Risk of Poor Neonatal Adaptation Syndrome Among Infants Exposed to Second-Generation Atypical Antipsychotics Compared to Antidepressants:

Results From the National Pregnancy Registry for Psychiatric Medications

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ABSTRACT

Objective: While poor neonatal adaptation syndrome (PNAS) has been particularly well described among infants exposed to antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), this is not the case for second-generation antipsychotics (SGAs). In 2011, the US Food and Drug Administration (FDA) issued a drug safety warning regarding fetal antipsychotic exposure and risk for PNAS and extrapyramidal symptoms (EPS). The primary objective of this study was to examine the risk for PNAS among infants exposed to SGAs compared to SSRI/SNRI-exposed infants, leveraging the prospective, longitudinal design of the National Pregnancy Registry for Psychiatric Medications (NPRPM).

Methods: The NPRPM is a prospective pharmacovigilance program in which pregnant women, aged 18–45 years, are enrolled and followed prospectively. Medical records were systematically reviewed and data abstracted using a checklist of PNAS and EPS symptoms specifically outlined in the FDA drug safety warning. The two study groups included infants exposed to an SGA during pregnancy and infants exposed to an SSRI/SNRI during pregnancy. The primary outcome was the presence of at least one or more PNAS symptoms during the first month of life. Other neonatal outcomes following exposure to the medication of interest, including preterm birth, neonatal intensive care unit (NICU) admission, rates of EPS, and whether infants were discharged home with their mothers, are also reported.

Results: Of the 2,145 women enrolled in this study as of December 16, 2020, a total of 373 women and their infants (n = 384) were eligible for inclusion (n = 193 SGA-exposed infants and 191 SSRI/SNRI-exposed infants). Among SGA-exposed infants, 32.6% (63/193) experienced at least 1 PNAS sign compared to 34.6% of infants (66/191) in the SSRI/SNRI-exposed group. The majority of infants in each group showed no symptoms of PNAS. No differences were observed between the two groups with respect to rates of preterm birth, NICU admission, prevalence of EPS, and timing of infants being discharged home with their mothers.

Conclusions: PNAS symptomatology was comparable among infants exposed prenatally to an SGA or to an SSRI/SNRI. These preliminary findings provide an estimated risk of PNAS among infants exposed to SGAs of roughly 30%. Interestingly, these findings are also consistent with estimates in the literature of PNAS in SSRI/SNRI-exposed infants, suggesting a possible common pathway underlying this phenomenon.

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Exposure to psychotropics during pregnancy raises concern for potential teratogenic risks, as well as a spectrum of other adverse neonatal events including poor neonatal adaptation syndrome (PNAS). While a variety of terms (with variable definitions) have been used to refer to this particular complication, including *neonatal behavioral syndrome*, *neonatal withdrawal/discontinuation syndrome*, *transient neonatal symptoms*, and *neonatal discontinuation syndrome*, they all refer to the same phenomenon.[1–9] Historically, withdrawal syndromes have been extensively studied for many years in pregnant women with substance use disorders.[1,4] Initially described by Dr Loretta Finnegan in the 1970s, the term *neonatal abstinence syndrome* (*NAS*) emerged to describe infants who had been exposed in utero to illicit drugs, specifically opioids, and presented at delivery with a constellation of symptoms including central nervous system, respiratory, and gastrointestinal disturbances.[1,2,4,9] A similar syndrome was also observed in infants exposed to prescription medications, including psychotropics.[1,3–8] Some researchers have continued to use the term *NAS*. Perhaps in an effort to destigmatize this condition, others have adopted the term *PNAS*, which is now widely used in the literature to refer to withdrawal symptoms associated with non-opioid, prescription medications such as psychotropics.[1,3,4] However, the lack of a standardized definition and formal assessment tool for this syndrome has complicated the study of this phenomenon.[1–9]

PNAS encompasses a wide variety of symptoms including (*a*) neurologic symptoms such as jitteriness, muscle tone irregularities (either hypotonia or hypertonia), tremors, sleeping difficulties, high-pitched or frequent crying, agitation/irritability, and myoclonus;

Clinical Points

- Findings from the National Pregnancy Registry for Psychiatric Medications suggest that risk for poor neonatal adaptation symptoms (PNAS) is similar among infants exposed to second-generation antipsychotics (SGAs) compared to those exposed to selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants at roughly 30%. No differences between the two groups were observed for preterm birth, neonatal intensive care unit (NICU) admission, rates of extrapyramidal symptoms (EPS), and infants being discharged with mothers.
- The majority of infants in each exposure group (SGA vs SSRI/SNRI) showed no symptoms of PNAS; therefore, the rationale for stopping a maintenance psychotropic to avoid the risk of PNAS around delivery is unsound given the high risk of recurrence following discontinuation of maintenance psychotropic as well as the high risk of further decompensation during the postpartum period.
- The risk of serious adverse events from prenatal exposure to SGAs around delivery was low. The recommended clinical approach is to closely monitor the SGA-exposed infant at delivery and during the first few days of life for emergence of PNAS. Fortunately, most cases of PNAS are mild and of short duration, and symptoms generally resolve spontaneously without need for treatment.

(*b*) gastrointestinal issues such as feeding difficulties; and (*c*) respiratory difficulties, such as tachypnea and respiratory distress.[1,4] In most cases, the symptoms are non-specific given the limited repertoire of an infant's physiologic response to a stressor.[1] Therefore, it can be very difficult to differentiate PNAS from other neonatal syndromes, including infection, metabolic derangements, or neurologic symptoms such as extrapyramidal symptoms (EPS).[1,4] While some infants develop symptoms of PNAS, others do not.[1,3,4] Overall, the symptom expression of PNAS varies along a continuum, both in terms of signs/symptoms and severity, and therefore each psychotropic-exposed infant is unique in their expression of PNAS symptoms.[1,2,4] Clinically, there is no way to accurately predict the expression of PNAS or its severity in any given infant.[1,2,4] Additionally, other maternal, infant, and environmental factors are likely to modify the expression of PNAS, including comorbid medical conditions in the infant, prematurity, cigarette smoking, and timing of medication exposure.[1,4,10] Surprisingly, there are limited data regarding risk factors for PNAS, which include type and dose of antidepressant, tobacco smoking, maternal anxiety and depression, type of feeding, and prematurity.[1,10] Other risk factors such as maternal comorbidities have not been systematically studied.

