Collaborative Medical Decision Making for Providers and Patients for Pregnancy: The New FDA Pregnancy Labels and What They Mean

Marlene P. Freeman, MD
Associate Professor of Psychiatry, Harvard Medical School
Associate Director, Perinatal and Reproductive Psychiatry
Medical Director, CTNI
Massachusetts General Hospital
Boston, Massachusetts

Overview

• The context: Women of reproductive potential and psychiatric disorders
• US Food and Drug Administration labeling changes
• Approaching the data

When Do Disorders Start?

• “Mental illnesses are the chronic diseases of the young”
• One-half of all diagnoses presented by age 14
• Three-quarters by age 24

The Context:
Women of reproductive potential and psychiatric disorders

What percent of pregnancies globally are unplanned annually?

1. 10%
2. 20%
3. 30%
4. 40%
5. 50%

What percent of pregnancies in the United States are unplanned annually?

1. 10%
2. 20%
3. 30%
4. 40%
5. 50%

Treating Women of Childbearing Potential

- 49% of pregnancies in the United States are unintended
- 80% of teen pregnancies unintended
- 82% of US women have had a child by age 40

Context for Assessing Risk

- Rate of major malformations: 3% to 4%
- Rate of premature delivery: 11% to 12%
- Rate of gestational diabetes: 2% to 7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders

US Food and Drug Administration and Pregnancy Labeling Changes

- Rate of major malformations: 3% to 4%
- Rate of premature delivery: 11% to 12%
- Rate of gestational diabetes: 2% to 7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders

Depression During Pregnancy: Medication

FDA Ratings
A: Studies in humans show no risk
B: No evidence risk in humans; if no human data, animal data show no risk
C: Risk cannot be ruled out
D: Positive evidence of risk
X: Contraindicated in pregnancy

NOT HELPFUL OVERALL
Transitioning out of use

The Pregnancy and Lactation Labeling Rule (PLL) or “Final Rule”

- Revises the Physician Labeling Rule
- Subsections
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
- Principles
  - Revising labeling
  - Formatting
  - Cross-referencing
Revised Labeling

**Timeliness:** Must be updated when new information becomes available
**Focus on humans:** Includes evaluation of human data that mainly becomes available postmarketing
**Context:** Includes new information about background rates of adverse events

---

Pregnancy Subsection: Headings

- **Pregnancy Exposure Registry**
  - Scientifically acceptable registry and contact info
- **Risk Summary**
  - Human, animal, pharmacologic data
  - Adverse developmental outcomes
    - Structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth
  - Background risks from the US population (ie, CDC data)
- **Clinical Considerations**

---

Pregnancy Subsection: Risk Statement on Human Data

**Sources**
- Clinical trials
- Pregnancy exposure registries
- Other large scale epidemiologic studies
**To include**
- Incidence, effect of dose, effect of duration of exposure, effect of gestational timing
- Risk must be quantitatively compared to the risk for the same outcome in infants born to women not exposed to the drug, but who have the disease or condition for which the drug is indicated (ie, controls must be appropriate)

---

Pregnancy Subsection

**Clinical Considerations**
- More information for prescribers in order to further risk–benefit counseling
  - Disease-associated maternal/fetal risks
  - Dose adjustments during pregnancy and postpartum
  - Maternal adverse reactions
  - Fetal/neonatal adverse reactions
  - Labor/delivery

---

Guidance for Industry

Establishing Pregnancy Exposure Registries

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2002
Clinical/Medical

---

Prospectively Oriented Data

**What can be provided**
- Provide margins of reassurance RE: lack of risk
- Monitor for suspected risks
- Identify factors that affect adverse outcomes
- Medical product may be a good candidate if
  - Inadvertent exposures likely (high likelihood of use by women of reproductive age)
**Comparison Groups**

- **Internal**
  - Unexposed concurrently enrolled, matched or stratified
  - Women within a multidrug registry, common indication or underlying risk factors
- **External**

**FDA Considerations and Methodology**

- **Independent data monitoring committee**
  - For needed expertise, assessment, interpretation of data (ie, classification of birth defects), methodology, reporting
- **Multidrug registries**
  - Efficiency and economy
  - Avoid overburdening patients, health care providers

**Approaching the Data**

Can Nonrandomized Studies on the Safety of Antidepressants during Pregnancy Convincingly Beat Confounding, Chance, and Prior Beliefs?

