Effects of Prenatal Exposure to Second-Generation Antipsychotics on Development and Behavior Among Preschool-Aged Children:

Preliminary Results From the National Pregnancy Registry for Psychiatric Medications

Carol Swetlik, MD; Lee S. Cohen, MD; Lauren A. Kobylski, MPH; Ellen T. Sojka, BA; Parker C. Killenberg, BS; Marlene P. Freeman, MD; and Adele C. Viguera, MD

Abstract

Objective: Data are lacking on the neurodevelopmental outcomes of children prenatally exposed to second-generation antipsychotics (SGAs). The objective of this study is to examine neurodevelopmental outcomes of children exposed in utero to SGAs compared to those unexposed in a cohort of mothers with psychiatric morbidity.

Methods: We conducted a cross-sectional assessment of preschool-aged children whose mothers were enrolled in the National Pregnancy Registry for Psychiatric Medications. Two validated, parent-report developmental and behavioral screening assessments, the Ages and Stages Questionnaire, Third Edition (ASQ-3) and the Preschool Child Behavior Checklist for Ages 1½–5 (CBCL/1½–5), respectively, were delivered electronically to eligible participants. Outcomes of children exposed in utero to SGAs were compared to those unexposed to SGAs in a cohort of mothers with a history of psychiatric illness. Exposure to other psychotropic medications during pregnancy was not an exclusion criterion for either group.

Results: From January 2, 2018, to February 2, 2021, 520 children were eligible, and 352 responses were collected (67.7%), including 178 children in the SGA-exposed group (mean age = 2.6 years) and 174 children in the unexposed comparison group (mean age = 2.1 years). No significant differences between groups were detected (OR = 1.24, 95% CI, 0.74–2.09) with respect to developmental outcomes assessed by the ASQ-3. Similarly, for behavioral outcomes, adjusted analysis showed no significant differences in odds of an abnormal "clinical" score on the CBCL/1½–5 composite scales.

Conclusions: The current study is the first to examine neurobehavioral outcomes of preschool-aged children exposed prenatally to SGAs. No significant differences in overall development or behavior were detected in the exposed versus unexposed group. These preliminary findings are an important step in delineating neurodevelopmental effects of prenatal SGA exposure.

J Clin Psychiatry 2024;85(1):23m14965

Author affiliations are listed at the end of this article.

There is growing consensus that assessment of neurobehavioral outcomes for children exposed to specific classes of medications is imperative when weighing the risks and benefits of medication use during pregnancy.[1–3] Historically, research studies examining long-term neurodevelopmental effects from in utero psychotropic exposure have been difficult to conduct for several reasons, including cost, labor-intensive assessments, lack of randomization, biased patient recruitment, small sample sizes, and confounding by indication.[1,4] The selection of an appropriate comparison group is critical, as maternal psychiatric illness and its associated behaviors have been linked to adverse effects in child physical and mental health outcomes, independent of medication exposure.[5]

With the widespread use of second-generation antipsychotics (SGAs) for varied indications, reproductive safety data for these medications are accumulating, suggesting no clear teratogenic signal.[6–9] Most of the available literature on the long-term neurodevelopmental consequences of antipsychotics has focused on first-generation antipsychotics (FGAs). Studies involving

Scan Now See supplementary material for this article at Psychiatrist.com

Editor's Note
We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Joseph F. Goldberg, MD, at jgoldberg@psychiatrist.com.

Clinical Points

- Use of second-generation antipsychotics (SGAs) in pregnancy is often necessary for treatment of serious mental illness, but the impact of prenatal exposure to SGAs on child development and behavior has not been well described.
- Preschool-aged children exposed prenatally to SGAs were not found to have a higher risk of abnormal development or behavior on parent-completed measures compared with children unexposed prenatally to SGAs.

SGAs are few and methodologically heterogeneous.[4] Kulkarni et al[10] conducted an observational cohort study of approximately 100 babies up to 1 year of age who had been exposed to SGAs among mothers enrolled in the Australian National Register of Antipsychotic Medication in Pregnancy (NRAMP). No formal neurobehavioral assessments were conducted; based on maternal report, the majority of infants were "progressing well."[10] In a prospective, case-controlled study, Peng et al[5] examined 76 infants exposed to SGAs in utero (the majority exposed to clozapine) compared to 76 case-matched controls with no prenatal antipsychotic exposure or maternal psychiatric diagnosis. At 2 months of age, the exposed group exhibited delayed development in cognitive, motor, and social-emotional domains compared to unexposed controls. However, at the 12-month follow-up, there were no significant differences between the two groups.[5] Shao et al[11] examined the difference in cognitive scores between infants (N = 63) who were exposed to clozapine (n = 33) compared to other SGAs (n = 30; risperidone, olanzapine, and quetiapine) using the Bayley Scales of Infant and Toddler Development, 3rd edition. More clozapine-exposed infants had adaptive-behavior development delays at 2 and 6 months compared to those exposed to other SGAs; these differences, however, disappeared after 6 months of age.[11] In another prospective controlled study, Johnson et al[12] found that among 6-month-old infants, a history of maternal antipsychotic exposure (SGAs n = 12; FGAs n = 9) was associated with significantly lower scores on standard tests of neuromotor performance compared to antidepressant exposure or no psychotropic exposure. A smaller cohort study[13] compared 17 children (ages 6 to 14 years) with prenatal antipsychotic exposure (SGAs n = 7; FGAs n = 10) to 74 children with no prenatal antipsychotic exposure; mothers in both cohorts were diagnosed with severe mental illness. Intrauterine exposure to antipsychotics was not associated with any adverse effects on intelligence quotient (IQ) or global cognitive development.[13]

Similarly, 2 population-based studies[14,15] demonstrated no association between prenatal antipsychotic exposure (including both FGAs and SGAs) and psychiatric diagnostic outcomes, such as autism spectrum disorder and attention-deficit/hyperactivity disorders, from mid-childhood through early adulthood. Additionally, a large birth cohort study,[16] based on a Medicaid database, concluded that the observed unadjusted increased risk of neurodevelopmental disorders seen in children born to women who took antipsychotic drugs late in pregnancy was no longer observed after adjusting for maternal characteristics.