The precise etiology of PNAS is also not fully understood and is likely multifactorial given the variability in symptom presentation of PNAS among infants with histories of fetal exposure to psychiatric medications.[1,4,10] Some have speculated that these symptoms may be secondary to withdrawal and/or toxicity, but also may be due to other poorly examined factors, including genetic, epigenetic, and other environmental exposures like maternal depression and anxiety.[1,4] Assessment tools for PNAS are also highly variable further complicating the true prevalence of PNAS among psychotropic-exposed infants. The Finnegan Neonatal Abstinence Scoring System (FNASS) was initially developed to evaluate the clinical manifestations of NAS in opioid-exposed infants. The scoring system was based on direct observation, record review, and maternal report along 3 dimensions of withdrawal (central nervous system disturbances, metabolic, vasomotor and respiratory disturbances, and gastrointestinal disturbances).[2,9] However, this scale has never been validated in infants exposed to psychotropics.[4] Previously published studies have used other assessment instruments for PNAS, which are also highly subjective and lack standardization, over various observation periods. Tables 1 and 2 demonstrate the wide range of definitions previously used to categorize PNAS, along with percentages of infants observed to meet these definitions with antidepressant-exposed infants[11–29] and second-generation antipsychotic (SGA)–exposed infants.[30–39]

PNAS has been widely associated with selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) exposure. In 2004, the US Food and Drug Administration (FDA) issued a safety report update for SSRI and SNRI antidepressants introducing a warning about the association of third trimester exposure to antidepressants and signs and symptoms of withdrawal (ie, PNAS).[40] Since then, numerous published studies suggest a risk of around 30% for PNAS among prenatally SSRI/SNRI-exposed infants, although estimates have varied widely from 20% to 70%, which is likely due to the lack of a consensus definition of PNAS.[3,6–8,11–29] In most infants, PNAS symptoms tend to develop within 48 hours after birth. The majority of cases of PNAS are mild and of short duration; some reports have noted PNAS symptoms that appear to be more enduring.[41] Generally, symptoms tend to resolve spontaneously without need for a specific treatment intervention.[1,4]

In contrast to the literature on SSRI/SNRI exposure and PNAS, there is a marked paucity of data relating to PNAS in newborns exposed to SGAs,[1,4,5] although risks of extrapyramidal and withdrawal syndromes associated with third trimester exposure of first-generation antipsychotics have long been recognized.[38] In 2011, the US FDA issued a drug safety warning regarding concerns about fetal exposure to antipsychotics, including first- and second-generation, and risk for withdrawal symptoms and EPS based on data from the Adverse Event Reporting Systems (AERS).[42] The AERS database identified 69 cases between 2008 to 2011 of neonatal extrapyramidal or withdrawal symptoms associated with both first- and second-generation antipsychotics. The reported symptoms included hypertonia, hypotonia, tremor, agitation, somnolence, respiratory distress, and feeding disorder. Symptom onset occurred at delivery or up to 1 month after delivery. Symptoms also varied in severity, with some infants recovering within a few hours to days without any specific intervention, while others required neonatal

