The MGH National Pregnancy Registry for Atypical Antipsychotics

Lee S. Cohen, MD
Director, Center for Women’s Mental Health
Massachusetts General Hospital
Disclosures – 12 months

My spouse and I have the following relevant financial relationships to disclose:

• **NPRAA Support:** Alkermes Biopharamaceuticals; Otsuka Pharmaceuticals; Forest/Actavis Pharmaceuticals; Sunovion Pharmaceuticals, Inc.

• **Other Research Support:** JayMac Pharmaceuticals; National Institute on Aging; National Institutes of Health; Takeda/Lundbeck Pharmaceuticals

• **Advisory/Consulting:** N/A

• **Honoraria:** N/A

• **Royalty/Patent:** N/A
“I am 34 and have been diagnosed with depression/anxiety. I have been seeing a psychiatrist for seven years and during that time have been on Zoloft and Abilify.

My husband and I have been trying to conceive this past year but have been sidelined several times due to mental health issues. Namely, my attempt to wean myself off meds (with the approval of my psychiatrist and ob-gyn), and then a recent relapse due to being off of the meds. I am currently back on them due to this relapse, also taking Klonopin for several weeks until the Zoloft kicks back in. My psychiatrist also switched me to Seroquel instead of Abilify because I was having trouble sleeping when going back on the Zoloft.

I am very anxious to begin this next chapter of my life armed with the necessary knowledge, guidance and support. I know it is important to find someone to work with who will help me maintain my well-being and the well-being of my future child(ren).”
Relapse Risk of Psychiatric Disorder During Pregnancy
Relapse of Bipolar Disorder During Pregnancy

Time to Relapse in Patients who Maintained or Discontinued Antidepressant

Cohen et al. *JAMA* 2006
Reproductive Mental Health in Women Veterans: An Urgent Need

“Dear Dr. Cohen:

I am just back from a tour in Iraq and am finally getting settled back in my home life with my husband and 3 year old daughter. I am being treated for PTSD and anxiety with venlafaxine and a little bit of Seroquel at night to help me sleep. We would like to grow our family but I am worried about what happens to my PTSD symptoms during pregnancy and what do I do about the medicines. My doctor told me to ask you.”
Why is Reproductive Safety of Atypical Antipsychotics Important?

• Atypicals being used across disease states, and for off label indications
  – Schizophrenia
  – Bipolar Disorder
  – Depression
  – PTSD
  – OCD
  – Anxiety
  – Sleep
• Most second generation antipsychotics (SGAs) are prolactin sparing: implications for fertility across samples of women
• Rate of unplanned pregnancy is still ~50%
“...there are known knowns; there things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don’t know we don’t know.”
Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Huybrechts et al. *JAMA Psychiatry* 2016
Why Pregnancy Registries?

• Provides opportunity for rigorous determination of exposure to medication and verification of outcome
• Opportunity to confirm signal regarding risk of adverse outcomes noted in administrative databases (ex. claims data)
• Capacity to refine and confirm findings identified using algorithms developed to examine large administrative databases
Do we want to trust risk estimates for adverse outcomes on fuzzy claims data even when adjusted with elegant methodology?
What is the ideal way to inform clinicians who treat patients and patients themselves about reproductive safety of medicines?
Taking Antidepressants During Pregnancy Could Heighten The Risk Of Language Disorders In Children

SEPTEMBER 11, 2014
DEPRESSION AND PREGNANCY: THE TERRIFYING DILEMMA
BY ANDREW SOLOMON

Are Antidepressants Safe During Pregnancy?
By RONI CARYN RABIN
SEPTEMBER 1, 2014 6:17 PM

Pregnant women often go to great lengths to give their children the best start in life. They quit smoking and drinking, avoid the chardonnay, switch to aspirin. They say no to polio vaccines, politely decline Brie cheese.

Study links antidepressants in pregnancy with language disorders
By Susan Scutti, CNN
Updated 11:08 AM ET, Wed October 12, 2016
MGH National Pregnancy Registry for Atypical Antipsychotics

A **NEW** Research Study at the Massachusetts General Hospital Center for Women’s Mental Health

To determine the safety of atypical antipsychotics in pregnancy for women and their babies

Participation will involve 3 brief phone interviews over approximately 8 months

Call Toll-Free:
1-866-961-2388

Email:
registry@womensmentalhealth.org
National Pregnancy Registry for Psychiatric Medications ©

The National Pregnancy Registry for Psychiatric Medications® is dedicated to evaluating the safety of psychiatric medications that may be taken by women during pregnancy to treat a wide range of mood, anxiety, or psychiatric disorders. The goal of this Registry is to gather information on the safety of these medications during pregnancy, as current data is limited.