Thus far, existing literature either has focused on children 1 year of age and younger in relatively small cohorts, examining outcomes such as IQ, motor development, and other developmental domains, or has examined psychiatric diagnostic outcomes in older school-aged children using large administrative databases. The present study fills an important gap in the literature, examining developmental and behavioral outcomes in a relatively large cohort of preschool-aged children exposed to SGAs in utero compared to those unexposed to SGAs among mothers with a history of psychiatric morbidity using 2 validated, parent-report scales, the Ages and Stages Questionnaire, Third Edition (ASQ-3)[17] and the Preschool Child Behavior Checklist for Ages 1½–5 (CBCL/1½–5).[18]

METHODS

Established in 2008, the National Pregnancy Registry for Psychiatric Medications (NPRPM) is an ongoing prospective cohort study in which women with diagnosed psychiatric disorders who are taking psychotropic medications are enrolled.[7,9,19] The primary aim of the NPRPM is to compare the rate of major malformations in children exposed to SGAs during the first trimester to those who are unexposed to SGAs during pregnancy. In this analysis, use of an SGA at any point in pregnancy qualifies as an SGA exposure. Mothers in both the SGA-exposed and SGA-unexposed groups may be taking other classes of psychotropics.

Detailed methodology of the NPRPM has been described previously.[7,9,19] Participants are interviewed over the phone at 3 time points across pregnancy: at enrollment, 7 months gestation, and 3 months postpartum. The initial interview ascertains demographic characteristics, prenatal medication use and dosage, substance use, medical and psychiatric history, and family history of birth defects. The 7-month interview collects data on any changes in medication or dosage as well as medical problems across pregnancy. During the postpartum interview, information is gathered regarding labor, delivery, and neonatal outcomes. Child outcomes up to 6 months of age are obtained through systematic review of obstetric and pediatric medical records.

Data are entered electronically and stored in a secure online database, REDCap (Research Electronic Data Capture).[20,21] Release of findings and other major policy decisions are governed by a Scientific Advisory Board made up of experts in the fields of teratology, epidemiology, pediatrics, and pharmacology.

All study procedures are approved by the Mass General Brigham Institutional Review Board. The NPRPM is registered with ClinicalTrials.gov (NCT01246765).

Study Procedures

In 2018, the study procedures of the NPRPM were updated to assess neurobehavioral outcomes of children associated with the analysis. Only mothers who completed the postpartum interview and released medical records were eligible for the study. Eligible participants were e-mailed a study description and a unique link to the developmental and behavioral surveys. Participants were directed to age-appropriate surveys (the ASQ-3 and/or the CBCL/1½–5) with their child's name auto-populated.[17,18] Participants with multiple children associated with the NPRPM received multiple invitations.

Survey results were scored according to prescribed standards by research coordinators blinded to prenatal exposure status.

Assessments

Developmental and behavioral outcomes were assessed using the ASQ-3[17] and the CBCL/1½–5.[18] The two instruments were chosen to cover the majority of the ages of children in the NPRPM, which spanned from 1 month to 9 years of age at the surveys' implementation. These instruments are also validated for electronic completion, allowing for assessment of the NPRPM's nationwide cohort.

The ASQ-3 is a well-validated, parent-completed questionnaire suitable for children ages 2 months through 5.5 years and screens for child developmental delays based on pediatric milestone achievement.[17] The ASQ-3 evaluates 5 domains of development: (1) communication, (2) fine motor, (3) gross motor, (4) personal-social, and (5) problem solving, with each domain comprising 6 items. Age-appropriate and standardized point-based cutoffs exist for each domain, allowing children to score "Pass" or "Monitor" for that domain if within 2 standard deviations or greater of the mean. Children scoring 2 standard deviations below the mean score "Fail" for that domain. If children score "Fail" for any domain, their overall instrument status is "Fail." For this analysis, children whose overall scores were "Pass" or "Monitor" equated a "Pass" score.

The CBCL/1½–5 was developed to measure parent-reported behavioral problems in children ages 1.5 to 5 years.[18] The scale comprises 99 items, with 5 to 19 items in each subscale. Raw points are totaled and converted to *T* scores with a base value of 50 representing the 50th percentile and below. Composite scales include the *internalizing* problems (ie, emotionally reactive, anxious/depressed, somatic complaints, and withdrawn subscales), *externalizing* problems (ie, attention problems and aggressive behavior subscales), and *total* problems subscales of the CBCL/1½–5 (ie, all the previous subscales, as well as sleep problems and other problems subscales). Children scoring above a 60 on these composite scales are deemed to be in the abnormal, or "clinical," range, with scores at least moderately deviant compared with scores from a normative sample of peers.

The primary aim of the present analysis is to determine the odds of abnormal scores on these parent-reported measures of child development and behavior. Scoring in the "Fail" range on the ASQ-3 is defined as any one or more developmental domains having a score outside the normal range. An abnormal "clinical" score on the CBCL/1½–5 is defined as being outside the normal range of *T* scores for the composite subscales, evaluating *internalizing, externalizing,* and *total* problems. Children ages 9 months to 1.5 years completed the ASQ-3 alone, while children ages 1.5 years to 5.5 years completed both the ASQ-3 and CBCL/1½–5. Children older than 5.5 years but younger than age 6 years completed the CBCL/1½–5 alone.

