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Establishment of the National Pregnancy Registry for Atypical Antipsychotics

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ABSTRACT

Objective: Atypical antipsychotics are widely used by reproductive-age women to treat a spectrum of psychiatric illnesses. Despite widespread use of this class of agents in women of childbearing potential, reproductive safety data across these medicines remain limited. The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) at Massachusetts General Hospital was established in 2008 to address this knowledge gap.

Method: Data are prospectively collected from pregnant women, ages 18–45 years, using 3 phone interviews conducted at the following times: (1) proximate to the time of enrollment, (2) 7 months' gestation, and (3) 2–3 months postpartum. Subjects include pregnant women with histories of fetal exposure to second-generation antipsychotics and a comparison group of nonexposed pregnant women. Medical record release authorization is obtained for obstetric, labor and delivery, and newborn pediatric (up to 6 months of age) records. Information regarding the presence of major malformations is abstracted from the medical records along with other data regarding neonatal and maternal health outcomes. Identified cases of congenital malformations are sent to a dysmorphologist blinded to drug exposure for final adjudication.

Results: As of May 2014, 428 subjects have enrolled in the NPRAA. Efforts continue to increase enrollment for the purpose of enhancing the capacity to define risk estimates of in utero exposure to atypical antipsychotics.

Conclusions: The NPRAA gathers prospective data regarding risk for critical outcomes following use of atypical antipsychotics during pregnancy. The NPRAA offers a systematic way to collect reproductive safety information that informs the care of women who use these agents to sustain psychiatric well-being.

Trial Registration: ClinicalTrials.gov identifier: NCT01246765

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Pregnancy registries have emerged as a rapid and systematic means of collecting important reproductive safety data on risk for major malformations following prenatal exposure to a particular medication.[1,2] Over the past decade, several registries have been established to evaluate the reproductive safety of a broad range of drugs including medications used to treat human immunodeficiency virus, certain cancers, epilepsy, and diabetes.[3] Other registries have been created specifically for psychiatric medications including bupropion,[4] fluoxetine,[5] lithium,[6] and antipsychotics.[7] Although second-generation antipsychotics (SGAs) have been available since the mid-1990s and are increasingly used as primary or adjunctive therapy across a wide range of psychiatric disorders including bipolar disorder, schizophrenia, unipolar depression, and anxiety disorders, reliable data regarding the reproductive safety of these compounds remain incomplete.[8–11]

The existing safety information on SGAs derives largely from observational case studies, manufacturer reports, and, more recently, a select number of larger cohort studies.[12–19] Thus far, available data from these sources suggest that SGAs are not major teratogens. Preliminary data from other studies suggest that fetal exposure to these agents may be associated with a host of adverse neonatal and maternal outcomes including increased infant birth weight, large size for gestational age, gestational diabetes, and delayed development.[10,20–24]

Incomplete data regarding associated risks of fetal exposure to atypical antipsychotics prompted the establishment of the National Pregnancy Registry for Atypical Antipsychotics (NPRAA) in 2008. The NPRAA is modeled after the North American AED (antiepileptic drug) Pregnancy Registry.[1,25] Based at Massachusetts General Hospital in Boston, the NPRAA is the first hospital-based pregnancy registry for atypical antipsychotics in North America that systematically and prospectively evaluates risk of malformations among infants exposed in utero to atypical antipsychotics including aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. The objective of this registry is to obtain, in expeditious and rigorous fashion, important reproductive safety data, including teratogenicity as well as risk for adverse obstetrical and neonatal outcomes associated with in utero exposure to atypical antipsychotics. More accurate quantification of risks of fetal exposure allows for more carefully delineated risk/benefit decisions regarding use of these agents during pregnancy. This report describes the design and procedures used in the NPRAA.

METHOD

The NPRAA is designed to assess, in a prospective, observational manner, the risk of major congenital malformations associated with first-trimester exposure to SGAs. Systematic assessment of maternal and neonatal outcomes is also performed during pregnancy and postpartum across 3 separate time points (enrollment, pregnancy, and the postpartum period). Secondary outcomes evaluated include neonatal outcomes such as birth weight and

extrapyramidal symptoms, as well as maternal health outcomes including weight gain across pregnancy and risk for gestational diabetes and pregnancy-associated hypertension. All methods and procedures have been approved by the institutional review board (IRB) at Massachusetts General Hospital (MGH). The study is registered at ClinicalTrials.gov (identifier: NCT01246765).

Inclusion Criteria

Subjects eligible for inclusion in the Registry are pregnant women between the ages of 18–45 years who have taken 1 or more SGAs during pregnancy (exposed group). Nonexposed subjects (comparison group) are also enrolled and are prospectively assessed using the same methods as those for exposed subjects.

