely contributed to imprecise point estimates (wide 95% CIs), limited power, and the inability to perform PS-weighted analyses for all comparisons. Other factors may have interfered with PNA case identification, including limited validity of screening tools, such as the Finnegan scale, for the detection of PNA and loss to follow-up, the extent of which was not evaluated in this cohort. Record abstraction and adjudication were unblinded with respect to antidepressant exposure status. We did not identify bupropion use for smoking cessation. Such cases may have differed in important ways from women who were depressed. Maternal anxiety and depression were based on diagnosed conditions and not symptom scales, which may have increased the chance of false negatives. Some of the differences in the frequencies of PNA between serotonergic antidepressants and bupropion may be partially accounted for by bupropion being less likely to be prescribed for anxiety disorders, which was a risk factor for PNA in this study. This study highlighted PNA associated with only a limited number of medication combinations and did not consider the effects of concomitantly prescribed antipsychotic drugs, the latter of which have been recently associated with a similar risk of PNA as serotonergic antidepressants in a registry-based cohort.[71] The magnitude of exposure was based on peak doses; therefore, changes in antidepressant doses and cumulative antidepressant exposures were not addressed. Although exposure to substances of abuse were accounted for in the propensity score model, we cannot exclude the possibility of residual confounding by exposure to substances of abuse and neither standard screening tools nor urine toxicology results


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were used to define these exposures. The characteristics of the REP population may not generalize to the general US population. Finally, our study did not focus on the associations between PNA and longer-term neurodevelopmental and behavioral outcomes or shorter-term effects on hospital stay.

## CONCLUSION

This cohort study documented an increased risk of PNA in infants exposed to serotonergic antidepressants, particularly SSRIs at higher doses, during the third trimester of pregnancy, compared with bupropion. The risk factors for PNA also included third-trimester use of paroxetine (especially at higher doses) and maternal anxiety. To minimize the risk of PNA, our findings support, whenever possible, using standard antidepressant doses, avoiding polydrug therapy, and considering alternatives to paroxetine if antidepressants are needed during late pregnancy.

## POTENTIAL COMPETING INTERESTS

Dr Bobo reports having received royalties or licenses from UpToDate for chapters contributed on pharmacotherapy for people with bipolar disorders. Dr Brumbaugh reports internal funding from institution for statistician time from the Department of Development and Department of Pediatric and Adolescent Medicine Small Grants Program, Department of Medicine Small Grants Program — Influence of Language Barriers on Hospital Readmission and ED Re-visitations, CCaTS-CBD Pilot Award for Team Science — Understanding the connection between mother and infant in breast milk driven protection of neonatal sepsis, and Ultrasound Research Pilot—Assessment of metabolic bone disease of prematurity using an acoustic method; receiving external funding from the National institute of Arthritis and Musculoskeletal and Skin Diseases; being the Past President of District VI Association of Neonatologists (2019-2021); and being the Past Secretary of District VI Association of Neonatologists (2016-2019).

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Dr Bobo had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bobo, Carey, and Crook were involved in study concept and design. Drs Bobo and Crook and Authors Ball and Stoppel were involved in acquisition, analysis, or interpretation of data. Author Ball and Dr Crook performed the statistical analysis. Dr Bobo drafted the manuscript. Authors Ball and Stoppel and Drs Brumbaugh, Carey, and Crook were involved in critical revision of the manuscript for important intellectual content. The current study was supported by the Rochester Epidemiology Project records-linkage system in terms of administrative, technical, or material support. All authors have read and approved the final version of the manuscript. Drs Carey and Bobo contributed equally to this work.

## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CI,** confidence interval; **EHR,** electronic health record; **PNA,** poor neonatal adaptation; **PS,** propensity score; **REP,** Rochester Epidemiology Project; **RR,** relative risk; **SNRI,** serotonin-norepinephrine reuptake inhibitor; **SSRI,** selective serotonin reuptake inhibitor

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