Statistical Analysis

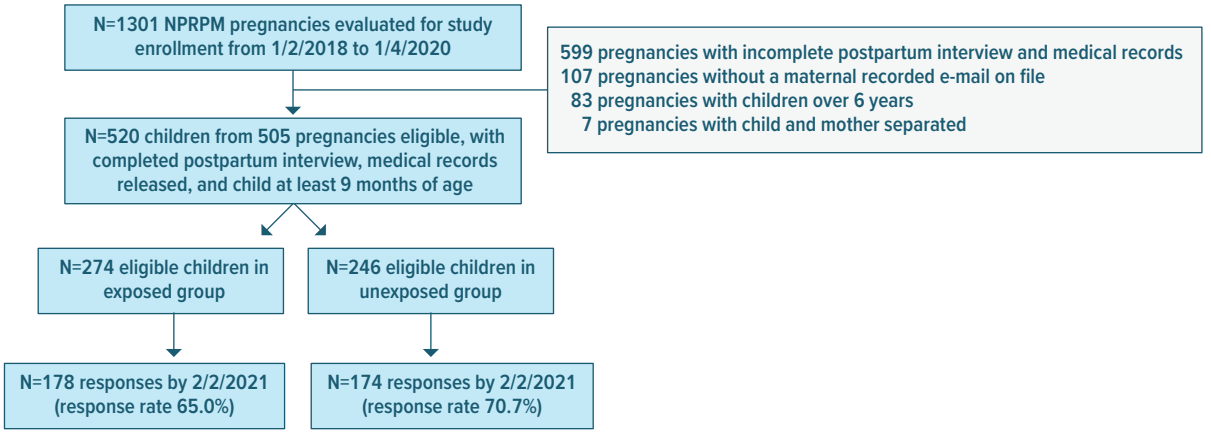
All analyses were conducted using statistical software, JMP, Version 16.23.[22] Maternal and pediatric characteristics were compared via parametric or nonparametric *t* tests and χ^2 tests, as appropriate. The primary exposure in this study was structured as a binary variable: use of an SGA at any point in pregnancy (exposed) or no use during the entire pregnancy (unexposed). Odds of a "Fail" score on the ASQ-3 were calculated, as well as odds of an abnormal "clinical" score on each of the 3 composite subscales of the CBCL/1½–5. Given the limited sample size and low frequency of the outcome, emphasis was placed on interpretation of the crude outcome for these measures. As a supplemental sensitivity analysis, potential confounding factors were identified, and each was added individually to the crude logistic regression models to examine the change in odds ratio from the unadjusted model. Secondary outcomes included odds of an abnormal score on specific domains of the ASQ-3 and comparison of continuous scores of the CBCL/1½–5 empiric and *DSM-5* subscales between groups via *t* tests.

RESULTS

From January 2, 2018, to February 2, 2021, 520 children were eligible for this study; 274 were prenatally exposed to an SGA and 246 were unexposed (Figure 1). 352 complete responses were collected, resulting in an overall response rate of 67.7%, with 178 responses from the exposed group (response rate of 65.0%) and 174 from the unexposed group (response rate of 70.7%) (Figure 1). With respect to timing of SGA exposure, 167 (93.8%) occurred in the first trimester and 157 (88.2%) occurred across all 3 trimesters. Of 352 responses, the ASQ-3 was completed 331 times and the CBCL/1½–5 was completed 254 times.

Table 1 summarizes demographic characteristics of the cohort, who were born from 345 pregnancies. Of note, maternal primary psychiatric diagnosis varied;

Figure 1.
CONSORT Diagram



Abbreviation: NPRPM = National Pregnancy Registry for Psychiatric Medications.

a majority (64.4%) of the exposed group reported bipolar disorder, compared to 11.6% of the unexposed group. The most reported psychotropic exposure in the comparison group was selective serotonin reuptake inhibitors (SSRIs). The most used SGAs in the exposed group were quetiapine, aripiprazole, and lurasidone, consistent with previous NPRPM reporting.[9]

Table 2 describes characteristics of the children, ranging from 0.84 years (10.1 months) to 5.96 years (71.5 months). Children in the exposed group were older at the time of survey completion (mean = 2.6 years, SD = 1.4) compared with the unexposed group (mean = 2.1 years, SD = 1.1). Children in the unexposed group were more likely to be breastfed than the exposed group (80.5% versus 41.6%, respectively).

Developmental Outcomes as Assessed by the ASQ-3

The mean age of SGA-exposed children for whom an ASQ-3 was completed was 2.5 years (SD = 1.2) compared to 2.0 years (SD = 1.0) for unexposed children. Table 3 demonstrates the odds of a "Fail" score on the ASQ-3 across domains. No significant difference was found between the two groups with respect to odds of a "Fail" score on the ASQ-3 (OR = 1.24, 95% CI, 0.74–2.09). Children prenatally exposed to SGAs had higher odds (OR = 2.96, 95% CI, 1.21–7.24) of an abnormal communication domain score, with 11.5% of exposed children showing an abnormal score compared with 4.2% of unexposed children. No differences were found regarding other domains.

A sensitivity analysis was performed in which potential confounders were added individually to the crude unadjusted logistic regression model to examine the resulting change in the odds ratio estimate (Supplementary Figure 1). After controlling for primary diagnosis of maternal bipolar disorder, a significant difference was noted between the two groups regarding odds of a "Fail" score on the ASQ-3 (OR = 1.92, 95% CI, 1.04–3.56). Adjustment for differences in breastfeeding between the two groups revealed an 18.5% change in effect estimate, moving the odds ratio closer to the null (OR = 1.01, 95% CI, 0.57–1.78), suggestive of a possible confounding effect.

Behavioral Outcomes as Assessed by the CBCL/1½–5

The mean age of SGA-exposed children for whom a CBCL/1½–5 was completed was 3.0 years (SD = 1.3) compared with 2.5 years (SD = 1.08) for unexposed children. Table 4 demonstrates the odds of an abnormal "clinical" score on the CBCL/1½–5 across subscales. Unadjusted analysis showed that children in the exposure group had increased odds (OR = 3.16, 95% CI, 1.01–9.89) of a "clinical" internalizing score on the CBCL/1½–5 compared with children who were unexposed, but that finding was no longer statistically significant after adjustment for child age (OR = 2.27, 95% CI, 0.70–7.36). A 10% change in effect estimate was noted for some variables, supportive of confounding, and odds ratio estimates approached the null when controlling for differences in maternal education (OR = 2.70, 95% CI, 0.84–8.72), primary diagnosis of maternal depression (OR = 2.73, 95% CI, 0.86–8.86), and maternal anxiety (OR = 2.82, 95% CI, 0.81–9.77).