Table 1. Literature Definitions of PNAS With Antidepressant Exposure

Article	Sample and Source	Definition/Measurement of PNAS	Study Type and Results
Costei et al, 2002[11]	n = 55 Women with 3rd trimester paroxetine usage n = 27 Women with 1st or 2nd trimester paroxetine usage n = 27 Control Maternal phone interview performed after delivery of women who called MotherRisk about 3rd trimester paroxetine exposure	Neonatal complications that required prolonged hospitalization	Prospective Neonatal complications: 22% 3rd trimester vs 6% other
Laine et al, 2003[12]	n = 20 Women on 20–40 mg/d of citalopram or fluoxetine for depression or panic disorder n = 20 Control not on any medications Patients referred to study by their PCP	Serotonin Syndrome Scale (blood pressure, HR, temp, myoclonus, restlessness, tremor, shivering, hyperreflexia, incoordination, rigidity) during first 4 days of life Tremor > restlessness > rigidity	Prospective n = 17 SSRI vs n = 9 control OR = 6.9 (95% CI, 1.6–2.92)
Källén 2004[13]	n = 997 Infants of mothers on any antidepressant during pregnancy n = 582,796 Infants not exposed to antidepressants during pregnancy Medical records at delivery and during pediatric exam	Respiratory distress diagnostic codes in Swedish Medical Birth Registry	Prospective Swedish Medical Birth Registry AOR = 2.21 (95% CI, 1.71–2.86)
Oberlander et al, 2004[14]	n = 28 Women on SSRI alone n = 18 Women on SSRI and clonazepam n = 23 Healthy controls Assessment by attending physician	Transient neonatal symptoms that suggest "altered adaptation in the newborn period" (jitteriness, respiratory difficulties, hypoglycemia, lethargy, weak or absent cry, desaturation on feeding)	Prospective PNAS in 30% exposed vs 9% control LR = 5.64 (95% CI, 1.1–25.3)
Levinson-Castiel et al, 2006[15]	n = 60 Women on SSRI alone n = 60 Women not on any medications Finnegan scoring by nurses/physicians at 2 hours, then every 8 hours after meals for 48 hours	NAS; Finnegan > 3	Prospective NAS in 30% exposed vs 0% in control Tachypnea in 12 SSRI vs 0 control Tremor in 37 SSRI vs 11 control
Oberlander et al, 2006[16]	n = 1,451 Women on SSRI and depressed n = 14,234 Women not on SSRI and not depressed 5 Separate administrative sources of medical records	*ICD-9* codes for respiratory distress, jaundice, convulsions, or feeding difficulties	Prospective Respiratory distress in 13.9% exposed vs 7.8% in unexposed
Davis et al, 2007[17]	n = 874 Women using SSRI during pregnancy n = 75,219 Women not using SSRIs Automated health system databases	*ICD-9* codes: convulsions, feeding problems, temperature regulation	Retrospective RR of respiratory distress = 1.97 (95% CI, 1.65–2.35)
Ferreira et al, 2007[18]	n = 76 Women taking SSRI or venlafaxine during pregnancy n = 90 Women not using SSRI/venlafaxine Chart review	Composite of signs and symptoms involving CNS, respiratory, and digestive systems, as well as hypoglycemia and the need for phototherapy—must have at least 1 CNS > respiratory	Retrospective chart review OR = 3.1 (95% CI, 1.3–7.1) for late exposure to SSRIs/venlafaxine Tachypnea in 40.8% exposed vs 15.6% unexposed Shaking in 19.7% exposed vs 6.7% unexposed
Boucher et al, 2008[19]	n = 73 Infants exposed to antidepressant during last 3 weeks of pregnancy n = 73 Infants not exposed to antidepressants during the last 3 weeks of pregnancy Hospital chart review	Categories of symptoms: alertness, muscular tone, neurologic function, GI/feeding, respiratory function, serotonergic/adrenergic activity Tachypnea > tremors > decreased reactivity > feeding difficulties	Case-control (retrospective AE in 78% exposed vs 38% unexposed OR = 7.0 (95% CI, 3.2–15.3) Tachypnea in 43% exposed vs 26% unexposed OR = 2.5 (95% CI, 1.1–5.3) Tremors in 30% exposed vs 3% unexposed
Maschi et al, 2008[20]	n = 200 Infants exposed to antidepressants during pregnancy n = 1,200 Infants not exposed to antidepressants during pregnancy Maternal interviews prior to delivery and 1 month postpartum	Conglomeration of conditions, including respiratory distress, hypoglycemia, jitteriness, lethargy, hypotonia, weak or absent cry, feeding difficulties, neonatal convulsions, and hyperbilirubinemia	Prospective Nonsignificant differences in PNAS symptoms as defined OR = 2.31 (95% CI, 1.14–4.63) for prematurity rate of antidepressant-exposed infants
Galbally et al, 2009[21]	n = 23 Women taking an antidepressant during pregnancy n = 27 Women not taking an antidepressant during pregnancy Maternal questionnaires within 1 week of delivery	Neonatal Abstinence Scoring System (Finnegan): 8 items for CNS, 4 items for GI, 8 items for other; score > 0	Prospective Respiratory distress in 21.7% exposed vs 11.1% control RR = 1.957 (95% CI, 0.52–7.32) Tremor in 56.5% exposed vs 0% unexposed RR = 31.5 (95% CI, 1.98–502.48) Sleeping soon after feeding > tremors > feeding difficulties

(continued)

Table 1 (continued).

Article	Sample and Source	Definition/Measurement of PNAS	Study Type and Results
Galbally et al, 2017[22]	n = 52 AD n = 230 Control NASS administered by midwives twice a day for 3 days	Neonatal Abstinence Scoring System (Finnegan): 8 items for CNS, 4 items for GI, 8 items for other—score > 0 Sleeping soon after feeding > tremors > feeding difficulties	Prospective 30/31 infants exposed at birth experienced withdrawal symptoms within 5 days of birth (97%) vs 2/11 not exposed at birth (18%)
Rampono et al, 2009[23]	n = 38 Women on SSRI or SNRI n = 18 Women not taking SSRI or SNRI during pregnancy Daily assessment by midwives using NAS scale	NAS; Finnegan > 12 or 3 scores > 8	Prospective NAS in 5% exposed with median Finnegan = 2 on day 1
Zeskind and Stephens, 2004[24]	n = 17 Infants exposed to SSRIs n = 17 Infants not exposed to SSRIs	Behavioral state, startles, tremulousness, motor activity, HRV for 1 hour in between feedings between 14 and 39 hours of age	Prospective Significant differences in tremulousness and behavioral states
Suri et al, 2007[25]	n = 49 Women with MDD taking antidepressant n = 22 Women with MDD not taking antidepressant for > 10 days during the pregnancy or who had discontinued in first trimester n = 19 Healthy controls	Rates of admission to the special care nursery	Prospective Significant differences between groups in rates of SCN admission (21% vs 9% vs 0%)
Suri et al, 2011[26]	n = 33 Women with MDD taking antidepressants n = 16 Women with MDD not taking antidepressants for > 10 days during the pregnancy or who had discontinued in first trimester n = 15 Healthy controls	Apgar scores, special care nursery admissions, BNBAS	Prospective No significant differences between groups on any of the BNBAS clusters
Chambers et al, 1996[27]	n = 228 Women using fluoxetine during their pregnancy n = 254 Women not using fluoxetine during pregnancy Maternal interview perinatally and postpartum + medical records	PNAS defined as jitteriness, tachypnea, hypoglycemia, hypothermia, poor tone, respiratory distress, weak or absent cry, or desaturation on feeding	Prospective 3rd trimester exposure to fluoxetine associated with increased SCN admission RR = 2.6 (95% CI, 1.1–6.9) and PNAS RR = 8.7 (95% CI, 2.9–26.6)
Lund et al, 2009[28]	n = 329 Women treated with SSRI during pregnancy n = 4,902 Women with history of psychiatric illness but no antidepressant treatment n = 51,770 Women with no psychiatric illness Maternal questionnaire during second trimester + midwife assessment at birth	5-min Apgar, NICU admission	Prospective SSRI-exposed had increased risk of NICU admission OR = 2.39 (95% CI, 1.69–3.39) vs control and OR = 2.04 (95% CI, 1.42–2.94) vs +psych/no SSRI SSRI-exposed had increased risk of low 5 min Apgar OR = 4.44 (95% CI, 2.58–7.63) vs control and OR = 6.58 (95% CI, 3.39–12.74) vs +psych/no SSRI
Yang et al, 2017[29]	n = 41 Women exposed to serotonin reuptake inhibitor n = 94 Women diagnosed with depression or bipolar disorder not taking SRI n = 79 Women not taking SRI or diagnosed with mood disorder Finnegan administered by HCP between 2 and 4 weeks of life	Finnegan > 1	Prospective No significant differences—prevalence across all groups ~33% Restless sleep > tremors > nasal stuffiness/sneezing > mottling