- 7% to 13% of pregnant women in the United States use antidepressants
- Studies usually not controlled for by indication
- Usually do not control for depression during pregnancy
  - Some do, but not for severity
- Questions
  - Why do women who use antidepressants have an increased risk of reported perinatal outcomes?
  - Does depression play an etiologic role?
  - Do maternal behaviors that are caused by depression/anxiety increase risk?
  - Are there genetic or environmental associations that cause both psychiatric disorders and adverse perinatal outcomes?
  - Or are antidepressants toxic in pregnancy?

**Challenges**

- Outcomes of interest rare, eg, specific malformations
- Outcomes may differ by specific medication
- Findings suggest that risks are small to moderate
  - Need large databases
  - Large databases typically lack detail indication and severity
- **Confounding**
  - Depression and/or its severity among the group of interest and not among the control group
- **A priori beliefs – interpretation**
  - ie, 1.5-fold increase in risk could be evidence of safety or evidence of risk

**What is the impact of appropriate controls?**

**Are Antidepressants Associated with an Increased Risk of Spontaneous Abortion?**

- Danish Medical Birth Registry and the Danish National Hospital Registry
- 1,005,319 pregnancies: 114,721 (11.4%) ended in SA
- 22,061 pregnancies exposed to antidepressants and 1843 with a diagnosis of depression with no antidepressant use, of which 2637 (12.0%) and 205 (11.1%) ended in SA, respectively
- Antidepressant exposure was associated with an RR of 1.14 (95% CI = 1.10–1.18) for SA compared with no exposure to antidepressants
- Among women with a diagnosis of depression, the RR for SA after any antidepressant exposure was 1.00 (95% CI = 0.80–1.24)
- No SSRI was associated with SA
- In unadjusted analyses: mirtazapine, venlafaxine, duloxetine associated with SA among women with depression—small Ns, lack of data RE: severity

**Conclusion**
- Slightly increased risk of SA associated with the use of antidepressants
- When comparing women with depression, antidepressants in general or individual SSRI in particular were not associated with SA

**Unadjusted RR for SA after Exposure to Specific Types of Antidepressants Compared to the Unexposed Cohort**

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>1.21 (1.16–1.26)</td>
<td>.0007</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>1.43 (1.34–1.53)</td>
<td>.0000</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.45 (1.30–1.62)</td>
<td>.0000</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.65 (1.44–1.90)</td>
<td>.0000</td>
</tr>
<tr>
<td>TCA</td>
<td>1.47 (1.28–1.70)</td>
<td>.0000</td>
</tr>
<tr>
<td>Imipramine</td>
<td>1.69 (1.59–1.82)</td>
<td>.0000</td>
</tr>
<tr>
<td>Citalopram</td>
<td>1.50 (1.40–1.61)</td>
<td>.0000</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.70 (1.56–1.86)</td>
<td>.0000</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1.84 (1.69–2.01)</td>
<td>.0000</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>2.12 (1.52–2.86)</td>
<td>.0000</td>
</tr>
</tbody>
</table>

**Unadjusted RR for SA after Exposure to Specific Types of Antidepressants Among Women with a Hospital-Based Diagnosis of Depression**

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>0.80 (0.62–1.03)</td>
<td>.274</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>0.60 (0.38–0.96)</td>
<td>.024</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1.11 (0.79–1.55)</td>
<td>.949</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.52 (0.55–1.37)</td>
<td>.306</td>
</tr>
<tr>
<td>TCA</td>
<td>0.94 (0.46–1.94)</td>
<td>.918</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>1.04 (0.60–1.78)</td>
<td>.955</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>1.77 (0.80–3.96)</td>
<td>.135</td>
</tr>
<tr>
<td>clomipramine</td>
<td>0.87 (0.43–1.80)</td>
<td>.614</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>2.30 (1.70–3.31)</td>
<td>.001</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2.23 (1.34–3.70)</td>
<td>.001</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1.80 (1.19–2.72)</td>
<td>.003</td>
</tr>
<tr>
<td>MitrafloX</td>
<td>3.12 (1.55–6.31)</td>
<td>.001</td>
</tr>
</tbody>
</table>

