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Accumulation of Reproductive Safety Data for Second-Generation Atypical Antipsychotics: A Call to Accelerate the Process

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Second-generation atypical antipsychotics are being increasingly used by reproductive-aged women as primary or adjunctive therapy across a wide range of psychiatric disorders (including bipolar disorder, schizophrenia, unipolar depression, and anxiety disorders).¹ Despite the high prevalence of the use of these medications among women of childbearing age, progress in understanding the safe use of atypical antipsychotics across pregnancy, delivery, and breastfeeding has been relatively slow. There is an urgent public health need for more rapid accumulation of systematic reproductive safety data across these medications.

In their article, Yakuwa et al² investigate the risk of major congenital malformations associated with exposure to second-generation antipsychotics (SGAs) in the first trimester. The study cohort consisted of pregnant women who contacted and received a consultation on drug exposure from the Japan Drug Information Institute in Pregnancy, a teratogen information service (TIS) established in 2010. Women who contacted this service from October 2005 to December 2016 were asked to complete a questionnaire at 1 month after their expected delivery date on pregnancy outcomes including date of delivery; gestational age at delivery; birth height, weight, head circumference, and chest circumference; and major malformations in the infant based on maternal report. The exposure group consisted of infants with at least 1 SGA exposure during the first trimester. The comparison group consisted of infants not exposed to SGAs or any other medications known to be teratogenic (such as warfarin, valproic acid, and phenytoin) during pregnancy.

Overall, 7,249 pregnant women contacted the teratogen information service during the study period. Response rates were similarly high among the exposed group (77.7%) and the non-exposed group (89.7%). The rate of major

malformations among live-born infants was 0.9% (3/351) in the SGA group and 1.8% (70/3,899) in the comparison group. The adjusted odds ratio for major malformations among live-born infants of pregnant women with first-trimester use of SGAs compared to the unexposed group was 0.44 (95% CI, 0.12–1.48), suggesting no significant teratogenic signal.

Major strengths of this study design are the determination of the primary outcome (major malformations) prospectively, which limits the potential for recall bias. In addition, malformations were diagnosed and confirmed by local pediatricians at 1 month during routine medical examination, and all suspected major malformations were subsequently verified using the European Congenital Anomaly Monitoring classification system by a dysmorphologist blinded to exposure group. With respect to limitations, the extent to which these results are generalizable to the larger population of women taking atypical antipsychotics is unknown. Women who participate in teratogen information services tend to self-select as those who may be higher functioning, more motivated, and better informed than nonparticipants. Also, instead of using a healthy comparison group of women not exposed to a teratogenic medication, a more meaningful comparison group would have been women with histories of psychiatric illness not taking an SGA, thereby limiting confounding by indication, which is a frequent flaw in studies involving large insurance claims databases or national birth registries or teratogen counseling service databases.

The quest for robust reproductive safety data for SGAs reminds us of the strong clinical parallels between the challenges facing pregnant women with epilepsy and those with psychiatric disorders (including mood, anxiety, and psychotic disorders). For both epilepsy and psychiatric conditions, treatment discontinuation poses a very high risk of recurrence of severe maternal morbidity and its potential adverse effects on the fetus.^{3,4} Therefore, balancing protection from recurrences and potential harm to the fetus from medication exposure is an important clinical objective. Perhaps we can learn a lesson from our colleagues in neurology who in the 1990s had the foresight to establish pregnancy registries as a means to collect rapidly reproductive safety data on antiepileptic drugs (AEDs).³ These registries have been operational for over 20 years and include the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP), The North American Antiepileptic Pregnancy Registry, the International Lamotrigine

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Pregnancy Registry, the United Kingdom Epilepsy and Pregnancy Register, and the Australian Pregnancy Register.^{4,5} While they differ with respect to methods of data collection and definitions of major malformations, they are uniformly prospective in study design, allowing for the assessment of potential confounding variables and the selection of controls (ie, either healthy subjects or subjects with similar illnesses to those exposed), which is so critical to the interpretation of reproductive safety outcomes. The growth of these AED registries also catalyzed the elimination of the category labeling system of A, B, C, and X of the United States Food and Drug Administration (FDA), which was overly simplistic, in favor of the Pregnancy and Lactation Labeling Rule (PLLR), requiring a more descriptive summary of outcomes of exposure to medications during pregnancy and lactation on drug labels.⁶ In fact, the FDA endorses registries as an ideal mechanism for collecting reproductive safety data and now requires manufacturers to state in their label whether a pregnancy registry exists for their particular medication.⁷

By enrolling large numbers of pregnancies with exposure to AEDs, these registries have accrued an impressive amount of reproductive safety data over a relatively short period of time. Moreover, such research endeavors have advanced research agendas to focus on assessment of neurobehavioral outcomes of children exposed to AEDs in utero as well as outcomes of children following exposure to AEDs through breastmilk—two issues that are also of great concern to mothers and their providers.^{8,9} Again, these coordinated efforts, both nationally and internationally, have significantly informed the care of pregnant women with epilepsy around the world.