Subject Recruitment

Registry participants are recruited from multiple sources. Existence and goals of the Registry are publicized predominantly through mailings, newsletters, and e-mails to health care providers serving relevant patient populations. In addition to direct referrals by health care providers and patients in the community, the MGH Center for Women's Mental Health also lists the Registry on its website (http://womensmentalhealth.org). Study updates and announcements are disseminated through established listservs of multiple organizations: Postpartum Support International, American Society of Clinical Psychopharmacology, Organization of Teratology Information Specialists, and Postpartum Progress, as well as other continuing medical education forums. Study staff also raise awareness of the NPRAA at multiple venues, including national and community-based meetings, reproductive psychiatry listservs, and websites of organizations with a focus on women's mental health. Lastly, information regarding the Registry is available through the website of the US Food and Drug Administration Office of Women's Health (http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm). The initial enrollment goal of the NPRAA is to recruit 400 prospective exposures and 400 comparison participants.

Informed Consent and Study Enrollment

Methods for obtaining informed consent, like all other NPRAA study procedures, are approved on an annual basis by the MGH IRB. Information is maintained in a database with limited staff access, and subjects are identified only by study number to protect confidentiality of obtained information. Following initial contact regarding potential subject participation, a phone screen is conducted with women to confirm eligibility. Following the phone screen, informed verbal consent is obtained from eligible participants to complete 3 phone interviews.

Enrollment and Interviews

Enrolled subjects participate in 3 interviews conducted by a trained research coordinator. The 3 interviews include (1) a baseline interview at enrollment, (2) an interview at 7 months' gestation, and (3) a final postpartum interview 8 to 12 weeks after the expected date of delivery. The structured baseline interview includes information regarding demographic characteristics, medication use and dosages, social habits (ie, smoking, alcohol consumption, and illicit drug use), medical and psychiatric history, and family history of birth defects. The 7 month interview is a follow-up designed to ascertain information regarding changes in medication or dosages, habits, medical/psychiatric difficulties during pregnancy, and antenatal course to date. The final postpartum interview obtains information since last contact with the subject with respect to pharmacotherapy as well as information regarding labor, delivery, and neonatal health outcomes.

Subjects who enroll in the Registry later than 28 weeks' gestation complete only 2 of the 3 phone interviews. The 7 month interview is omitted, and the baseline interview is conducted in its place. The final postpartum interview occurs along the usual timeline. Participants who indicate interest in enrolling following delivery are classified as "retrospective" and complete a single interview that combines baseline and postpartum interview questions. Data obtained retrospectively are not included in primary analyses.

Medical Records of Mothers and Infants

Following the second interview at 7 months' gestation, medical release forms are mailed to all participants requesting authorization to access obstetric, labor and delivery, and newborn pediatric records. Upon return of release of information documents, medical records are then requested from health care providers at 6 months following the delivery date. Additional records from medical specialists seen since birth and noted in obtained medical records are also requested.

Upon receipt of subjects' medical records, information is abstracted by a trained research coordinator who uses a neonatal/maternal outcome report form designed to collect information from the records with respect to primary and secondary outcomes. The record review procedure is repeated by a senior study investigator. If a major malformation is noted, pediatric medical records are redacted and sent to a dysmorphologist, blinded to medication exposure, to confirm the "case," that is, the primary outcome of interest. Concurrently, the dysmorphologist receives additional redacted records to review of infants in whom no malformation has been identified in order to reduce bias.

Definition of Outcomes

Following review, data are entered into REDCap, an electronic data capture tool hosted at Massachusetts General Hospital, for later analysis. With respect to the primary outcome, a major malformation is defined as a structural abnormality with surgical, medical, or cosmetic importance.[25,26] Exclusions include (1) minor anomalies; (2) deformations; (3) physiologic features due to prematurity, such as undescended testes; (4) birthmarks; (5) genetic disorders and chromosomal abnormalities; and (6) any finding by prenatal sonography, such as absence of 1 kidney, or at surgery (or autopsy) that was not identified by an examining

pediatrician. As noted above, the written descriptions in the pediatricians' examination are reviewed independently by a Registry dysmorphologist, blinded to exposure status, who determines whether a noted abnormality is a frank major malformation.

Analytic Considerations

For examining the primary and secondary outcomes, exposed cases will be compared to a comparison group composed of pregnant women not exposed to atypical antipsychotics. For the primary outcome, monotherapy is defined as the use of only 1 SGA taken during the first trimester during pregnancy, and polytherapy is defined as the use of more than 1 SGA taken concurrently during the first trimester. Risk estimates will be calculated based on the absolute number of major malformations noted, and 95% confidence intervals for this risk and other outcomes of interest will be determined. These risks will be compared with those among a reference group of women not exposed to atypical antipsychotics during pregnancy. Given that subjects have obviously not been randomized to specific treatments, accounting for potential effects of heterogeneous characteristics across treatment groups on the observed association between SGA exposure and teratogenic outcome is important and will be performed. Other potential confounders including family history of birth defects and other environmental factors such as smoking, use of alcohol, and use of other concomitant medications and comorbidities, will also be taken into account during the analyses since these factors have been noted to influence rates of birth defects and other relevant obstetrical outcomes in samples of healthy, nonexposed, pregnant women.[27]