Abbreviations: AD = antidepressant, AE = adverse event, AOR = adjusted odds ratio, BNBAS = Brazelton Neonatal Behavioral Assessment Scale, CNS = central nervous system, GI = gastrointestinal, HCP = health care provider, HR = heart rate, HRV = heart rate variability, LR = likelihood ratio, NAS= neonatal abstinence syndrome, NASS = Neonatal Abstinence Scoring System, NICU = neonatal intensive care unit, OR = odds ratio, PCP = primary care provider, PNAS = poor neonatal adaptation syndrome, RR = risk ratio, SCN = special care nursery, SNRI = serotonin-norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 2. Literature Definitions of PNAS With SGA Exposure

Article	Sample and Source	Definition/Measurement of PNAS	Study Type; Results
Habermann et al, 2013[30]	n = 561 Women on SGA n = 284 Women on FGA n = 1,122 Controls	"Postnatal disorders" (ie, respiratory, digestive, cardiac and nervous system)	Prospective, Teratology Information service 15.6% SGA-exposed infants 21.6% FGA-exposed infants 4.2% Control group
Vigod et al, 2015[31]	n = 1,021; 90% on SGA exclusively n = 1,021 Controls not exposed to SGA	"Neonatal adaptation syndrome"	Population-based administrative database 13.3% SGA-exposed 2.1% Controls (when adjusted, 12.9% SGA vs 10.9% controls)
Hatters Friedman et al, 2016[32]	n = 45 Subjects exposed to SGAs	"Perinatal complications" (tremors, respiratory distress, and withdrawal)	Retrospective chart review 9% SGA-exposed
Newport et al, 2007[33]	n = 54 Subjects on SGA or haloperidol Maternal umbilical cord samples and placental passage Maternal report and medical records	"Neonatal complications" Respiratory complications Hypotonia	Prospective observational Respiratory complications, hypotonia: Haloperidol: 7.7%, 7.7% Olanzapine: 30.8%, 7.7% Quetiapine: 33.3%, 0.0% Risperidone: 0.0%, 0.0%
Coppola et al, 2007[34]	n = 516 Prospective receiving risperidone n = 197 Retrospective receiving risperidone	"Perinatal syndromes" (tremor, jitteriness, irritability, feeding problems, somnolence)	Retrospective and prospective observational study 18% With perinatal syndromes
Sadowski et al, 2013[35]	n = 133 Women on SGAs n = 133 Matched healthy controls	Poor neonatal adaptation (CNS, respiratory, GI problems, perinatal conditions)	Prospective cohort 13.2% SGA-exposed 5.17% Healthy controls (higher risk with polytherapy: 21.2% polytherapy vs 4% monotherapy)
Brunner et al, 2013[36]	n = 610 SGA (risperidone only) exposed	"Perinatal conditions" Defined as any adverse event ≤ 7 days post birth	Eli Lilly pharmacovigilance database; retrospective 8%
Kulkarni et al, 2014[37]	n = 147 Infants	"Respiratory distress and withdrawal"	Prospective registry 37% 40% Admitted to NICU or SCN
Petersen et al, 2016[38]	n = 322 Women prescribed an antipsychotic n = 318,434 Control group (not prescribed an antipsychotic)	"Poor birth outcomes" (ie, tremor, agitation, breathing difficulties, muscle tone issues)	Retrospective cohort study UK primary care database 16% Antipsychotic-exposed infants 6.5% Control group
Ellfolk et al, 2020[39]	n = 1,181,090 Women n = 4,225 SGA use in pregnancy n = 1,576 FGA use during pregnancy n = 21,125 Unexposed to FGA or SGA during pregnancy	"Neonatal complications" Apgar 1 and 5 min < 7; NICU, hospitalization within 7 days of birth, neonatal and post-neonatal death	Population based birth cohort in Finland—national register data NICU admission: SGA 23.6%, FGA 21.4%, unexposed 10.1% Hospitalization at 7 days: SGA 14.3%, FGA 14.9%, unexposed 5.3%

Abbreviations: CNS = central nervous system, FGA = first-generation antipsychotic, GI = gastrointestinal, NICU = neonatal intensive care unit, SCN = special care nursery, SGA = second-generation antipsychotic.

intensive care unit (NICU) admission and prolonged hospitalization.[42]

Several heterogeneous studies have also included secondary outcomes data on the frequency of PNAS in SGA-exposed infants. The risk estimate for PNAS among SGA-exposed infants varies widely from 9% to 37%.[30–39] For example, in a published report of 142 live births from the Australian National Register for Antipsychotic Medications in Pregnancy,[37] SGA medication withdrawal symptoms were observed in 37% of infants. Similarly, a prospective observational study of outcomes of pregnancies exposed to SGAs[35] found a significant increase in NICU admissions and a 13.2% risk for poor neonatal adaptation signs, including central nervous system (CNS), respiratory, and gastrointestinal problems, among neonates exposed to SGAs when compared with controls. In another study of 197 retrospective reports from women who used risperidone during pregnancy,[34] 18.7% of infants (37/197) experienced perinatal syndromes. Of these cases, the majority involved behavioral or motor disorders that were considered to be due to drug withdrawal or described events that possibly represented a withdrawal-emergent syndrome. In a prospective study of 54 pregnant women taking first-generation or second-generation antipsychotics,[33] infants exposed to antipsychotics with the highest placental passage ratio, specifically olanzapine, had higher rates of low birth weight and neonatal intensive care admissions compared to those exposed to haloperidol, risperidone, and quetiapine.