The National Pregnancy Registry is currently studying the safety of atypical antipsychotics, antidepressants, and other psychiatric medications taken during pregnancy. All pregnant women ages 18–45 are eligible to enroll in the registry. If you are pregnant and have taken an atypical antipsychotic, an antidepressant, or another psychiatric medication, please select the appropriate button below. Women who are pregnant and have not taken either an atypical antipsychotic or an antidepressant are also welcome to enroll in the Registry.

For more information & enrollment:

- National Pregnancy Registry for Atypical Antipsychotics
- National Pregnancy Registry for Antidepressants
- Other Psychiatric Medications (Stimulants, Anxiolytics, and other medications)
National Pregnancy Registry for Atypical Antipsychotics Staff

Principal Investigators:
Lee S. Cohen, MD; MGH
Adele C. Viguera, MD, MPH; MGH, Cleveland Clinic

Co-Investigator: Marlene P. Freeman, MD; MGH

Dysmorphologist: David Chitayat, MD, FABMG, FAMG, FCCMG, FRCPC; Mount Sinai

Program Coordinator: Alexandra Sosinsky

Research Coordinators: Gina Savella, Lauren Cheng
Scientific Advisory Board

Sonia Hernandez-Diaz, DrPH
Professor of Epidemiology
Director, Pharmacoepidemiology Program
Harvard T.H. Chan School of Public Health

Gideon Koren, MD, FRCPC, FACMT
Professor of Physiology/Pharmacology
University of Western Ontario; and
Professor, Tel Aviv University

Caitlin R. Smith, MPH
Director, Universal Pregnancy Registry (Pregistry)
Methods Paper

Establishment of the National Pregnancy Registry for Atypical Antipsychotics

Lee S. Cohen, MD; Adele C. Vigueras, MD, MPH; Katriyn A. McInerney, ScM; Molly A. Kwiatkowski, BA; Shannon K. Murphy, BA; Elizabeth L. Lemon, MA; and Sonia Hernández-Díaz, MPH, DrPH

ABSTRACT

Objective: Atypical antipsychotics are widely used for schizoaffective disorders to treat a spectrum of psychiatric illnesses. Despite widespread use of this class of agents in women of childbearing potential, reproductive safety data are sparse. These medicines remain untested. The National Pregnancy Registry for Atypical Antipsychotics (NPR-AAP) was established General Hospital to address this knowledge gap.

Methods: Data were prospectively collected from pregnant women, aged 18-45 years, using the Patient Information System (EPIS) at the following times: 1) before admission; 2) 7 months postpartum; and 3) 2-4 months postpartum. Subjects included pregnant women with exposure to second-generation antipsychotics and a comparison group of nonpregnant women. Ultrasound was performed to confirm pregnancy and to record the presence of major malformations. Details of adverse events are abstracted from the medical records and after determining the causality and maternal health outcomes identified cases of congenital malformations. Data are sent to the Centers for Disease Control and Prevention for further analysis.

Results: A total of 395 subjects were enrolled in the NPR-AAP. Of the 395 subjects, 150 were exposed to atypical antipsychotics. The NPR-AAP offers a systematic way to collect reproductive safety information that is critical to the care of women who use these agents to sustain psychotropic well-being.

Post Registration ClinicalTrials.gov identifier: NCT01727679

Funding: NCI/NIH/PHS Drug Evaluations Program, Inc.

Submission: Jul 20, 2014; accepted January 8, 2015.

Corresponding author: Lee S. Cohen, MD, 555 Cambridge St, 4th Floor, Boston, MA 02114. E-mail: lsc@mc.harvard.edu

© 2015 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISSEMINATION, OR COMMERCIAL PURPOSES

Study Design

• Primary aim: Prospectively evaluate rates of major malformations among infants exposed to atypical antipsychotics in utero relative to unexposed infants

• Secondary aims: Evaluate:
  1. Obstetrical outcomes
  2. Neonatal outcomes
  3. Maternal health outcomes
Eligibility Criteria

• Exposed Group: Pregnant women between the ages of 18 to 45 years old who have taken an atypical antipsychotic during pregnancy (at any time point)