No significant difference was detected in the odds of children with an abnormal "clinical" externalizing score between the two groups (OR = 1.78, 95% CI, 0.77–4.14) (Table 4). Annual income less than $50,000 (OR = 1.57, 95% CI, 0.66–3.72), older child age (OR = 1.62, 95% CI, 0.68–3.84), primary diagnosis of maternal depression

Table 1.
Maternal Characteristics (N = 352)

		Overall (N = 352)		Exposed to SGA (n = 178)		Unexposed to SGA (n = 174)		
	Valid N	Mean	SD	Mean	SD	Mean	SD	*P* value
Demographic characteristics								
Maternal age, y	352	33.5	4.2	33.3	4.4	33.6	4.1	.562
Baseline BMI (kg/m^2)*	316	26.8	6.5	27.7	6.7	25.8	6.1	.008
Gravida	351	2.1	1.4	2.2	1.4	1.9	1.5	.045
Number of psychiatric hospitalizations*	352	1.2	2.6	1.9	3.2	0.5	1.6	<.001
	Valid N	N	%	n	%	n	%	*P* value
White	352	329	93.5	162	91.0	167	96.0	.060
College educated*	351	303	86.3	141	79.2	162	93.6	<.001
Married	352	321	91.2	162	91.0	159	91.4	.903
Paternal psychiatric illness	340	101	29.7	55	31.8	46	27.5	.392
Annual income < $50,000*	333	31	9.3	25	14.0	6	3.5	<.001
Pregnancy characteristics								
Planned pregnancy	349	296	84.8	145	82.4	151	87.3	.203
Prior pregnancy	352	191	54.3	105	59.0	86	49.4	.072
Prior miscarriage	190	108	56.8	63	60.6	45	52.3	.253
History of postpartum depression and/or psychosis*	170	65	38.2	42	45.2	23	29.9	.041
1st Trimester use								
Cigarettes	352	21	6.0	15	8.4	6	3.45	.049
Alcohol	352	91	25.9	41	23.0	50	28.7	.222
Illicit drugs	350	12	3.43	6	3.4	6	3.5	.952
Prenatal vitamins*	352	278	79.0	133	74.7	145	83.3	.047
Maternal primary psychiatric diagnosis								
Bipolar disorder*	341	133	39.0	114	64.4	19	11.6	<.001
Schizophrenia	341	2	0.6	2	1.1	0	0	—
Depression*	341	91	26.7	30	17.0	61	37.2	<.001
Anxiety*	341	67	19.7	7	4.0	60	36.6	<.001
Psychotropic medication use in pregnancy								
First-generation antipsychotic	352	5	1.4	4	2.3	1	0.6	.185
SSRI*	352	155	44.0	52	29.2	103	59.2	<.0001
SNRI	352	29	8.2	16	9.0	13	7.5	.605
Tricyclic antidepressant	352	1	0.3	0	0	1	0.6	—
Atypical antidepressant*	352	68	19.3	25	14.0	43	24.7	.011
Lithium	352	13	3.7	10	5.6	3	1.7	.053
Anticonvulsant*	352	98	27.8	71	39.9	27	15.5	<.001
Antianxiety medication	352	49	13.9	25	14.0	24	13.8	.946
Sedative	352	18	5.1	12	6.7	6	3.5	.161
Stimulant*	352	20	5.7	5	2.8	15	8.6	.019
Polytherapy*	352	204	58	135	75.8	69	40.0	<.001

*Statistically significant differences between exposure and comparison groups.
Abbreviations: BMI = body mass index, SGA = second-generation antipsychotic, SNRI = serotonin norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

(OR = 1.40, 95% CI, 0.59–3.32), and maternal bipolar disorder (OR = 1.32, 95% CI, 0.49–3.56) each shifted the estimate closer to the null when added to the model.

Similarly, odds of an abnormal "clinical" total problems score did not differ significantly between the two groups in the unadjusted model (OR = 2.71, 95% CI, 0.95–7.69). Controlling for child age (OR = 2.11, 95% CI, 0.72–6.18), severity of maternal illness prior to pregnancy (OR = 2.14, 95% CI, 0.73–6.3), and primary diagnosis of maternal anxiety (OR = 2.14, 95% CI, 0.73–6.93) shifted the odds ratios toward the null, with overall modest impact compared with the unadjusted model.

No significant differences were detected regarding internalizing, externalizing, or total problems *T* scores when operationalized as a continuous variable ($P > .05$). Other subscale analyses showed

Table 2.
Pediatric Characteristics (N = 352)

		Overall (N = 352)		Exposed to SGA (n = 178)		Unexposed to SGA (n = 174)		
	Valid N	Mean	SD	Mean	SD	Mean	SD	*P* value
Child age at study completion, y*	352	2.3	1.3	2.6	1.4	2.1	1.1	<.001
	Valid N	N	%	n	%	n	%	*P* value
Female	350	167	47.7	79	44.9	88	50.6	.286
Premature (< 37 wk)	352	48	13.6	29	16.3	19	10.9	.142
Breastfed*	352	214	60.8	74	41.6	140	80.5	<.001

*Statistically significant differences between exposure and comparison groups.
Abbreviations: SGA = second-generation antipsychotic, wk = week, y = years.