Table 3. Maternal Characteristics

Characteristic	SGA (n = 185)	SSRI/SNRI (n = 188)
Demographics		
Age, y		
n	185	188
Mean (SD)	32.8 (4.74)	33.6 (3.83)
95% CI	24.0–42.0	27.0–41.0
Baseline BMI		
n	174	172
Mean (SD)	27.9 (6.33)	25.4 (4.98)
95% CI	18.8–43.9	19.0–38.3
White		
n (%)	173 (93.5)	180 (95.7)
95% CI	0.89–0.96	0.92–0.98
College educated*		
n (%)	142 (76.8)	176 (93.6)
95% CI	0.70–0.82	0.89–0.97
Married		
n (%)	164 (88.6)	179 (95.2)
95% CI	0.83–0.93	0.91–0.98
First-Trimester Exposure		
Cigarettes*		
n (%)	25 (13.5)	6 (3.2)
95% CI	0.09–0.19	0.01–0.07
Alcohol*		
n (%)	30 (16.2)	57 (30.3)
95% CI	0.11–0.22	0.23–0.37
Illicit drugs		
n (%)	7 (3.8)	6 (3.2)
95% CI	0.02–0.08	0.01–0.07
Prenatal vitamins		
n (%)	142 (76.8)	154 (81.9)
95% CI	0.70–0.82	0.75–0.87
Pregnancy History		
Planned pregnancy		
n (%)	152 (82.2)	159 (84.6)
95% CI	0.75–0.87	0.79–0.90
Multigravid		
n (%)	65 (35.1)	49 (26.1)
95% CI	0.28–0.42	0.20–0.33
History of PPD or psychosis		
n (%)	75 (40.5)	65 (34.6)
95% CI	0.70–0.87	0.57–0.76
Primary Diagnosis		
Depression*		
n (%)	12 (6.5)	69 (36.7)
95% CI	0.03–0.11	0.31–0.45
Anxiety*		
n (%)	7 (3.8)	76 (40.4)
95% CI	0.01–0.07	0.33–0.47
Bipolar disorder*		
n (%)	142 (76.8)	7 (3.7)
95% CI	0.71–0.83	0.01–0.07
Schizophrenia*		
n (%)	13 (7.0)	0
95% CI	0.04–0.12	0
Psychiatric Illness Severity		
Lifetime No. of psychiatric hospitalizations		
n	185	188
Mean (SD)	1.8 (3.10)	0.4 (1.68)
95% CI	0.0–10.0	0.0–4.0
Age at onset, y		
n	118	155
Mean (SD)	19.3 (4.56)	20.8 (5.65)
95% CI	12.0–30.0	11.0–34.0
Chronicity		
n	118	155
Mean (SD)	0.4 (0.13)	0.4 (0.16)
95% CI	0.1–0.6	0.0–0.7

*Statistically significant difference between groups.
Abbreviations: BMI = body mass index, NICU = neonatal intensive care unit, PPD = postpartum depression, SGA = second-generation antipsychotic, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 4. Infant Characteristics

Birth Outcome Characteristic	SGA (n = 193)	SSRI/SNRI (n = 191)
Preterm birth		
n (%)	21 (10.9)	21 (11.0)
95% CI	0.07–0.16	0.07–0.16
Birth weight, lb		
n	190	189
Mean (SD)	7.3 (1.30)	7.2 (1.13)
95% CI	4.4–9.6	5.0–9.5
Vaginal delivery*		
n (%)	99 (51.3)	131 (68.6)
95% CI	0.45–0.59	0.61–0.75
1-minute Apgar		
n	152	183
Mean (SD)	7.8 (1.66)	7.2 (1.71)
95% CI	2.0–9.0	2.0–9.0
5-minute Apgar		
n	184	188
Mean (SD)	8.8 (0.91)	8.5 (0.98)
95% CI	7.0–10.0	5.0–9.0
Admission to NICU		
n (%)	34 (17.6)	42 (22.0)
95% CI	0.13–0.24	0.17–0.29
Duration of time in NICU, d		
n	31	40
Mean (SD)	12.0 (13.98)**	4.8 (3.83)
95% CI	0.5–55.0	0.6–14.0
Infants discharged home with mother		
n (%)	161 (83.4)	165 (86.4)
95% CI	0.79–0.90	0.81–0.91

*Statistically significant difference between groups.
**Due to outlier twin pair with extended stay in NICU for prematurity.
Abbreviations: NICU = neonatal intensive care unit, SGA = second-generation antipsychotic, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

A retrospective cohort study[38] based on a UK primary care database noted transient poor birth outcomes including tremor, agitation, and breathing difficulties among 10.7% of antipsychotic-exposed infants compared to controls (4.4%). More recently, a population-based birth cohort study[39] noted that infants exposed to SGAs compared to non-exposed infants were more likely to suffer from neonatal complications such as lower Apgar scores, transfer to NICU, and prolonged hospitalizations.

Given the lack of systematically collected data on the frequency of PNAS at delivery among infants exposed to SGAs, the primary objective of this study was to examine the risk for PNAS/EPS among infants exposed to SGAs compared to SSRI/SNRI-exposed infants leveraging the prospective, longitudinal design of the National Pregnancy Registry for Psychiatric Medications (NPRPM). Other neonatal outcomes, including preterm birth, NICU admission, rates of EPS, and whether infants went home with their mothers, were also considered. Because of a lack of a clear definition for PNAS (as well as EPS) in psychotropic-exposed infants, we decided a priori to systematically apply a verbatim checklist of PNAS symptoms (ie, agitation, sleepiness, breathing difficulties, tremor, and feeding difficulties) and EPS symptoms (ie, abnormal muscle movements such as hypertonia or hypotonia) specifically outlined in the 2011 FDA drug safety warning to this infant cohort.

