Current PSYCHIATRY

# Pregnant and nursing patients benefit from 'ambitious' changes to drug labeling for safety

## FDA's new system improves on the limited utility of the 'A-B-C-D-X' scheme

In December 2014, the FDA issued draft guidance for sweeping changes to labeling of pharmaceutical treatments in regard to pregnancy and lactation information. These changes are now in effect for use in practice.[1] The undertaking has been years in the making, and is truly ambitious.

The outdated system of letter categories (A, B, C, D, X) falls short of clinical needs in several ways:

- the quality and volume of data can be lacking
- comparative risk is not described
- using letters can led to oversimplification or, in some cases, exaggeration of risk and safety (***Box, page 38***).

Other drawbacks include infrequent updating of information and omission of information about baseline rates of reproductive-related adverse events, to provide a more meaningful context for risk assessment.

A note before we continue discussion of labeling: Recognize that pregnancy itself is inherently risky; poor outcomes are, regrettably, not uncommon. The rate of birth defects in the United States is approximately 3%, and obstetric complications, such as prematurity, are common.[2,3]

continued

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A statement of commercial sponsorship of the National Pregnancy Registry for Atypical Antipsychotics appears at: https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/atypicalantipsychotic.

ANDERSEN ROSS

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

**Adele C. Viguera, MD, MPH**
Assistant Professor
Cleveland Clinic Lerner College of Medicine
Director, Women's Mental Health
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

**Lee S. Cohen, MD**
Edmund N. and Carroll M. Carpenter Professor of Psychiatry
Harvard Medical School
Director
Center for Women's Mental Health
Massachusetts General Hospital
Boston, Massachusetts

Drug safety labeling

**Clinical Point**

**The literature on reproductive safety of psychotropics is fraught with confounding variables other than the medications**

Box

### 3 Ways the letter-category system of drug safety information is deficient

**Data are insufficient or flawed.** In the past, when the FDA approved a new drug, the letter was determined based on available data at the time—without, understandably, any requirement for human data. A letter typically has been assigned based on only a modest amount of animal data. Also, a letter does not take into account the relative amount or quality of the body of data available for each medication. For some medications, the amount of information is vast and complex.

**Comparative risk is not described.** Letters do not take into account the risk to mother and fetus of the untreated condition.

**The system tends toward oversimplification.** Letter categorization is overly simple, providing a misleading sense of how relatively safe or risky a medication might be in pregnancy, without acknowledging the complexities of the data, or sometimes lack thereof. Health care providers and patients often only look at the letter and not the body of evidence itself on which the letter assignment was based.

## New system described

The new labeling content has been described in the FDA's Pregnancy and Lactation Labeling Rule (also called the "final rule"), issued in December 2014. For each medication, there will be subsections in the labeling:

- Pregnancy
- Lactation
- Females and Males of Reproductive Potential.

In addition, FDA instructions now state that labeling:

- must be updated when new information becomes available
- needs to include evaluation of human data that becomes available mainly after the drug is approved
- needs to include information about the background rates of adverse events related to reproduction.

**Labeling in pregnancy**. As an example, the "Pregnancy" section of every label contains 3 subsections, all of great clinical importance. First is information about pregnancy exposure registries, with a listing of scientifically acceptable registries (if a registry is available for that drug) and contact information; this section focuses on the high value of data that are systematically and prospectively collected. The second summarizes risk associated with the drug during pregnancy, based on available human, animal, and pharmacologic data. Third is a discussion of clinical considerations.

**Need for appropriate controls**. Psychiatric disorders increase the risk of pregnancy complications, and often are associated with variables that might increase the risk of a poor pregnancy outcome. For example, a patient who has a psychiatric disorder might be less likely to seek prenatal care, take a prenatal vitamin, and sleep and eat well; she also might use alcohol, tobacco, or other substances of abuse.

The medical literature on the reproductive safety of psychotropic medications is fraught with confounding variables other than the medications themselves. These include variables that, taken alone, might confer a poorer outcome on the fetus or newborn of a pregnant or lactating woman who has a psychiatric illness (to the extent that she uses psychotropics during a pregnancy), compared with what would be seen in (1) a healthy woman who is not taking such medication or (2) the general population.

On the new labels, detailed statements on human data include information from clinical trials, pregnancy exposure registries, and epidemiologic studies. Labels are also to include:

- incidence of adverse events
- effect of dosage
- effect of duration of exposure
- effect of gestational timing of exposure.

The labels emphasize quantifying risk *relative to* the risk of the same outcome in infants born to women who have not been exposed to the particular drug, but who have the disease or condition for which the drug is indicated (ie, appropriate controls).

**Clinical considerations** are to include information on the following related to the specific medication (when that information is known):

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- more information for prescribers, to further risk-benefit counseling
- disease-associated maternal-fetal risks
- dosage adjustments during pregnancy and postpartum
- maternal adverse reactions
- fetal and neonatal adverse reactions
- labor and delivery.