• Comparison Group: Pregnant women with psychiatric illness between the ages of 18 to 45 years old who have **NOT** taken an atypical antipsychotic during pregnancy
Study Participation Overview

Potentially eligible women call our toll free number: 1-866-961-2388

Phone screen conducted, and if eligible, verbal consent is obtained

Baseline interview as soon as possible after consent (~30 min)

Second interview at 7 mo. gestation (~10 min)

Medical record release forms sent to subjects after 7 mo. interview

Final interview at 2-3 mo. postpartum (~15 min)
Data Collection Across Pregnancy

• Baseline Interview: Demographics, medication exposure, medical and psychiatric health history, drug and alcohol use
• 7 Month Interview: Medication exposure, status of prenatal testing, obstetrical course and complications, maternal medical illness
• Postpartum Interview: Medication exposure, neonatal health outcomes, maternal health outcomes
Medications Being Studied

- Aripiprazole
- Aripiprazole lauroxil
- Asenapine
- Brexpiprazole
- Cariprazine
- Clozapine
- Iloperidone
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone
13 retrospective exposures

N=554 exposed to SGA

13 retrospective exposures

N=541 prospectively enrolled

69 dropped/LTFU (12.8%)

80 not yet eligible for analysis

N=392 with evaluable data

N=357 with evaluable data AND first-trimester exposure

N=901

N=347 in comparison group

26 dropped/LTFU (7.5%)

116 not yet eligible for analysis

N=205 with evaluable data

Data extracted 3/14/17
Gestational Timing of Atypical Antipsychotic Use

Data extracted 3/14/17
Major Malformations: Case Identification

• Determination of cases of major malformations derives from a priori algorithms: maternal report and medical records are taken into account
  – Medical record procurement rate: 81.4%

• Record Review: RA, PI
  – Potential cases sent to dysmorphologist for adjudication
Risk of Major Malformations among Exposed and Control Participants

- **Exposed**: 312 live births with first trimester exposure to atypical antipsychotics
  - N=4 major malformations confirmed
  - Absolute risk: 1.3%

- **Unexposed**: 177 live births
  - N=1 major malformation confirmed
  - Absolute risk: 0.6%

- **Risk Ratio**: 2.27 (95% CI: 0.26-20.15)

- **Anticipated** aggregate sample 12/2017: N=550

Data presented at ACNP 12/2016
Summary of Secondary Outcomes

• No significant differences between the exposed and unexposed groups in rates of:
  – Live birth, neonatal death, SAB, TAB, IUFD
  – Birth weight, APGAR, preterm deliver, low birth weight, macrosomia, NICU admission, EPS symptoms
  – Gestational weight gain, gestational diabetes, preeclampsia, gestational hypertension

• Exposed participants were significantly more likely than unexposed participants to have:
  – Shorter gestational period
  – Higher pre-gravid and at term BMI
  – Preterm delivery
  – Delivery via cesarean section

• Trend for higher birth weight in exposed group
Reproductive Safety of SGAs: Current Data from the MGH NPRAA

Limitations of Pregnancy Registries

• Time required to gather outcome data
• Procurement and review of medical records is time intensive
• Generalizability of sample of subjects who volunteer for registry participation
• Sample size requirements to obtain meaningful data
Funding for the NPRAA

• All manufacturers of SGAs are approached for potential funding
• Funding amount requested represents a proportion of the Registry’s operating budget
• Regardless of which entities support the Registry, all medications in the class are studied
• Sponsorship status and duration of support is outlined on CWMH website: https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/atypicalanti-psychotic/
Funding for a National Pregnancy Registry: Lessons Learned

• Process of applying for funding, business units involved (pharmacovigilance vs. medical affairs), and priority of pregnancy registry varies greatly company to company

• Availability of funding as a function of medication lifecycle

• Interpretation “required vs. recommended” re: FDA policy on pharmacovigilance varies among manufacturers

• Placement of Registry information into product label does not imply financial support

• Funding for Pregnancy Registries ≠ I.I.T.
Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format
Guidance for Industry

1. Pregnancy Exposure Registry

The purpose of including information on a scientifically acceptable pregnancy exposure registry in the Pregnancy subsection is to inform health care providers of the availability of a pregnancy exposure registry for a product. FDA believes that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving their usefulness. The Agency considers a pregnancy exposure registry scientifically acceptable when it is consistent with FDA guidance.7

If there is a scientifically acceptable pregnancy exposure registry for the drug, the following statement must appear under the subheading Pregnancy Exposure Registry (§ 201.57(c)(9)(i)(A)):

“There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy.”