Table 3.
Developmental Outcomes as Assessed by the ASQ-3: Odds of a "Fail" Score on the ASQ-3 (N = 331)

ASQ-3 domain	N	Prevalence (%)	95% CI	Odds ratio	95% CI
All domains					
Exposed to SGA (n = 165)	40	24.20	18.33–31.32	1.24	0.74–2.09
Unexposed to SGA (n = 166)	34	20.50	15.04–27.26	Reference	Reference
Communication*					
Exposed to SGA (n = 165)	19	11.52	7.50–17.28	2.96	1.21–7.24
Unexposed to SGA (n = 166)	7	4.22	2.06–8.45	Reference	Reference
Gross motor					
Exposed to SGA (n = 165)	19	11.50	8.43–18.57	0.9	0.46–1.74
Unexposed to SGA (n = 166)	21	12.65	7.50–17.28	Reference	Reference
Fine motor					
Exposed to SGA (n = 165)	7	4.24	2.07–8.50	0.62	0.24–1.65
Unexposed to SGA (n = 166)	11	6.63	3.74–11.48	Reference	Reference
Problem solving					
Exposed to SGA (n = 165)	12	7.27	4.21–12.28	1	0.43–2.31
Unexposed to SGA (n = 166)	12	7.23	4.18–12.21	Reference	Reference
Personal-social					
Exposed to SGA (n = 165)	15	9.09	5.59–14.46	1.18	0.54–2.56
Unexposed to SGA (n = 166)	13	7.83	4.63–12.94	Reference	Reference

*Statistically significant differences between exposure and comparison groups.
Abbreviations: ASQ-3 = Ages and Stages Questionnaire, Third Edition, SGA = second-generation antipsychotic.

a significant difference in attention-deficit/hyperactivity problems, with SGA-exposed children having a higher score (mean = 52.5, SD = 5.32) compared to unexposed children (mean = 51.3, SD = 3.06; $P = .03$), with differences on all other subscales not detected ($P > .05$).

DISCUSSION

This study is one of the largest and most comprehensive in its prospective evaluation of long-term developmental and behavioral outcomes of children prenatally exposed to SGAs. With respect to overall developmental scores based on the ASQ-3, no significant differences were detected between children who were exposed and unexposed to SGAs. No differences were found in unadjusted analyses for either *externalizing* problems or *total* problems scores of the CBCL/1½–5. Similarly, no differences in internalizing problems scores were detected after controlling for child age. Due to the available sample size, more complex multivariable modeling was deferred, although controlling for potential confounders shifted the odds ratio closer to the null, indicating that the true strength of the relationship between SGA exposure and neurobehavioral outcomes may be weaker than expected.

Thus, these findings are consistent with the limited published literature suggesting no clinically significant adverse neurobehavioral sequelae in children exposed prenatally to SGAs. Of note, there are likely other factors that may contribute to neurodevelopmental outcomes that were not included in this study, including prenatal medical comorbidities, neonatal outcomes, and maternal mental health severity during early childhood. However, given that no differences were found on primary neurodevelopmental endpoints, the presence of these potential differences would be unlikely to drive the results described here. When adjusting for potential confounding variables, confidence intervals between adjusted and unadjusted models overlapped considerably, supporting limited impact of these variables on primary outcomes and the role of chance in driving marginal shifts in the adjusted odds ratio.

In examining the subscales of the ASQ-3 and the CBCL/1½–5, some notable differences were detected between groups, such as the ASQ-3's subdomain of communication skills, which includes both receptive and expressive communication. Children prenatally exposed to SGAs had a higher odds of an abnormal communication domain score compared with children unexposed to SGAs. This observation may be partially driven by age, as younger children may not display missed milestones until later in toddlerhood when speech delays emerge. Additionally, mothers who took SGAs prenatally were noted to have a slightly higher gravida, which may indicate a higher average

Table 4.

Behavioral Outcomes as Assessed by the CBCL/1½–5: Odds of an Abnormal "Clinical" Score on the CBCL/1½–5 (N = 254)

	N	Prevalence (%)	95% CI	Odds ratio	95% CI
Clinical Internalizing Score*					
Exposed to SGA (n = 138)	14	10.14	6.14–16.31	3.16	1.01–9.89
Unexposed to SGA (n = 116)	4	3.45	1.35–8.52	Reference	Reference
Clinical Externalizing Score					
Exposed to SGA (n = 138)	18	13.04	8.41–19.68	1.78	0.77–4.14
Unexposed to SGA (n = 116)	9	7.76	4.14–14.09	Reference	Reference
Total Problems Score					
Exposed to SGA (n = 138)	15	10.87	6.70–17.16	2.71	0.95–7.69
Unexposed to SGA (n = 116)	5	4.31	1.86–9.69	Reference	Reference

*Statistically significant differences between exposure and comparison groups.
Abbreviations: CBCL/1½–5 = Preschool Child Behavior Checklist for Ages 1½–5, SGA = second-generation antipsychotic.

number of older siblings at home, leading to differences in language emergence.[23,24] It is not clear if these differences in language ability are clinically meaningful or persist over time. Of note, another study[16] found that communication was affected specifically in children exposed to aripiprazole. Such findings could represent a signal that requires future investigation.

With respect to the CBCL/1½–5, differences were noted regarding attention-deficit/hyperactivity problems between the two groups, with a slightly higher mean score in the exposure group compared with unexposed children. However, the clinical significance of this difference is unknown, as mean scores in both groups were well below the clinically significant cutoff. Furthermore, a statistically significant difference between groups was not corroborated on the attention problems subscale. Further investigation into attention deficits, including impact of age, may be warranted, along with verification of clinical diagnoses.

Strengths of this study include a robust pool of prospective data collected from mothers during their pregnancy and during their offspring's early childhood. The relatively high return rate of assessments not only ensures that the study can be expected to reliably comment on several years of pediatric outcomes beyond infancy but also underscores the NPRPM's emphasis on building relationships with participants during their pregnancy and the postpartum period. Importantly, the inclusion of an internal comparison group consisting of women with psychiatric illnesses who were not exposed to SGAs limits confounding by indication, which is so often a major limitation in other studies using healthy comparison groups unaffected by the underlying condition. Lastly, while direct assessment of children by trained personnel blinded to exposure status allows for more nuanced measures of cognitive, social, and motor abilities, our current study design allows for practical screening-level assessment of a nationwide cohort that could also support more targeted and rigorous evaluation in the future. While the current data are cross-sectional, the study design has since been adapted to follow this cohort longitudinally, as the instruments are validated for serial administration.