Clearly, this overdue shift in providing information regarding reproductive safety has the potential to inform clinicians and patients in a meaningful way about the risks and benefits of specific treatments during pregnancy and lactation. Translating that information into practice is daunting, however.

## Important aspects of implementation

**Pregnancy exposure registries will play a crucial role**. For most medications, no systematic registry has been established; to do so, rigorous methodology is required to acquire prospective data and account for confounding variables.[4] Appropriate control groups also are required to yield data that are useful and interpretable. Primary outcomes require verification, such as review of medical records. Last, registries must be well-conducted and therefore adequately funded, yet labeling changes have not been accompanied by funding requirements set forth by regulators to pharmaceutical manufacturers.

**Labeling must be updated continually**. Furthermore, it is unclear who will review data for precision and comprehensiveness.

**Data need to be understandable** to health care providers across disciplines and to patients with varying levels of education for the label to have a meaningful impact on clinical care.

As noted, there is no mandate for funding the meticulous pharmacovigilance required to provide definitive data for labeling. It is unclear if the potential benefits of the new labeling can be reaped without adequate financing of the pharmacovigilance mechanisms required to inform patients adequately.

## Role of pregnancy registries

Over the past 2 decades, pregnancy registries have emerged as a rapid, systematic means of collecting important reproductive safety data on the risk for major malformations after prenatal exposure to a medication or a class of medications.[5,6] Such registries enhance the rigor of available cohort studies and other analyses of reproductive safety data that have been derived from large administrative databases.

**NPRAA and NPRAD**. Recently, the National Pregnancy Registry for Atypical Antipsychotics (NPRAA) and the National Pregnancy Registry for Antidepressants (NPRAD) were established in an effort to obtain reproductive safety data about fetal exposure to second-generation antipsychotics (SGAs) and to newer antidepressants.[7] Based at Massachusetts General Hospital in Boston, NPRAA and NPRAD systematically and prospectively evaluate the risk of malformations among infants who have been exposed in utero to an SGA or an antidepressant.

The structure of both registries are the same, modeled after the North American Antiepileptic Drug Registry.[5,8] Data are collected prospectively from pregnant women, age 18 to 45, by means of 3 telephone interviews conducted proximate to enrollment, at 7 months' gestation, and at 2 or 3 months' postpartum.

Participants include (1) pregnant women who have a history of fetal exposure to an SGA or an antidepressant, or both, and (2) a comparison group of non-exposed pregnant women who have a history of a psychiatric illness. Authorization for release of medical records is obtained for obstetric care, labor and delivery, and neonatal care (≤6 months of age).

Information on the presence of major malformations is abstracted from the medical record, along with other data on neonatal and maternal health outcomes. Identified cases of a congenital malformation are sent to a dysmorphologist, who has been blinded to drug exposure, for final adjudication. Release of findings is dictated by a governing Scientific Advisory Board.

continued

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**Clinical Point**

**Details about human data on new labels are based on clinical trials, pregnancy exposure registries, and epidemiologic studies**

Drug safety labeling

## Related Resources

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**Drug Brand Names**

Thalidomide • Thalomid
Valproate • Depakote

**Clinical Point**

**Results gleaned from the NPRAA registry reasonably lead to the conclusion that second-generation antipsychotics are not major teratogens**

**Results so far**. Results are available from the NPRAA.[9] As of December 2014, 487 women were enrolled: 353 who used an SGA and 134 comparison women. Medical records were obtained for 82.2% of participants. A total of 303 women completed the study and were eligible for inclusion in the analysis. Findings include:

- Of 214 live births with first-trimester exposure to an SGA, 3 major malformations were confirmed. In the control group (n = 89), 1 major malformation was confirmed
- The absolute risk of a major malformation was 1.4% for an exposed infant and 1.1% for an unexposed infant
- The odds ratio for a major malformation, comparing exposed infants with unexposed infants, was 1.25 (95% CI, 0.13–12.19).

It is reasonable, therefore, to conclude that, as a class, SGAs are not major teratogens. Although the confidence intervals around the odds ratio estimate remain wide, with the probability for change over the course of the study, it is unlikely that risk will rise to the level of known major teratogens, such as valproate and thalidomide.[10,11]

## Help with decision-making

Given recent FDA guidance about the importance of pregnancy registries (www.fda.gov/pregnancyregistries), such carefully collected data might help clinicians and patients make informed choices about treatment. Future efforts of NPRAA and NPRAD will focus on sustaining growth in enrollment of participants so that the reproductive safety of SGAs and newer antidepressants can be delineated more clearly.

Last, you can refer potential participants to NPRAA and NPRAD by calling 1-866-961-2388. More information is available at www.womensmentalhealth.org.

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