Structure, Support, and Governance of the NRPAA

The staff of the Registry includes 2 principal investigators, a study coordinator, a pharmacoepidemiologist, a dysmorphologist, 2 research assistants and interviewers. Other staff used by the NPRAA have included those performing data abstraction, data analysis, and database programming consultation. In addition, major policy decisions, such as establishing release criteria and actual decisions to release findings, are made by a Scientific Advisory Board (SAB) that consists of experts in the fields of teratology, epidemiology, and psychiatry. The SAB meets annually with the Registry's staff to discuss issues related to study methods and to review major findings. The funding structure of this project was modeled after that of the North American AED Pregnancy Registry, and multiple manufacturers of atypical antipsychotics were approached to support it. Funds secured in this manner cover a fixed proportion of the operating costs of the Registry. Release of findings regarding reproductive safety of specific atypical antipsychotics is dictated *exclusively* by the SAB. Representatives from sponsoring entities are invited to an annual meeting typically concurrent with that of the SAB and at that time are informed about decisions of the SAB or relevant findings that the SAB has endorsed for release.

DISCUSSION AND UPDATE

The last decade has seen expanded use of atypical antipsychotics across psychiatric disease states. Patients who use these SGAs frequently include reproductive-age women who suffer from mood and anxiety disorders. Clinicians lack ample evidence on which to base risk/benefit decisions with respect to potential use of atypical antipsychotics during pregnancy. This report describes the scientific and administrative infrastructure used by the NPRAA and some preliminary descriptive information regarding the enrolled subjects to date. As of May 2014, 428 subjects had enrolled in the NPRAA. On average, participants enrolled in the registry at 18.1 weeks of gestation and were 32 years of age at the time of enrollment; 60.4% of participants have at least a college education, 74.8% are married, and 89.9% are Caucasian.

The NPRAA was modeled to a significant extent after the North American AED Pregnancy Registry, in which women exposed to anticonvulsants have been prospectively followed for over 15 years to better quantify rates of malformations associated with first-trimester exposure to this class of agents. Strengths in the methods used by NPRAA include prospective assessment of outcomes, an internal comparison group, and confirmation of major malformations with actual medical record review followed by blinded confirmation of findings by a dysmorphologist. This rigor is lacking in available small cohort studies[14] or other analyses of reproductive safety data derived from large administrative databases.[18] However, there are also important limitations that may affect the generalizability of the registry's results. Only a small percentage of the pregnancies of women receiving SGAs in North America are likely captured by this Registry, and there may also be regional differences in ascertainment. In addition, the requirement of self-enrollment in the NPRAA is likely to introduce a bias toward more motivated and informed women. These differences would bias the results if the traits that lead to participation are also related to use of an SGA. To avoid this bias, similar recruitment mechanisms are used for both the exposed and comparison participants. This strategy allows obtainment of comparable groups of women differing only in medication regimens. Due to the observational nature of this study, our population of exposed and comparison women may differ on a few additional factors. Therefore, a large number of baseline descriptive factors are obtained and examined for group differences, and the final estimates will be adjusted accordingly.

Despite these limitations, the NPRAA offers a systematic way to collect important reproductive safety information so that clinicians may provide accurate and needed advice to women who either plan to conceive or are pregnant and are treated with these medicines. Future efforts of the NPRAA will focus on sustaining growth in enrollment of subjects so that the reproductive safety of the SGAs as a class, as well as that of individual agents within the family of molecules, may be more clearly delineated.

Drug names: aripiprazole (Abilify), asenapine (Saphris), bupropion (Wellbutrin, Aplenzin, and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), iloperidone (Fanapt), lithium (Lithobid and others), lurasidone (Latuda), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Cohen** has received National Pregnancy Registry for Atypical Antipsychotics (NPRAA) research support from AstraZeneca, Bristol-Myers Squibb/Otsuka, Ortho-McNeil-Janssen, and Sunovion; has received other research support from Cephalon, GlaxoSmithKline, National Institute of Mental Health, and National Institute on Aging; and has received consulting fees (eg, for advisory board participation) from Noven. **Dr Viguera** has received NPRAA research support from AstraZeneca, Bristol-Myers Squibb/Otsuka, Ortho-McNeil-Janssen, and Sunovion. **Dr Hernández-Díaz** has received Antiepileptic Drug Registry research support from Abbott, Eisai, Novartis, Ortho-McNeil-Janssen, Pfizer, and Sunovion; has received consulting fees (eg, for advisory board participation) from AstraZeneca, GlaxoSmithKline Biologicals, and Novartis; and has received other financial/material support from Pfizer. **Mss McInerney**, **Kwiatkowski**, **Murphy**, and **Lemon** report no potential conflict of interest.

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Potential subjects can be referred to the National Pregnancy Registry for Atypical Antipsychotics (http://womensmentalhealth.org) by calling 1-866-961-2388.