The study has several important limitations. These analyses are limited in power to assess results for individual SGAs, and potential smaller differences may not have been detected because of the sample size. While it would be ideal to estimate the developmental and behavioral outcomes in a pure SGA monotherapy group, this was not feasible; the majority of women who participate in the NPRPM are on psychotropic polytherapy, reflecting the clinical reality of caring for pregnant women with serious mood and anxiety disorders.[3] In addition, our cohort was young when the assessments were completed, with a mean age of around 2 years. It has been recommended to evaluate children when they are at least 4 years old to more accurately assess behavioral and developmental trajectories.[2,25,26] Our cohort is also fairly homogenous with regard to race, education, and income distribution. Therefore, generalizability of these findings is limited. We have limited information regarding paternal risk factors for development, though we have a balanced prevalence of paternal psychiatric illness between groups. Additionally, data are lacking regarding mothers' psychiatric courses beyond the immediate postpartum period. Some smaller studies[27,28] have suggested maternal mental illness at the time of the pediatric evaluation is more predictive of children's behavioral profile than maternal mental illness severity at the time of pregnancy and birth. While completion of the study's surveys could indicate a relatively high-functioning cohort of mothers, nonresponse bias is another important limitation given that nonrespondents may be more burdened by psychiatric symptoms or other life stressors. Lastly, the majority of the exposure group was exposed to an SGA throughout all 3 trimesters in pregnancy and exact data regarding medication doses were not included in this analysis, limiting the opportunity to evaluate critical windows of exposure during pregnancy.[29]

Despite these limitations, this study represents a novel undertaking to begin to characterize yet unknown childhood outcomes. These findings are consistent with other studies that have not found an association between prenatal SGA exposure and adverse developmental or behavioral effects. Continued recruitment will ensure appropriate power for study outcomes. Furthermore, as the NPRPM begins to publish molecule-specific data with regard to malformation risk,[3,30–32] continued evaluation of this cohort will ideally provide dose- and medication-specific data regarding developmental and behavioral outcomes that families and providers can use to determine optimal psychiatric management strategies during the perinatal period.

Article Information

Published Online: March 13, 2024.
https://doi.org/10.4088/JCP.23m14965

Submitted: June 8, 2023; accepted November 9, 2024.

To Cite: Swetlik C, Cohen LS, Kobylski LA, et al. Effects of prenatal exposure to second-generation antipsychotics on development and behavior among preschool-aged children: preliminary results from the National Pregnancy Registry for Psychiatric Medications. *J Clin Psychiatry*. 2024;85(0):23m14965.

Author Affiliations: Ammon-Pinizzotto Center for Women's Mental Health, Massachusetts General Hospital, Boston (all authors); Cleveland Clinic, Cleveland Clinic Neurological Institute, Ohio (Swetlik, Viguera); Department of Psychological and Brain Sciences, George Washington University, Washington, DC (Kobylski).

Corresponding Author: Adele C. Viguera, MD, MPH, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (viguera@ccf.org).

Relevant Financial Relationships: Dr Cohen as of 1/20/2023: research support: Dr Cohen is an employee of Massachusetts General Hospital and works with the MGH National Pregnancy Registry. MGH National Pregnancy Registry: current sponsors: Alkermes, Inc. (2016–present); Eisai, Inc. (2022–present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019–present); Otsuka America Pharmaceutical, Inc. (2008–present); Sage Therapeutics (2019–present); Supernus Pharmaceuticals (2021–present); Teva Pharmaceutical Industries Ltd. (2018–present). As an employee of MGH, Dr Cohen works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and NIMH. Other research support: Brain & Behavior Research Foundation; National Institute on Aging; National Institutes of Health; SAGE Therapeutics. Advisory/consulting: JDS Therapeutics LLC. **Dr Freeman** as of 1/20/2023: research support: Dr Freeman is an employee of Massachusetts General Hospital and works with the MGH National Pregnancy Registry. MGH National Pregnancy Registry: Current Sponsors: Alkermes, Inc. (2016–present); Eisai, Inc. (2022–present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019–present); Otsuka America Pharmaceutical, Inc. (2008–present); Sage Therapeutics (2019–present); Supernus Pharmaceuticals (2021–present); Teva Pharmaceutical Industries Ltd. (2018–present). As an employee of MGH, Dr Freeman works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and NIMH. Other research support: SAGE Therapeutics, JayMac. Advisory/consulting, data safety committees: independent data safety and monitoring committees: Janssen (Johnson & Johnson), Novartis, Neurocrine; Advisory Boards: Eliem, Sage; Brainify; Everly Health; Tibi Health; Relmada; Beckley Psytech. Speaking/honoraria: WebMD, Medscape, Pri-Med, Postpartum Support International. Royalty/patent, other income: scale royalties through MGH Scale, the Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire (Freeman et al 2013). **Dr Viguera** as of 1/20/2023: research support: Dr Viguera works with the MGH National Pregnancy Registry. MGH National Pregnancy Registry: Current Sponsors: MGH National Pregnancy Registry: Current Sponsors: Alkermes, Inc. (2016–present); Eisai, Inc. (2022–present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019–present); Otsuka America Pharmaceutical, Inc. (2008–present); Sage Therapeutics (2019–present); Supernus Pharmaceuticals (2021–present); Teva Pharmaceutical Industries Ltd. (2018–present). Advisory/consulting: Up to Date. Speaking/honoraria: None. Royalty/patent, other income: None. Past sponsors of the National Pregnancy Registry: Forest/Actavis/Allergan (2016–2018, declined to sponsor: 2018–present), AstraZeneca Pharmaceuticals (2009–2014, declined to sponsor: 2014–present); AuroMedics Pharma LLC (2021–2022, declined to sponsor 2022–present); Aurobindo Pharma (2020–2022, declined to sponsor: 2022–present); Ortho-McNeil-Janssen Pharmaceuticals, Inc (2009–2014, declined to sponsor: 2015–present); Pfizer, Inc. (2009–2011, declined to sponsor: 2012–present); Sunovion Pharmaceuticals, Inc. (2011–2022, declined to sponsor: 2023–present). **Dr Swetlik** and **Mss Kobylski**, **Sojka**, and **Killenberg** declare no conflicts of interest.