Table 5. PNAS Symptoms

Characteristic	SGA (n = 193)	SSRI/SNRI (n = 191)
PNAS Symptoms		
Agitation		
n (%)	1 (0.5)	1 (0.5)
95% CI	0.0–0.03	0.0–0.03
Sleepiness		
n (%)	2 (1.0)	1 (0.5)
95% CI	0.00–0.04	0.0–0.03
Difficulty breathing		
n (%)	32 (16.6)	46 (24.1)
95% CI	0.12–0.23	0.18–0.31
Difficulty feeding		
n (%)	36 (18.7)	22 (11.5)
95% CI	0.13–0.25	0.07–0.17
Tremor		
n (%)	0	4 (2.1)
95% CI	0	0.01–0.05
Withdrawal		
n (%)	2 (1.0)	5 (2.6)
95% CI	0.00–0.04	0.01–0.06
Abnormal muscle movements[a]		
n (%)	5 (2.6)	7 (3.7)
95% CI	0.01–0.06	0.01–0.07
No. of PNAS Signs		
0		
n (%)	129 (66.8)	125 (65.4)
95% CI	0.60–0.74	0.58–0.72
1		
n (%)	49 (25.4)	50 (26.2)
95% CI	0.20–0.32	0.20–0.33
2+		
n (%)	14 (7.3)	16 (8.4)
95% CI	0.04–0.12	0.05–0.13

[a]Symptoms also considered EPS symptoms per FDA 2011 safety warning.
Abbreviations: PNAS = poor neonatal adaptation syndrome, SGA = second-generation antipsychotic, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

METHODS

The NPRPM was established in 2008 to prospectively and rigorously obtain reproductive safety data focused on the risk for major malformations associated with SGA use during pregnancy. SGAs included in the Registry consist of any medication and its formulations that are approved by the US FDA, including both brand names and generic versions of each medication, if available. Although the Registry's primary outcome is the rate of major malformations among infants exposed to an SGA, source data regarding neonatal outcomes are also obtained; the focus of this article is on such secondary neonatal outcomes, including rates of PNAS, EPS, NICU admissions, and whether the infant was discharged home with the mother.

Methods of data collection, assessments of outcomes, and guidelines for release of findings for the NPRPM have been previously described.[43–45] In brief, pregnant women between the ages of 18 and 45 years with histories of psychiatric disorders are enrolled. Following verbal consent, participants are prospectively interviewed twice during pregnancy (at enrollment and at 7 months' gestation) and once postpartum (at 3 months following delivery). Information collected includes demographic data, obstetrical history, all medication use (including prescriptions, over-the-counter medications, and supplements) and dosages, psychiatric diagnoses, medical history, and family history of major malformations. Subjects also consent to collection of labor and delivery, neonatal, and pediatric medical records through 6 months of age.

Medical records are reviewed and data abstracted using a standardized neonatal outcomes form developed by the investigators. The neonatal outcomes form is used to collect data, including method of delivery, gestational age, Apgar scores, birth weight, head circumference, length, and any neonatal complications. In addition, the neonatal outcomes form includes a verbatim checklist of withdrawal (ie, agitation, sleepiness, breathing difficulties, tremor, and feeding difficulties) and EPS symptoms (ie, abnormal muscle movements such as hypertonia or hypotonia) described in the FDA drug safety warning.

The neonatal outcomes form is completed for all participants by a trained research assistant and confirmed by one of the study co-principal investigators. For inclusion in this analysis, only data from infants whose mothers completed all interviews and released medical records were considered.

The two study groups consisted of infants exposed to an SGA during pregnancy (without the use of any SSRI/SNRI but with exposure to other psychotropics) and infants exposed to an SSRI/SNRI prenatally (without any exposure to SGAs but with exposure to other psychotropics). Other psychotropics included lithium, anticonvulsants, stimulants, benzodiazepines, and hypnotics.

The primary outcome was the presence of at least one PNAS symptom during the first month of life. Baseline demographics and clinical characteristics were summarized using descriptive statistics. Other neonatal outcomes, including preterm birth, NICU admission, rates of EPS, and whether infants went home with their mothers, were also examined. For continuous variables, data are presented as means and standard deviations.

All study procedures were approved by the Massachusetts General Hospital Institutional Review Board. The study is registered with clinicaltrials.gov (NCT01246765); recruitment is ongoing.

Funding for the Registry derives from manufacturers of second-generation atypical antipsychotic medications who agree to support the reproductive safety initiative with a fixed proportion of the operating costs of the Registry. All manufacturers of second-generation atypical antipsychotics, including generics and brand name compounds, are approached for funding. Regardless of which entities have supported this initiative, all medications in this class are studied. For transparency, a list of the manufacturers who are current sponsors or past sponsors or who have declined to sponsor are displayed on the Registry's website: https://womensmentalhealth.org/research/pregnancyregistry/.

Major policy decisions, such as establishing release criteria for accumulated data and actual making of decisions to release specific study findings, are the responsibility of a

Scientific Advisory Board, independent of the pharmaceutical sponsors, which consists of experts in the fields of teratology, epidemiology, and psychiatry. The Scientific Advisory Board meets twice annually with the Registry's staff to discuss issues related to study methods and to review major findings. Release of findings regarding reproductive safety of specific atypical antipsychotics is dictated by the Scientific Advisory Board and not a given individual sponsor.

RESULTS

Of the 2,145 women enrolled in the study as of December 16, 2020, a total of 1,004 were eligible based on the inclusion criteria of completion of all interviews and agreement to release medical records. Participants who had taken both an SGA and an antidepressant during their pregnancy were excluded from this analysis. Only women who had either taken an SGA(s) and no antidepressant(s) (n = 193 infants) or an antidepressant(s) and no SGA(s) (n = 191 infants) were included in the final analysis (n = 373 women).