**Paroxetine and Pregnancy**

- **Public Health Advisory: Paroxetine**
- **12/8/2005**
- The FDA has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations. At the FDA’s request, the manufacturer has changed paroxetine’s pregnancy category from C to D and added new data and recommendations to the Warnings section of paroxetine’s prescribing information. The FDA’s conclusions and changes in paroxetine’s prescribing information are based on preliminary analyses of 2 recent unpublished epidemiology studies.

**RESULTS**

- 19 studies were above quality threshold and make up the primary meta-analyses. Pooled RRs were derived by using random-effects methods. Antidepressant exposure was not associated with congenital malformations (RR = 0.93; 95% CI, 0.85–1.02; P = .113) or major malformations (RR = 1.07; 95% CI, 0.99–1.17; P = .867). However, increased risk for cardiovascular malformations (RR = 1.36; 95% CI, 1.08–1.71; P = .008) and septal heart defects (RR = 1.40; 95% CI, 1.10–1.77; P = .005) were found; the RR for ventral septal defects was similar to septal defects, although not significant (RR = 1.54; 95% CI, 0.71–3.33; P = .274). Pooled effects were significant for paroxetine and cardiovascular malformations (RR = 1.43; 95% CI, 1.08–1.88; P = .012). These results are contrasted with those addressing methodological limitations but are typically consistent.

**Paroxetine**

- No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs
Risk of Cardiovascular Malformation following SSRI Exposure

- Recent analysis of 949,504 pregnant women enrolled in Medicaid
  - 3 months prior to pregnancy to 1 month following pregnancy
- 6.8% use of SSRIs during first trimester
- Risk for cardiac defects attenuated with increasing levels of adjustment for confounding

Cardiovascular Malformation and Fetal SSRI Exposure

What is the impact of adequate numbers?

Lamotrigine: North American AED Pregnancy Registry

- 2008
  - $N = 792$ with lamotrigine monotherapy; limited to those with medical records
  - 16/684 (2.3%) – major malformations
  - 5/684 (7.3/1000, or 0.73%) – oral clefts – 10-fold increase from external reference (0.7/1000)
  - From other registries: 4/1623 (2.5/1000)

Lamotrigine: North American AED Pregnancy Registry

- 2012
  - $N = 1562$ with lamotrigine monotherapy
  - 31/1562 (2.0%) – major malformations
  - 7/1562 (0.45%; CI 0.20–0.88) – oral clefts
  - External reference – 0.11%

IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs

- The results are based on regression models for the intention-to-treat population (598 children). See Table 3 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was impaired for 77 of the original 369 children born alive who were not assessed at that age ($C = 0$ of these children died from severe malformations).
- The confidence intervals for differences among treatment groups are valid only for comparisons among the groups. The confidence intervals for the differences between carbamazepine and valproate and between phenobarbital and valproate do not include zero.
- P values are for the comparison with the valproate group. Values from tests of the null hypothesis of no difference from the valproate group means were calculated for multiple comparisons.
**Antidepressants during Pregnancy: Later Pregnancy Considerations**

- Persistent pulmonary hypertension of the newborn
  - Lung abnormality in newborns
  - 1 to 2 out of 1000 live births
  - Abnormal persistence of high pulmonary vascular resistance at birth disrupts normal transition from fetal to newborn blood flow in lungs, shunting of the blood away from lungs and lack of oxygen; fatal in 10% to 20%
- Established risk factors
  - Cesarean delivery; late preterm or postterm birth; large for gestational age; maternal black or Asian race, overweight/obesity, diabetes, asthma