Funding/Support: Funding support for the National Pregnancy Registry for Psychiatric Medications: Alkermes, Inc.; Eisai, Inc.; Johnson & Johnson/Janssen Pharmaceuticals, Inc; Otsuka America Pharmaceutical, Inc.; Sage Therapeutics; Supernus Pharmaceuticals; and Teva Pharmaceutical Industries Ltd.

Role of the Funders/Sponsors: The funding bodies had or have no involvement in study design; collection; management, analysis, and interpretation of data; or the decision to submit for publication.

Acknowledgments: The authors thank Ella T. Rossa, BA, for assistance with manuscript preparation. They also thank Sara McElheny, BA; Taylor R. Church, BS; Alexandra Z. Sosinsky, MSc; and Heather A. Harmon, MPH, for assistance with data collection. These individuals have no conflicts of interest to declare.

Supplementary Material: Available at Psychiatrist.com.

References

1. Bromley RL, Bickle Graz M, Bluett-Duncan M, et al. Expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies. *Front Pharmacol*. 2023;14:1094698.
2. Gentile S. Neurodevelopmental effects of prenatal exposure to psychotropic medications. *Depress Anxiety*. 2010;27(7):675–686.
3. Viguera AC, Freeman MP, Kobylski LA, et al. Risk of major malformations following first-trimester exposure to olanzapine: preliminary data from the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications. *J Clin Psychopharmacol*. 2023;43(2):106–112.
4. Poels EMP, Schrijver L, Kamperman AM, et al. Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;27(9):1209–1230.
5. Peng M, Gao K, Ding Y, et al. Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study. *Psychopharmacology (Berl)*. 2013;228(4):577–584.
6. Toh S, Li Q, Cheetham TC, Prevalence and trends in the use of antipsychotic medications during pregnancy in the US, 2001–2007: a population-based study of 585,615 deliveries. *Arch Womens Ment Health*. 2013;16(2):149–157.
7. Cohen LS, Viguera AC, McInerney KA, et al. Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry*. 2016;173(3):263–270.
8. Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry*. 2016;73(9):938–946.
9. Viguera AC, Freeman MP, Góez-Mogollón L, et al. Reproductive safety of second-generation antipsychotics: updated data from the Massachusetts General Hospital National Pregnancy Registry for atypical antipsychotics. *J Clin Psychiatry*. 2021;82(4):20m13745.
10. Kulkarni J, Worsley R, Gilbert H, et al. A prospective cohort study of antipsychotic medications in pregnancy: the first 147 pregnancies and 100 one year old babies. *PLoS One*. 2014;9(5):e94788.
11. Shao P, Ou J, Peng M, et al. Effects of clozapine and other atypical antipsychotics on infants development who were exposed to as fetus: a post-hoc analysis. *PLoS One*. 2015;10(4):e0123373.
12. Johnson KC, LaPrairie JL, Brennan PA, et al. Prenatal antipsychotic exposure and neuromotor performance during infancy. *Arch Gen Psychiatry*. 2012;69(8):787–794.
13. Schrijver L, Robakis TK, Kamperman AM, et al. Neurodevelopment in school-aged children after intrauterine exposure to antipsychotics. *Acta Psychiatr Scand*. 2023;147(1):43–53.
14. Hálfdánarson Ó, Cohen JM, Karlstad Ø, et al. Antipsychotic use in pregnancy and risk of attention/deficit-hyperactivity disorder and autism spectrum disorder: a Nordic cohort study. *Evid Based Ment Health*. 2022;25(2):54–62.
15. Wang Z, Chan AYL, Coghill D, et al. Association between prenatal exposure to antipsychotics and attention-deficit/hyperactivity disorder, autism spectrum disorder, preterm birth, and small for gestational age. *JAMA Intern Med*. 2021;181(10):1332–1340.
16. Straub L, Hernández-Díaz S, Bateman BT, et al. Association of antipsychotic drug exposure in pregnancy with risk of neurodevelopmental disorders: a national birth cohort study. *JAMA Intern Med*. 2022;182(5):522–533.
17. Squires J, Twombly E, Bricker D, et al. Psychometric Studies of ASQ. In: *ASQ-3 User's Guide*. 3rd ed. Brookes Publishing; 2009.
18. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev*. 2000;21(8):265–271.
19. Cohen LS, Viguera AC, McInerney KA, et al. Establishment of the National Pregnancy Registry for atypical antipsychotics. *J Clin Psychiatry*. 2015;76(7):986–989.
20. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
21. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–381.
22. SAS Institute Inc. Basic Analysis 16. SAS Institute Inc.; 2020–2021.
23. Havron N, Ramus F, Heude B, et al. The effect of older siblings on language development as a function of age difference and sex. *Psychol Sci*. 2019;30(9):1333–1343.
24. Hoff-Ginsberg E. The relation of birth order and socioeconomic status to children's language experience and language development. *Appl Psycholinguist*. 1998;19(4):603–629.

25. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. *Neurology*. 2012;78(16):1207–1214.
26. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12(3):244–252.
27. Misri S, Reebye P, Kendrick K, et al. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. *Am J Psychiatry*. 2006;163(6):1026–1032.
28. Suri R, Lin AS, Cohen LS, et al. Acute and long-term behavioral outcome of infants and children exposed in utero to either maternal depression or antidepressants: a review of the literature. *J Clin Psychiatry*. 2014;75(10):e1142–e1152.
29. Brody BA, Kinney HC, Kloman AS, et al. Sequence of central nervous system myelination in human infancy, I: an autopsy study of myelination. *J Neuropathol Exp Neurol*. 1987;46(3):283–301.
30. Cohen LS, Church TR, Freeman MP, et al. Reproductive safety of lurasidone and quetiapine: update from the National Pregnancy Registry for psychiatric medications. *J Womens Health (Larchmt)*. 2023;32(4):452–462.
31. Cohen LS, Góez-Mogollón L, Sosinsky AZ, et al. Risk of major malformations in infants following first-trimester exposure to quetiapine. *Am J Psychiatry*. 2018;175(12):1225–1231.
32. Freeman MP, Viguera AC, Góez-Mogollón L, et al. Reproductive safety of aripiprazole: data from the Massachusetts General Hospital National Pregnancy Registry for atypical antipsychotics. *Arch Womens Ment Health*. 2021;24(4):659–667.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Effects of Prenatal Exposure to Second-Generation Antipsychotics on Development and Behavior Among Preschool-Aged Children: Preliminary Results From the National Pregnancy Registry for Psychiatric Medications