Because the accumulated body of research is sufficiently robust, neurology has led the way not only in developing and disseminating consumer information on clinical issues related to the use of AEDs in women of reproductive age, but also in developing extensive consensus guidelines for neurologists regarding the use of AEDs in women with epilepsy during pre-pregnancy planning, pregnancy, the postpartum period, and breastfeeding. Moreover, these expert consensus guidelines have been sponsored by major national medical societies. For example, in 2009, the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) published a Practice Parameter Update on the pregnant woman with epilepsy.¹⁰ The Epilepsy Foundation also provides a 2-page pregnancy fact sheet on their organization's website directed at patients and their families that distills the essential information into question-and-answer format. What is also striking about this literature is its tone, which is sensible and reassuring rather than ambiguous and anxiety-provoking.

In contrast to the various pregnancy registries for AEDs, there are currently only two existing pregnancy registries in psychiatry for SGAs—one in Australia and one in the United States. Currently enrolling women from Australia and New Zealand, the National Register of Antipsychotic Medication in Pregnancy (NRAMP) was established as an

ongoing prospective observational cohort study.¹¹ In the United States, the National Pregnancy Registry for Atypical Antipsychotics was established in 2008. Modeled after the North American Antiepileptic Drug Registry and based at Massachusetts General Hospital, the Registry is the first hospital-based pregnancy registry in North America to systematically and prospectively examine the risk of major malformations among infants exposed in utero to SGAs.¹²⁻¹⁴ In addition, other important secondary outcomes, including neonatal, obstetrical, and neurobehavioral outcomes, are also being collected.

With respect to a coordinated effort to synthesize and disseminate reproductive safety information on SGAs, progress on guideline development and direct-to-consumer information has been slow. Few national organizations like the American Psychiatric Association, World Psychiatric Association, or the American Society of Clinical Pharmacology have provided clear, practical, up-to-date consensus recommendations for patients and providers. Such efforts from reputable organizations would go a long way, especially with the removal of the familiar and straight-forward (albeit flawed and overly simplistic) FDA category labeling system, in providing balanced information and reassurance to physicians and patients that maintaining maternal well-being is ultimately in the best interest of the child. Sacrificing maternal mental health to avoid in utero medication exposure is counterproductive and no longer acceptable.

The question remains as to why we are so behind in the year 2022 compared to our colleagues in neurology with respect to our treatment of pregnant women with psychiatric morbidity. Perhaps there remains residual professional and popular bias against pregnancy and motherhood for women with psychiatric illness. In a previous study,⁴ our group found, surprisingly, that approximately half of pregnant women diagnosed with bipolar disorder had been advised against pregnancy by their psychiatrist.

Despite some limitations, the reproductive safety data on SGAs from Yakuwa and colleagues² in Japan are indeed encouraging and reassuring and add to the accumulating evidence from a variety of sources, including large insurance claims databases, birth registers, registries, and teratogen information services that SGAs are not major teratogens. It is reassuring that we do not see a signal for teratogenicity across the accumulated data on reproductive safety of SGAs, nor do we see a clear pattern of malformation in the cases of congenital anomalies noted following fetal exposure to this class of medication. While comparing the risk for malformations across heterogeneous studies has multiple methodological difficulties, data deriving from different sources is a strength, as findings may be either confirmed or disproved by others. If, as a class, SGAs consistently exhibit no increased risk of major malformations across multiple study designs, this is indeed a reassuring signal.

Yakuwa et al² emphasize the urgent need for reproductive safety data of SGAs given that suicide is currently a major perinatal problem in Japan. Such tragic consequences

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inspire a call to action to collaborate and coordinate our collective efforts, nationally and globally, across academic medical centers, teratogen services, federal agencies, and pharmaceutical pharmacovigilance systems. As a field, we can do better for our pregnant women suffering from psychiatric illness and accelerate the pace of data acquisition. Imagine the clinical benefits that could arise from such unified and deliberate efforts.

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