**Antidepressant Use Late in Pregnancy and Risk of PPHN**

- Large Medicaid Database – 3.8 million pregnancies
  - 128,950 women (3.4%) filled at least 1 prescription for antidepressants last 90 days of pregnancy; 2.7% used an SSRI and 0.7% used a non-SSRI
  - Overall, 7630 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95% CI, 20.4-21.3 per 10,000 births) compared with 322 infants exposed to SSRIs (31.5; 95% CI, 28.3–35.2 per 10,000 births), and 78 infants exposed to non-SSRIs (29.1; 95% CI, 23.3–36.4 per 10,000 births)
- Absolute Risks
  - With SSRI: 31.5/10,000 = 0.3%
  - No antidepressant: 20.8/10,000 = 0.2%
- Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment

**Are Antidepressants Associated with an Increased Risk of Spontaneous Abortion?**

- Rates of SA in women taking antidepressants compared with non-depressed women were combined into a relative risk using a random effects model
- Results
  - Of 15 potential articles, 6 cohort studies of 3567 women (1934 exposed, 2033 nonexposed) provided extractable data
  - All matched on important confounders
  - The baseline SA rate (95% CI) was 8.7% (7.5–9.9%; n = 2033)
  - For antidepressants, the rate was 12.4% (10.8–14.1%; n = 1534), significantly increased by 3.9% (1.9–6.0%; RR was 1.45 (1.19–1.77; n = 3567)
  - No differences were found among antidepressant classes

**Atypical Antipsychotics in Pregnancy**

- Motherisk Program (2005): prospective study N = 151, comparison with controls (no exposure to antipsychotic medication)
  - Rates of malformations did not differ between group exposed to atypicals and control group (0.9% vs 1.5%)
- German study (2013): n = 561 exposed to atypicals, n = 284 exposed to typicals, n = 1122 controls
  - No significant difference between rates of major malformations between those exposed to atypicals (5.1%) or typicals (4.2%)
- Motherisk Program (2013): matched with controls not taking a psychotropic
  - 70% quetiapine, 16.5% olanzapine, 10.5% risperidone, 1.5% aripiprazole
  - most common malformations were cardiovascular (8 of 12) were atrial or ventricular septal defects
- Motherisk Program (2013): matched with controls not taking a psychotropic
  - 70% quetiapine, 16.5% olanzapine, 10.5% risperidone, 1.5% aripiprazole
  - 72% polytherapy with psychotropics; majority treated for mood disorder
  - No significant difference in congenital malformations
  - more NICU admissions among exposed
  - Greater percentage of C-sections

**Australian registry study 2014**

- 147 pregnancies: most commonly used agents were quetiapine (n = 74), olanzapine (n = 24), aripiprazole (n = 19), and risperidone (n = 15). There were 142 live births, and data were available for 100 children at 1 year of age
- No control group
- Rate of gestational diabetes was 22%
- 18% of babies were born prematurely, with higher doses of antipsychotic medication correlating with an increased likelihood of premature delivery
- 43% required special care nursery or intensive care after birth; many also exposed to other psychotropics
- Congenital anomalies were seen in 8 out of 142 infants (5.6%)
Atypical Antipsychotics in Pregnancy (continued)

- April 2014, N = 408 enrolled (n = 300 exposed, n = 108 unexposed); medical records obtained from 90%
- Rates of major malformations in the 2 groups similar
  - 1.5% (3/200 live births) in exposed group
  - 1.2% (1/84) in the comparison group

National Pregnancy Registry for Atypical Antipsychotics

- 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

Questions

- How do we capture accurate risks and benefits of fetal exposures to medications while taking into account the risks of the untreated or undertreated disorders?
- How do we ensure that adequate numbers of patients are enrolled in studies to provide meaningful results?
- How do we communicate findings clearly to multidisciplinary health care providers and to consumers?
- Who will fund such research?
- What about the tracking of long-term outcomes of children following fetal exposure?

Practical Take-Aways

- The risk–benefit analyses of medication exposure for individual women are complex
  - Take into account pregnancy data and quality
  - Data must be interpreted in context – pregnancy itself is inherently risky
    - Risk of poor outcomes in the general population
    - Risk of untreated psychiatric disorders
  - Study methodology contributes to quality of data in a profound way
    - Size of studies
    - Control for confounding variables
  - Collaborative decision-making is the goal