Authors: Carol Swetlik, MD; Lee S. Cohen, MD; Lauren A. Kobylski, MPH; Ellen T. Sojka, BA; Parker C. Killenberg, BS; Marlene P. Freeman, MD; and Adele C. Viguera, MD

DOI Number: 10.4088/JCP.23m14965

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

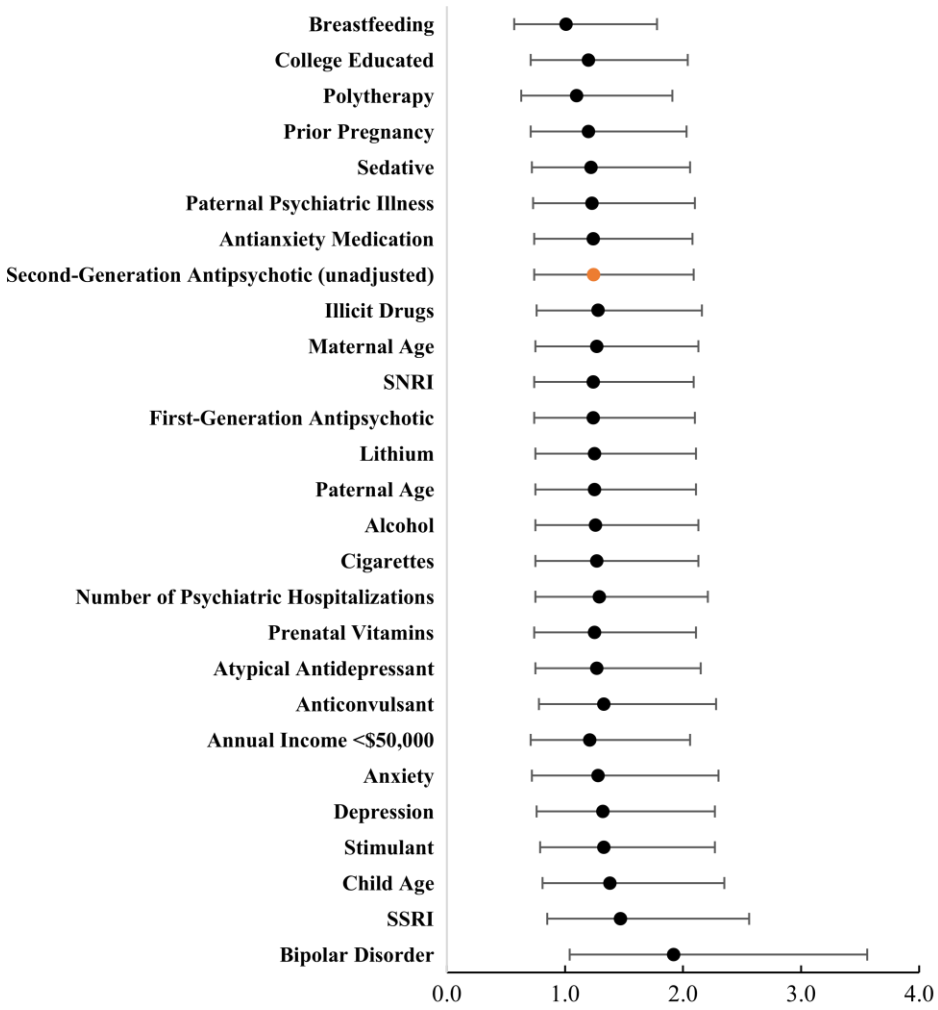
1. Figure 1 Odds of a "Fail" Score on the ASQ-3 Following Adjustment for Potential Confounders

DISCLAIMER

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

Supplementary Figure 1: Odds of a "Fail" Score on the ASQ-3 Following Adjustment for Potential Confounders



Covariate	Odds Ratio	95% CI: Lower Bound	95% CI: Upper Bound
Breastfeeding	1.01	0.57	1.78
College Educated	1.20	0.71	2.04
Polytherapy	1.10	0.63	1.91
Prior Pregnancy	1.20	0.71	2.03
Sedative	1.22	0.72	2.06
Paternal Psychiatric Illness	1.23	0.73	2.10
Antianxiety Medication	1.24	0.74	2.08
Second-Generation Antipsychotic (unadjusted)	1.24	0.74	2.09
Illicit Drugs	1.28	0.76	2.16
Maternal Age	1.27	0.75	2.13
SNRI	1.24	0.74	2.09
First-Generation Antipsychotic	1.24	0.74	2.10
Lithium	1.25	0.75	2.11
Paternal Age	1.25	0.75	2.11
Alcohol	1.26	0.75	2.13
Cigarettes	1.27	0.75	2.13
Number of Psychiatric Hospitalizations	1.29	0.75	2.21
Prenatal Vitamins	1.25	0.74	2.11
Atypical Antidepressant	1.27	0.75	2.15
Anticonvulsant	1.33	0.78	2.28
Annual Income <$50,000	1.21	0.72	2.07
Anxiety	1.28	0.72	2.30
Depression	1.32	0.76	2.27
Stimulant	1.33	0.79	2.27
Child Age	1.38	0.81	2.35
SSRI	1.47	0.85	2.56
Bipolar Disorder	1.92	1.04	3.56

Abbreviations: SNRI=serotonin norepinephrine reuptake inhibitor SSRI=selective serotonin reuptake inhibitor

In a sensitivity analysis, potential confounders were added individually to the crude unadjusted logistic regression models to examine the resulting change in odds radio estimates.