Table 3 presents the characteristics of the maternal sample (185 mothers who had taken an SGA during their pregnancy and 188 mothers who had taken an SSRI and/or SNRI during their pregnancy.) The majority of women in each group used these medications across the entire course of their pregnancy, including the third trimester. Women in the SSRI/SNRI-exposed group were more likely to be college educated and married, while women in the SGA-exposed group had higher pre-pregnancy body mass indexes (BMIs) than those in the SSRI/SNRI-exposed group. Importantly, mean maternal age did not appreciably differ between groups. With respect to substance use, cigarette use was significantly more prevalent among the SGA-exposed group, while alcohol use was more prevalent in the SSRI/SNRI-exposed group.

Table 4 presents the characteristics of the infants born to mothers in this sample (193 infants in the SGA-exposed group and 191 infants in the SSRI/SNRI-exposed group.) The two groups did not differ significantly in preterm delivery rates or birth weight, which are two factors that can contribute to poor neonatal adaptation symptoms following delivery.[18,46] Rates of vaginal delivery were significantly higher in the SSRI/SNRI-exposed group compared to the SGA-exposed group. NICU admission rates and duration of time spent in the NICU did not differ significantly between groups. Similar proportions of infants were discharged home with their mothers in both exposure groups.

Table 5 delineates the PNAS outcomes noted in this sample of infants. Overall, 33.6% (129/384) presented with at least 1 sign of PNAS, with 32.6% of SGA-exposed infants (63/193) presenting with at least 1 sign and 34.6% (66/191) of SSRI/SNRI-exposed infants presenting with at least 1 sign. The most commonly observed signs in each group included difficulty breathing and difficulty feeding. However, the majority of infants in each group (66.8% of SGA-exposed infants and 65.4% of SSRI/SNRI-exposed infants) showed no signs or symptoms of PNAS, and only a minority of infants experienced 2 or more PNAS signs (7.3% in the SGA group and 8.4% in the SSRI/SNRI group.) With respect to EPS, defined rather vaguely as "abnormal muscle movements" per the FDA warning, similar proportions of infants experienced abnormal muscle movements among the SGA- and SSRI/SNRI-exposed.

DISCUSSION

While PNAS has been well-described with exposure to SSRI/SNRIs for the last two decades, estimates for the risk of PNAS among SGA-exposed infants has not been systematically studied.[1,4] The prospective design of the National Pregnancy Registry for Psychiatric Medications provided an ideal study design to assess such a risk. Our findings suggest that the risk of PNAS symptomatology is comparable among infants exposed prenatally to an SGA or to an SSRI/SNRI. In fact, the prevalence of PNAS among SGA-exposed infants observed in this study is consistent with estimates in the literature of PNAS in SSRI/SNRI-exposed infants of roughly 30%.[3,8,29] The similarity in prevalence of PNAS between the SGA and SSRI/SNRI-exposed groups suggests a possible common pathway underlying these symptoms.

These findings are also consistent with other studies involving SGA-exposed infants, including data from the Australian National Register for Antipsychotic Medications in Pregnancy[37] and data from another prospective observational study by Newport et al,[33] documenting neonatal complications (ie, cardiovascular, respiratory, and hypotonia) of around 30% for olanzapine- and quetiapine-exposed infants. Other studies have noted lower prevalence rates of PNAS, from around 8%–18%.[30–32,34–36,38] This rather wide range of PNAS prevalence rates in the literature is not surprising given the heterogeneity of the studies, including variable definitions and assessment tools for this syndrome.

With respect to other neonatal outcomes, we found similar rates of premature birth (around 10%) for both the SGA-exposed and SSRI/SNRI-exposed groups, consistent with rates of prematurity in the general population. This finding is reassuring and consistent with some studies,[47,48] but not all.[38,49–52]

We also found similar NICU admission rates in both the SSRI/SNRI-exposed group and the SGA-exposed group (22% vs 17.6%, respectively). Overall, admission rates for this study sample were higher than rates of NICU admission observed in the general population (10%–15% of live births).[53] In addition, infants in the SGA-exposed group spent longer in the NICU compared to infants in the SSRI/SNRI-exposed group (4.8 days) and to infants in the general population (4.9 days).[54] However, it is notable that the majority of infants in each group were discharged home with their mother (83.4% in the SGA group and 86.4% in the SSRI/SNRI group). This important objective clinical outcome can be considered a proxy variable for overall infant well-being.

The strengths of this analysis and the NPRPM include the following: (1) its prospective design; (2) inclusion of a

control group with psychiatric diagnoses; (3) systematic ascertainment of information regarding potential confounders such as comorbidity, substance use, and use of concomitant medications; (4) confirmation of outcomes with medical records; and (5) verification of the neonatal outcomes from medical records using a standardized collection tool completed by a trained research assistant and confirmed by the study coprincipal investigator. In addition, the two exposed groups experienced similar psychiatric morbidity, an important confounder that can contribute to poor neonatal outcomes in addition to medication use alone.[45] Comparisons with the general population of pregnant women are generally inadequate, as they exclude the ability to assess for confounding by other variables that are often associated with psychiatric disorders. Therefore, the lack of significant differences between the groups allows conclusions to be drawn on the effects of medication exclusive to the effects of maternal illness.

There are several important limitations, however, to consider with these analyses. While the sample size of this study is small, it is among the largest prospective studies to date. The extent to which these results are generalizable to the larger population of women taking atypical antipsychotics is unknown. For instance, the demographics of our study population, are overwhelmingly White, married, and well-educated women. Recruitment bias is also inherent in pregnancy registries. Typically, women voluntarily enroll in registries and thus may be higher functioning, better informed, and more motivated to monitor closely their own health and their newborn's health than non-participants.[55] Therefore, interpretation of findings based on women who participate in registries may differ in some respects from interpretation of those of nonparticipants.