This statement must be followed by contact information (e.g., a toll-free telephone number, web site) needed to enroll in or to obtain information about the registry (§ 201.57(c)(9)(i)(A)).

When there is no pregnancy exposure registry, this subheading should be omitted.

The availability of a pregnancy exposure registry should be noted in the PATIENT COUNSELING INFORMATION section, and a cross-reference should be included to 8.1 Pregnancy for the contact information necessary to enroll.
12. Multidrug pregnancy exposure registries

A multidrug pregnancy exposure registry actively collects information on exposure to various drug therapies in specific diseases, such as human immunodeficiency virus (HIV) (White et al., 1997), epilepsy (The North American Pregnancy and Epilepsy Registry 1998), or asthma (Lipkowitz 1999; Scialli 1999). In some cases, a general multidrug registry, such as that conducted by a teratogen information service, collects information on drugs for unrelated indications. Multidrug registries have advantages over single drug registries with respect to efficiency and economy. They also have the advantage of having comparison groups of pregnant women unexposed to the medical product of interest readily available.

To help avoid redundancy and to prevent overburdening patients, physicians, and scientific experts with multiple requests to participate in individual studies, we encourage companies to work together to develop multidrug registries. It has been suggested that rather than conduct a separate pregnancy exposure registry for new drugs, a centralized pregnancy exposure registry should be established for drugs of unknown human teratogenicity that are likely to be used by women of reproductive age (Honein et al., 1999).

7 A draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees was issued on November 11, 2001. When finalized, it will represent the Agency’s thinking on this issue.
### PLLR Implementation Schedule

<table>
<thead>
<tr>
<th>PLLR Implementation Date (6/30/2015)</th>
<th>NDAs, BLA, ESs</th>
<th>Required Submission Date of PLLR Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Applications</td>
<td>Submitted on or after 6/30/2015</td>
<td>At time of submission</td>
</tr>
<tr>
<td>For applications approved prior to 6/30/2001 in old format labeling</td>
<td>Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018</td>
<td></td>
</tr>
</tbody>
</table>
Welcome

Welcome to The Ammon–Pinizzo Center for Women's Mental Health at MGH. Our Center, established in 1999, has been renamed following the generous gift from Carol Ammon and Dr. Marie Pinizzo. These resources will be used to realize the overarching mission of the Center.

This website provides a range of current information including discussion of new research findings in women's mental health and how such investigations inform day-to-day clinical practice. Despite the growing number of studies being conducted in women's health, the clinical implications of such work are frequently controversial, leaving patients with questions regarding the most appropriate path to follow. Providing these resources to patients and their doctors so that individual clinical decisions can be made in a thoughtful and collaborative fashion dovetails with the mission of our Center.

The National Pregnancy Registry for Psychiatric Medications:

All pregnant women ages 18-45 are eligible to enroll in the registry. The primary goal of this Registry is to determine the frequency of major malformations, such as heart defects, cleft lip, or neural tube defects. In infants exposed to atypical antipsychotics and antidepressants during pregnancy. We are currently seeking both controls and those being treated with atypical antipsychotics and/or antidepressants. For more information, please visit this page, call 1-866-991-2388 or email registry@womensmentalhealth.org.

Latest News from our Blog

Nourokin-1 Receptor Antagonists: A Novel Approach to the Treatment of Menopausal Symptoms

April 20, 2017

Over the last few years, we have seen a number of articles suggesting that the burden of menopausal symptoms is probably greater than generally perceived. About 80% of women experience vasomotor symptoms (VMS) – hot flashes and night sweats – as they transition into menopause. For most, the symptoms are manageable, but for a ...

Weekly Roundup for APRIL 14, 2017: Recent Publications in Women's Mental Health

April 15, 2017

The first article on the list from Andrade is an excellent discussion of the difficulties in assessing outcomes in studies of antidepressants during pregnancy. In addition, there are two articles, one from Vigod and colleagues and a review from Anderson et al. which address the issue of perinatal depression in migrant women. Offspring Outcomes in ...

In Brief: PTSD in Women Comes With Cognitive Impairment

April 13, 2017

While we know that PTSD is about twice as common in women as men, most PTSD research has focused on PTSD in men. As such, we don't have as much information on how it affects women, particularly in terms of cognitive function.

Read more