In addition, the assessment of PNAS symptoms was neither completed prospectively using a valid assessment tool like the Finnegan Scale nor done by a trained pediatrician blinded to medication exposure. However, our design did include the systematic application of the FDA's description of PNAS symptoms to a prospective cohort of infants.

Given that the majority of women in the NPRPM are on psychotropic polytherapy, inclusion in the exposure and comparison group was not limited to only SGA or SSRI/SNRI monotherapy exposure. In addition to the exposure of interest of either an SGA or an SSRI/SNRI, both groups included exposures to other psychiatric medications like lithium, anticonvulsants, benzodiazepines, stimulants, and/or hypnotics. While it would be ideal to estimate the frequency of PNAS in a pure SGA monotherapy group and a pure SSRI/SNRI group, this was not feasible given that the majority of women who participate in the NPRPM are on psychotropic polytherapy, which reflects the reality of caring for pregnant women with serious mood and anxiety disorders. Additionally, the fact that we observed a frequency of PNAS in the SSRI/SNRI group, despite exposure to other psychotropics, similar to the frequency of PNAS observed in the literature on SSRI/SNRIs, (approximately 30%) is also reassuring. Our findings also suggest that even with exposure to an SGA plus other psychotropics or an SSRI/SNRI plus other psychotropics, the estimate of PNAS for both groups remains around 30% and not significantly higher. Clinically, polytherapy is the rule, not the exception. Therefore, our preliminary estimates for PNAS associated with SGA exposure reflect real-world treatment.

Moreover, other potential confounding variables that were unaccounted for could have contributed to the rates of PNAS independent of medication exposure. The study participants, in both the SGA and the SSRI/SNRI group, were obese (mean BMIs of 27.9 and 25.4, respectively). A much larger percentage of the SGA-exposed patients (50%) underwent cesarean deliveries versus the general population (30%). Both maternal BMI and cesarean delivery are factors associated with increased rates of neonatal respiratory distress and feeding difficulties after birth. The SGA-exposed group also had much higher rates of cigarette use compared to the general population, whereas the SSRI/SNRI-exposed group were drinking more alcohol in pregnancy than the general population. We could have also examined other maternal factors such as gestational diabetes and hypertension in the two groups to see if these factors had an effect on the overall primary outcome. Interestingly, the available studies of PNAS among SGA-exposed infants have not examined these potential risk factors. However, the fact that PNAS rates were similar in both groups suggests the important role of medication exposure independent of these other factors in the expression of PNAS.

Another important limitation of this study involved assessing EPS by applying the vague language described in the 2011 FDA drug safety warning. The FDA warning simply referred to EPS as "abnormal muscle movements"; however, EPS encompass other symptoms including acute dystonic reactions, akathisia, and akinesia. While the assessment of EPS in adults exposed to an antipsychotic is routine in psychiatric practice, such an assessment in an infant is highly unusual and particularly challenging given the overlap of some EPS with non-specific CNS symptoms of infancy.[1] The similar rates of EPS observed in the SGA and SSRI/SNRI groups support the lack of specificity of this definition. Moreover, the FDA warning conflates the two terms *PNAS* and *EPS*, further contributing to confusion. However, the fact that the EPS definition, despite its ambiguity and limitations, was applied a priori and systematically to all cases strengthens the methodological approach. An ideal study design would have been applying a well-validated scale for PNAS symptoms and EPS in a systematic and blinded fashion, but such validated scales do not exist for an infant population.

Additionally, the majority of women in this sample used an SSRI/SNRI or SGAs across the entire length of their pregnancy, making it difficult to determine the effect of third trimester usage in particular. The comparison group did not include women who had not received a psychiatric diagnosis or were not taking a medication for psychiatric reasons, so it was not possible to draw conclusions about how rates of PNAS differ among infants

of mothers using an SGA or an SSRI/SNRI compared to rates for infants of mothers unexposed to any psychiatric medications or psychiatric illness. Future research should consider use of 4 comparison groups, including SSRI/SNRI-exposed, SGA-exposed, psychiatric illness–exposed but not medication-exposed, and healthy non–medication-exposed controls.[28]

Overall, these findings represent a significant contribution to the literature on the risk of PNAS associated with SGA prenatal exposure. The similarity in prevalence of PNAS between the SGA- and SSRI/SNRI-exposed infants is notable and may suggest a possible common pathway underlying this phenomenon. These data also have important clinical implications for women of reproductive age, women planning pregnancy, and those who are pregnant as they make treatment decisions regarding medication use for serious psychiatric disorders. The risk for PNAS must be balanced with the real threat of destabilizing a pregnant woman maintained on an SGA should discontinuation of medication be pursued.[56–58] As noted, while about one-third of our SGA- and SSRI/SNRI-exposed infants experienced PNAS, the majority of infants did not experience PNAS symptoms (66.8% of SGA-exposed infants and 65.4% of SSRI/SNRI-exposed infants). Therefore, the rationale for stopping a maintenance psychotropic to avoid the risk of PNAS around delivery is limited given the high risk of recurrence following discontinuation of maintenance psychotropics as well as the high risk of further decompensation during the postpartum period. Furthermore, the impact of untreated maternal psychiatric illness is associated with significant maternal and infant morbidity and should not be underestimated in the overall risk and benefit assessment. Therefore, a recommended clinical approach is to closely monitor the SGA-exposed infant at delivery and during the first few days of life for emergence of PNAS symptoms. Fortunately, most cases of PNAS are mild and of short duration, and symptoms generally resolve spontaneously without need for treatment.[1,3,4] As our data suggest, the risk of serious adverse events from exposure to SGAs in utero around delivery is low, which is also consistent with the SSRI/SNRI data. Future research investigating underlying causes for PNAS associated with SGA exposure, including genetic susceptibility and management strategies, is needed. Additionally, larger sample sizes are needed to examine whether there is an additive effect from a combination of exposure to an SGA and an SSRI/SNRI on risk for PNAS.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.